

Contemporary Endocrinology
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Kevin T. McVary *Editor*

Contemporary Treatment of Erectile Dysfunction

A Clinical Guide

 Humana Press

Contemporary Endocrinology

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Editor

Contemporary Treatment of Erectile Dysfunction

A Clinical Guide

 Humana Press

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Preface

Erectile dysfunction (ED) was once considered psychogenic in origin and frequently neglected by healthcare providers. More recently, there is increasing recognition of its many physiological causes, its impact on the quality of life, and the potential for therapy to improve the quality of life, self-esteem, and the ability to maintain intimate relationships. Despite these important steps forward, the pathophysiology of ED remains incompletely understood.

This book represents the current state-of-the-art in the evaluation, diagnosis, and the treatment of this important and common global problem. The contributing authors represent the world's most experienced, knowledgeable, and most expressive investigators in the field and are able to update the reader on the current aspects of the clinical problem as well as the state-of-the-art in evaluation, pathophysiology, hormonal evaluation, oral and local therapies, psychotherapy, prosthetics, and areas of uncertainty pertaining to ED.

Kevin T. McVary
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Chapter 1

Animal Models for the Study of Erectile Function and Dysfunction

Kevin E. McKenna

Abstract The mechanisms of penile erection have been investigated using animal models from the beginning of modern investigative physiology. In 1863, Eckhard reported that electrical stimulation of the nervi erigentes (pelvic nerves) induced penile erection in the anesthetized dog. This study identified that erection is a vasodilatory event. Over 125 years of animal experimentation passed before the vasodilatory neurotransmitter was identified as nitric oxide. Now, due largely to the use of animal models, the hemodynamics, molecular biology, and neurobiology of penile erection are understood in their broad outline. Recent animal research has concentrated on identifying the mechanisms of erectile dysfunction (ED) in a variety of pathophysiological states.

Keywords Pelvic nerves • Sexual function • Erectile physiology and pathophysiology • Cardiovascular disease • Nonhuman primate erectile mechanisms • Rodent biology

Introduction

The mechanisms of penile erection have been investigated using animal models from the beginning of modern investigative physiology. In 1863, Eckhard [1] reported that electrical

stimulation of the nervi erigentes (pelvic nerves) induced penile erection in the anesthetized dog. This study identified that erection is a vasodilatory event. Over 125 years of animal experimentation passed before the vasodilatory neurotransmitter was identified as nitric oxide. Now, due largely to the use of animal models, the hemodynamics, molecular biology, and neurobiology of penile erection are understood in their broad outline. Recent animal research has concentrated on identifying the mechanisms of erectile dysfunction (ED) in a variety of pathophysiological states. One clear finding of these studies, since verified in human studies, is that the neural, endothelial, and smooth muscle defects which underlie erectile dysfunction, represent a powerful warning of the probability of developing serious cardiovascular disease. This is because the mechanisms regulating the vascular tissue of the penis are essentially the same in most other vascular beds. Thus, the animal models developed for the study of penile erection provide a useful tool for investigating the early cardiovascular effects of diabetes, obesity, diet, aging, etc.

Research in the area of sexual function critically depends on research models. Investigations into the anatomy, physiology, cell biology, biochemistry, and pharmacology of sexual function are necessary to develop new therapies for the treatment of human disease. It is especially important that researchers choosing to adopt an experimental approach be aware that any given model has strengths and limitations. No animal model can ever represent all aspects of human

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physiology and pathophysiology. Therefore, all animal models require a series of compromises on the part of the investigator. Several factors must be considered in the choice of a particular model. Researchers must consider whether the function being investigated is similar in the animal model and the human, the strength of the literature of that function in that species, the technical feasibility of the model, and cost. For example, hemodynamic studies often require larger species for purely technical reasons. Nonhuman primate erectile mechanisms and sexual behavior may more closely model the human. However, cost and animal welfare considerations present major barriers to the widespread use of nonhuman primate models. Rodent models are the most commonly used, largely driven by practical concerns and the huge literature on rodent biology. An essential point is that a very rich literature of studies of erectile function in monkeys, dogs, cats, rabbits, rats, mice, and other species demonstrate that physiology and neural control of penile erection is highly conserved in mammals. Further, results from these animal studies have been remarkably successful in providing insight into human erectile physiology and pathophysiology, which is the true measure of all animal research models.

Models Used in the Study of Penile Erection

Electrical Stimulation of Peripheral Nerves

The first model for the study of penile erection, and still an important model used today, is the electrical stimulation of peripheral nerves in anesthetized animals and examination of resulting changes in the penis. Early experiments by Eckhard, Goltz, Gaskell, and Langley performed in either dogs, cats, or rabbits [2] showed that electrical stimulation of sacral nerves, anterior sacral roots, or the lumbosacral spinal cord (i.e., activation of parasympathetic pathways) elicited penile erection. Electrical activation of sympa-

thetic pathways was antierectile. Simultaneous stimulation of parasympathetic and somatic nerves increased the erectile response [3]. Further refinements of the method came with measurements of penile size by plethysmography in response to peripheral nerve stimulation and systemically injected drugs in rabbits [4].

This work has been extended by more extensive hemodynamic measurements [5–7]. These studies required the use of large animals, anesthetized dogs, and monkeys. Parasympathetic stimulation caused a transient arterial blood flow increase in the internal pudendal artery, followed by a sustained increase in intracavernous pressure (ICP). This increase in ICP was converted to suprasystolic ICP levels when combined with pudendal nerve stimulation.

Pressure Recording in the Corpus Cavernosum

Direct measurement of ICP provides the most reliable and quantitative response of the penis to peripheral and CNS neural activation. In addition, intracavernous injections of a variety of agents can be used to identify the cellular and molecular mechanisms of the erectile process. Measurement of ICP is typically performed by inserting a hypodermic needle into the body or the crus of the corpus cavernosum. The needle is connected to tubing filled with heparinized saline to prevent clotting. The tubing is attached to a calibrated strain gauge whose output is fed to computerized data acquisition systems. In the absence of striated muscle contraction, the maximal ICP is systolic blood pressure (BP). That is, systemic blood pressure is the driving force for ICP. Changes in BP may induce changes in ICP, and could be wrongly interpreted as changes in penile function. For greatest accuracy, systemic blood pressure (BP) is usually measured, and the changes in penile function are expressed as the ratio of ICP/BP. In addition to measuring maximal ICP, the duration and amplitude of increases in ICP during an erectile response, rate of increase or decrease in ICP during tumescence and detumescence, and area under the ICP curve,

are all measures used to quantify the aspects of erectile function [8]. For pharmacological studies, a common approach is to construct a curve of the peak ICP/BP ratio achieved at either different stimulation frequencies or intensities. A change of this curve indicates the effect of pharmacological agents on penile erections. Results from the studies of peripheral efferent and afferent nerve stimulation and the modulation of inter- or intracellular signaling pathways have been reviewed and provide clear demonstration of the utility of this model [9].

The majority of such studies have been performed in rats, largely for practical reasons, such as cost, maintenance and handling, and for the fact that the results have been shown to be clinically relevant. Another advantage of the rat is that vasodilatory parasympathetic input to the penis is conveyed by a single, easily identified nerve, the cavernous nerve, which facilitates electrical stimulation. These techniques can be adapted for use in mice, to allow the study of erectile function using molecular or gene-based techniques [10–12].

The search for the agent(s) responsible for penile vasodilation has been an extremely active area from the beginning of the study of erectile function. The models typically used have been electrical stimulation of penile efferents in anesthetized animals combined with systemic or intracavernous injection of drugs. Attempts were made to block stimulation-induced erection with antagonists and mimic it with agonists. Numerous candidates were investigated until nitric oxide (NO) was identified as the primary vasodilator messenger, using animal models [13–15]. This discovery was responsible for the introduction of phosphodiesterase type 5 (PDE5) inhibitors for the treatment of erectile dysfunction.

Vascular Smooth Muscle Cells In Vitro as a Model System in Erectile Research

Tissue culture of smooth muscle cells from the corpus cavernosum have been used to investigate a variety of cellular and molecular mechanisms relevant to erectile function. Cell culture offers

numerous advantages over in vivo studies, such as the ability to precisely manipulate the environment, single cell imaging, characterizing ion channel and gap junction function, and transfection of cells for molecular studies. But, it is important to recognize that removing the cells away from their in vivo environment may significantly alter their biology due to the loss of the three dimensional architecture, and influences from other cells types, such as endothelial cells, and the loss of neural innervation. Thus, interpretation of findings must reflect an understanding of the balance between the advantages and disadvantages of the methodology.

Tissue culture techniques using penile tissue have been used to characterize the role of gap junctions between smooth muscle cells [16–18], potassium channels [19, 20], second messenger signaling pathways [21–23], and the mechanism of action of a variety of vasoactive agents [24–27].

Reflex Erection Elicited by Peripheral Sensory Stimulation

An early report indicated that sensory nerve stimulation did not induce reflex erection in cats deeply anesthetized with barbiturates [28]. More recent studies made use of the recognition that spinal sexual reflexes are under a tonic inhibitory control from supraspinal sites. Thus, following acute spinal section, genital sensory stimulation is effective in eliciting penile erection in anesthetized rats [29–32]. Stimulation of the dorsal nerve of the penis in acutely spinalized, anesthetized rats reliably elicits increases in intracavernous pressure, which may reach systolic pressure, indicating a full penile vasodilation [31, 32]. In some cases, concomitant perineal muscle contractions are observed, leading to suprasystolic ICP and full rigid erections. This technique is useful for the study of spinal reflex mechanisms and pharmacology.

The tonic descending inhibition of sexual reflexes arises from supraspinal sites and projects to the lumbosacral reflex centers [33, 34]. The anatomic site responsible for the inhibition has been identified in the rostral pole of the

paragigantocellular reticular nucleus, bilaterally located in the oblongata [35]. This area directly projects to pudendal motoneurons and interneuronal areas of the lumbosacral cord. Transection of the spinal cord facilitates spinal erectile reflexes by removing this descending inhibition. Obviously, spinal transection precludes the examination of supraspinal mechanisms controlling sexual responses. Experimental design requires careful consideration of these factors.

Urethrogenital Reflex

Sexual reflexes can be elicited in anesthetized male and female rats [30]. In urethane anesthetized, acutely spinalized rats, complex sexual responses can be elicited by a variety of pelvic stimuli, including the stimulation of the dorsal nerve of the penis. It was shown that urethral distension is a quantitative and highly reproducible stimulus. Hence, this response has been referred to as the urethrogenital (UG) reflex. In male rats, the UG reflex consists of rhythmic contractions of the perineal muscles, rhythmic firing in the cavernous nerve, rigid penile erections, and ejaculation. While this reflex includes penile erection, this model is now viewed primarily as a technique for investigating the expulsive phase of ejaculation. The perineal muscles are activated simultaneously in a series of rhythmic contractions, which are similar to those seen in human climax [36, 37], and in rats during copulation [38].

Penile Erection in Conscious Animals

Ex Copula Erections

The *ex copula* model was a commonly used unanesthetized rat model of erection; however, it has fallen out of favor in recent years due to its limitations [39, 40]. The rat is lightly restrained in a supine position, and the penis is retracted from the sheath. Relatively predictable “spontaneous” penile erections are thus elicited. The

effects of drugs administered into the CNS and CNS lesions have been examined in this model. It has the advantage in that it does not involve social interaction with the female and it examines penile reactions directly. However, the rats must be trained before if they are to stop struggling during the testing, and invasive measurements of neural activity or hemodynamics are not easily performed. Furthermore, the stimuli eliciting these erectile responses are unclear.

Noncontact Erections

Noncontact erection (NCE) is a centrally generated erection model in conscious rats. Pigmented strains of male rats develop penile erections in response to the presence of estrous female even when physical contact is prevented [41]. Volatile odors from the estrous females have been shown to be the necessary and sufficient stimulus for this response [42]. Note that this response is mediated by the vomeronasal organ and the accessory olfactory system (pathways for the processing of pheromone stimuli), not the main olfactory system responsible for the sense of smell. This model is the first in which erections are generated by environmental sexual stimuli, without genital stimulation, possibly similar to psychogenic erections in the human. However, there is little evidence that pheromonal cues play any significant role in sexual arousal in humans. Thus, it is likely that NCEs in rats and psychogenic erections in humans are mediated by very different forebrain sensory mechanisms. Nonetheless, this is a model of a physiologically relevant, CNS-driven erection in unanesthetized animals, without the confounding complex social and sensory stimuli of copulatory behavior.

Erection Induced by Electrical and Chemical Stimulation of CNS Structures

A large number of studies have investigated the central control of penile erection using

precisely localized electrical or pharmacological stimulation, in both anesthetized and unanesthetized rats. Conversely, electrical or chemical lesions of specific brain nuclei have also been used. Typically, these studies involve the electrolytic destruction of brain sites under anesthesia. After several days of recovery, the animals are tested in behavioral situations. The vast majority of our current knowledge of CNS mechanisms are derived from a combination of these methods.

Typical procedures for these studies use anesthetized rats. However, it is possible to use this technique in awake, behaving animals. Under anesthesia, the animal's head is mounted in a stereotaxic frame that provides a coordinate system to locate specific brain areas. Small holes are drilled into the skull for the placement of electrodes for electrical stimulation, micropipettes, or hypodermic tubing for the administration of drugs. Physiological recordings of ICP and blood pressure are taken during the stimulation. In addition, recordings of peripheral nerve, skeletal muscle activation, or other physiological responses may be performed. Following the end of the experiment, the brain is removed and sectioned for histological verification of stimulation sites. For the administration of precise quantities of drugs, experimenters have used microliter syringes. These can be mounted directly in the stereotaxic microdrive and inserted into the brain, or be connected by tubing to an implanted hypodermic needle. The latter method allows the use of precise syringe pumps for continuous infusion. Another method is to use micropipettes filled with the drug solution. The drug is injected into the brain by attaching tubing to the end of the micropipette and applying precise pulses of pressurized nitrogen. Visualization of the fluid level in the micropipette with a calibrated microscope allows precise injection volumes in the low nanoliter range [43]. Similar methods can be used in awake, behaving animals. The hypodermic needle or micropipette is inserted under anesthesia as described. It is then glued in place to the skull with dental acrylic. After a suitable recovery period, tubing is attached to the needle or micropipette and connected to a syringe or pressure device outside the cage. In this way, the effects of

drugs on behavior can be examined. Electrodes for electrical stimulation can be similarly implanted for later use in conscious animals.

Implantation of telemetric pressure recording devices can be combined with these techniques to allow precise measurement of ICP to electrical or pharmacological stimulation in conscious and freely moving conditions [8, 44]. Telemetric methods can also be used in copulatory studies, *ex copula* studies, and to study sleep-related erections [45].

A variation of the microinjection technique is intrathecal delivery. A fine catheter is threaded down the spinal column until the tip reaches the target spinal segment. The experiment can then be performed immediately, or the catheter can be secured by suture or cement and the animal allowed to recover from anesthesia and surgery for use in awake, behaving experiments. Many previous studies have suggested the importance of spinal control on modulating penile erection and sexual behaviors. For example, studies involving the intrathecal administration of oxytocinergic agents have identified a spinal pro-erectile role for this neurotransmitter [46, 47]. Such studies demonstrate that intrathecal administration is a useful tool for the investigation of spinal control erectile function.

Models of Erectile Dysfunction

A wide variety of pathophysiological models of ED have been proposed aiming to mimic the numerous pathological conditions responsible for ED in humans. The most common of these models are hypertensive rats, atherosclerotic rabbits, diabetic rats and rabbits, aged rats, castrated rats, and cavernous nerve-injured rats. Our understanding about the molecular mechanisms involved in the physiology of penile erection has advanced significantly in the last decade as a direct result of the use of animal models to study aberrant erectile mechanisms in various pathological situations. The purpose of this subchapter is to evaluate experimental disease animal models used to study ED and further our understanding

of species choice and end points associated with each animal model. These models have undoubtedly been useful, but caution must be observed on how closely they mimic human conditions.

Hypertension

Erectile dysfunction and hypertension are widely acknowledged to be associated, but there have been relatively few experimental investigations into the mechanisms. The animal model of hypertension most widely used to assess erectile function is the spontaneously hypertensive rat (SHR) [48]. A small number of investigations have also assessed the impact of secondary hypertension due to DOCA-salt treatment, aortoiliac balloon injury, experimental passive cigarette smoke inhalation, and increased alcohol consumption. In normotensive rats, these manipulations induced both hypertension and erectile dysfunction [49–52]. However, there remains considerable work remaining, linking the hypertension with specific pathologic derangements of the erectile microanatomy, cellular physiology, and molecular biology.

Aging

The development of ED with aging was first identified in copulatory studies [53, 54]. Subsequent studies using other models of erectile function discussed above, indicates that the ED in aged rats is due to the loss of smooth muscle and endothelium, fibrosis and decreases in nitric oxide signaling. These findings are congruent with studies in aging men, indicating that the aged rat model may be a valuable tool in analyzing this particular form of ED.

Diabetes

Of all the models of ED, the streptozotocin-induced diabetic rat is one of the most widely

employed. This model shows a robust ED when compared with age-matched controls [55]. An important finding is that nitric oxide signaling is decreased in diabetes, and after prolonged diabetes, this decrease of nitric oxide is irreversible, due to the loss of nitric oxide neurons as a result of oxidative stress and advanced glycosylation end products [56–58].

Other studies of diabetes-related ED use the genetically diabetic BB/WOR rat, which is insulin-dependent and ketotic prone form of type 1 diabetes. The BB/WOR rat exhibits severe neuropathy in somatic, sympathetic, and parasympathetic nerves without the compounding angiopathy associated with human diabetes [59]. The copulatory behavioral testing and the study of sexual reflexes confirmed the severe neuropathy associated with ED in the BB/WOR rat. Additionally, these diabetic animals exhibit considerable decreases in penile reflexes, indicative of peripheral neuropathy, but did not show any impairment of the cavernosal nerve-mediated erectile response at 3–5 months of diabetes [60]. Therefore, this animal model may be useful to distinguish between the role of neuropathy and vasculopathy on erectile function in diabetes.

A major research need is the development of robust and satisfactory models of Type 2 diabetes, as this is the most prevalent form of human disease and increasing with the ongoing obesity epidemic.

Hypercholesterolemia

Hypercholesterolemia and subsequent atherosclerosis are well-recognized risk factors for the development of vasculogenic ED [61]. Rarely is hypercholesterolemia-associated ED in men seen in isolation, without other risk factors such as obesity, smoking, age, and diabetes. Rabbits are the most used species in hypercholesterolemia. A high cholesterol/high triglyceride diet, sometimes combined with balloon injury of the aortoiliac arteries, is used to induce atherosclerotic plaques in the arterial supply to the penis. This results in the impairment of endothelium-dependent cavernosal

smooth muscle relaxation and agonist-induced penile erection with papaverine [50, 62, 63]. These defects could not be explained solely by the occlusion of blood flow, but were also accompanied by defects in smooth muscle signaling.

Cavernous Nerve Injury

Due to the high prevalence of ED following pelvic surgery as a result of injury to the neurovascular bundle, there has been a great interest in models of cavernous injury. The goal is to identify the mechanisms leading to the ED (e.g., penile apoptosis and fibrosis), as well as identifying methods of preventing these pathological changes or remediating them. The most widely used animal model of cavernous nerve injury (CNI) is the cavernous nerve-injured rat model. Injury can be induced by crush, cut or freezing rat models. Through a lower abdominal midline incision, the posterolateral area of the prostate is exposed on both sides and the major pelvic ganglions and cavernous nerves are identified. The cavernous nerves, unilaterally or bilaterally, are either sharply divided with knives to remove a segment of nerve, cauterized, or frozen using a thermocouple [64–68]. ED-observed postradical prostatectomy is most likely attributed to changes in the endothelium and smooth muscle cells from a loss in neural integrity. The absence of neural input to the penis after CNI in the rat results in cavernosal smooth muscle apoptosis, alterations in the endothelium and smooth muscle function, decrease in neuronal NOS nerve fibers in the penis, pelvic ganglia, and fibrosis. The CNI rat model has led to a more thorough understanding of the pathophysiological sequences involved in the development of postradical prostatectomy ED.

Hypogonadism

Androgens are necessary for the maintenance of the mammalian erectile response. In most animals, androgens are essential in maintaining sexual

behavior. However, evidence shows that androgens are also necessary to maintain the erectile apparatus of the penis. Effects of castration on sexual function are evaluated by the observation of copulatory behaviors, penile reflex, and erectile response electrical stimulation of the cavernous nerve. Particularly in the rat model, androgens act centrally to support copulatory behavior and peripherally to maintain constitutive NOS activity and support the veno-occlusive mechanisms. Thus, the erectile response in the rat is androgen dependent [69–74]. Castrated rats have been used as models to study veno-occlusive dysfunction because cavernosal sinusoidal smooth muscle fails to fully relax and blood flow continues during erection in castrated rats, suggesting the failure of veno-occlusion [70, 75]. Despite these reports of the importance of androgens in the erectile response of laboratory animals, the role of androgens in the maintenance of the human erectile response remains controversial. Even in severely hypogonadal men, the erectile response is not always lost. Therefore, the hypogonadal animal model of ED may be best utilized as a model of veno-occlusive ED.

Conclusions

A large number of models exist for the study of male sexual function. Each model has both strengths and limitations. Care must always be taken before extrapolating too quickly from experimental data to a seemingly parallel clinical situation. Practical considerations have led to a great reliance on rodent models. These have the advantage of cost, ease of handling, and a large foundation of biological knowledge. There are rodent models for examining every aspect of penile erection from higher neural control down to molecular events within the erectile tissue. The disadvantage of rodent models is that they do not always accurately reflect human physiology and pathophysiology, although they seem to share many basic mechanisms. Therefore, the validation of any given model must be assessed for a particular application. The utility of these

models is amply demonstrated by the great expansion of our understanding of male sexual physiology in recent years. Future challenges will be to develop more models of pathophysiological conditions.

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Chapter 2

Normal Erectile Physiology

Gregory B. Auffenberg, Brian T. Helfand, and Kevin T. McVary

Abstract The human penis is composed of the paired dorsal corpora cavernosa and the ventral corpus spongiosum each of which is encased within a fibrous sheath, the tunica albuginea, and then all of which are enclosed within Buck's fascia, Colles' fascia, and the skin. The spongiosum contains the urethra and is contiguous with the glans distally. The arterial supply to the penis is from the four terminal branches of the paired penile arteries, which are themselves branches of the internal pudendal arteries. The external iliac, obturator, vesical, and femoral arteries provide accessory arterial supply to the penile artery in some cases. Venous outflow originates from post-cavernous venules that coalesce to form emissary veins. These veins empty into the cavernous vein, the deep dorsal vein, and the superficial dorsal vein depending on their origin within the penis. Efferent innervation is from parasympathetic, sympathetic, and somatic sources. Somatosensory afferents course from the penis to central sites.

The maintenance of penile flaccidity and the erectile response are controlled via intercommunicating supraspinal and spinal reflex pathways. During the flaccid state, antierectional neural input, primarily via sympathetic efferents, acts to limit blood flow to the penis to a quantity sufficient to meet physiologic needs but insufficient for erection. Following either physical or psychological sexual stimulation proerectional neural signals are

sent to the penis primarily via parasympathetic tracts. This input initiates the erectile response via neurotransmitter release onto postsynaptic smooth muscle cells within the corporal bodies. Nitric Oxide (NO) is the main proerectional neurotransmitter. The resultant molecular cascade leads to a decrease in intracellular Ca^{2+} and arteriolar smooth muscle relaxation. This relaxation allows for increased blood flow and subsequent corporal engorgement with increasing penile rigidity. As the corpora become engorged, the emissary veins are compressed by within the tunica albuginea limiting venous outflow. The increased arterial inflow and limited venous outflow increases intracorporal pressure and leads to erection. As proerectional input ceases, the secondary molecular messenger cGMP is hydrolyzed allowing for a rise intracellular Ca^{2+} , subsequent smooth muscle contraction, decreased penile blood flow and a return to flaccid state physiology.

Keywords Corpora • Glans • Venous drainage • Peripheral innervations • Tumescence and erection • Detumescence • Spinal and supraspinal control • Proerectional transmitters

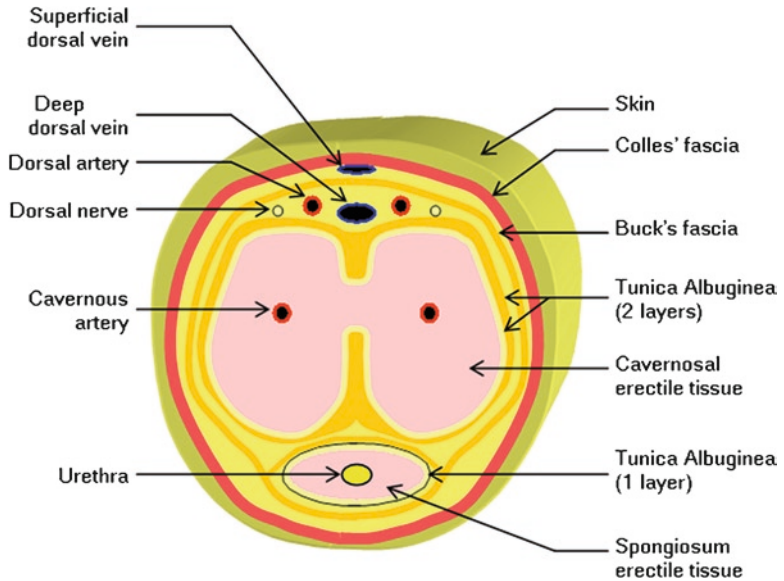
Anatomical Review

Gross Structure

The human penis is composed of the paired dorsal corpora cavernosa and the ventrally placed corpus spongiosum. The corpus spongiosum contains the

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Fig. 2.1 Penile cross-section, penile cross-section showing paired dorsal corpora cavernosa and the ventral corpus spongiosum. Note the double-layered tunica albuginea surrounding the cavernosa (inner circular and outer longitudinal) and the incomplete septum allowing communication of the two cavernosa. Note urethra coursing within the corpus spongiosum and the single-layered tunica (1 circular layer)



urethra and is contiguous with the glans penis distally. Each corpus is surrounded by a fibrous sheath, the tunica albuginea. Between the two corpora cavernosa is an incomplete perforated septum allowing them to function in unison [1]. Surrounding all three corpora is an additional fibrous layer, Buck's fascia. Superficial to Buck's fascia is Colles' fascia extending from the base of the glans to the urogenital diaphragm where it is contiguous with Scarpa's fascia. Superficial to Colles' fascia is the skin (see Fig. 2.1). Proximally, the corpora cavernosa form the penile crura, which are anchored to the pubic rami and are covered by the ischiocavernosus muscles [1]. The proximal corpus spongiosum forms the penile bulb, which is enveloped in the bulbospongiosus muscle. The suspensory ligament of the penis arises from the linea alba and pubic symphysis and inserts on the tunica albuginea to support the pendulous portion of the penis [2].

Corpora

The corpora cavernosa are two spongy cylinders comprised primarily of arterial sinusoids and smooth muscle surrounded by the tunica albuginea. The cavernosal tunica albuginea is

2–3 mm thick in the flaccid state and is composed mostly of collagen fibers with a smaller portion being elastic fibers [3]. The cavernosal tunica has an inner circular layer and an outer longitudinal layer of fibers [1].

The histologic appearance of corpus spongiosum is similar to the corpora cavernosa and it contains larger sinusoids. Additionally, the tunica albuginea surrounding this corpus is thinner, has only one circular fiber layer, and contains more elastic fibers [3].

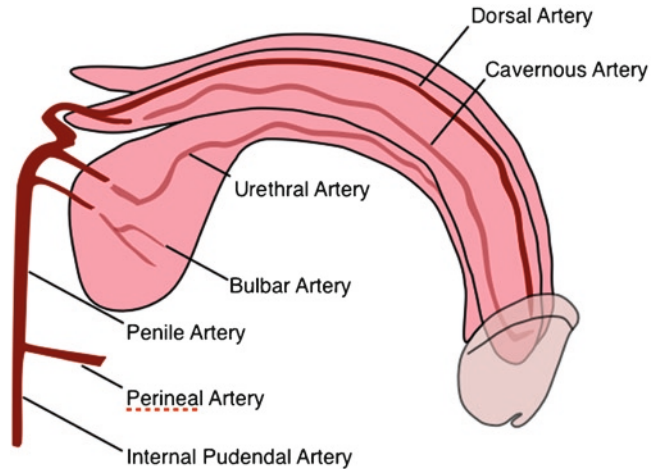
Glans

The glans forms the distal portion of the penis. It is contiguous with the corpus spongiosum. It is covered with very thin, firmly adherent skin. Additionally, the tunica on the glans [1] albuginea is absent.

Arterial Supply

Classically, the internal pudendal artery, a branch of the internal iliac, serves as the main blood supply to the penis [1]. After giving off the perineal artery, it becomes the penile artery. More

Fig. 2.2 Arterial supply to the penis. The internal pudendal artery forms the penile artery after giving off the perineal artery. The penile artery has four terminal branches: the bulbar, urethral, cavernous, and dorsal artery. Penile blood supply is bilaterally symmetric; only one side of supply is portrayed in this diagram



recently, accessory pudendal arteries, arising from the external iliac, obturator, vesical, and femoral arteries, have been shown to contribute to the blood supply of the penile artery in many men [4]. The penile artery has four paired terminal branches: the cavernous (deep penile), dorsal, urethral, and bulbar arteries [1, 5] (see Fig. 2.2). Each cavernous artery pierces the ipsilateral cavernosal tunica albuginea at the hilum of the penis and enters the penile crura. It runs the length of the corpora cavernosa giving off many tortuous branches, the helicine arteries. These helicine arteries open directly into the sinusoids of the erectile tissue. Each dorsal artery lies beneath Buck's fascia and courses distally between the laterally placed paired dorsal nerves and the deep dorsal vein. They are responsible for the engorgement of the glans during erection. The urethral arteries run through the corpus spongiosum lateral to the urethra and supply blood to the corpus spongiosum, the urethra, and the glans. The bulbar arteries enter the bulb of the penis supplying the proximal urethra and Cowper's gland.

Veins

Within the three corpora tiny post cavernous venules coalesce to form emissary veins that go

on to pierce the tunica albuginea [6]. In the proximal penis, the emissary veins drain into the cavernous vein that goes on to join the periurethral veins of the urethral bulb to form the internal pudendal vein. The emissary veins from the distal and middle penis combine to form circumflex veins that then drain into the deep dorsal vein of the penis. The deep dorsal vein runs the length of the dorsal penis and drains into the periprostatic plexus. The venous drainage of the skin and subcutaneous penile tissue is via many superficial veins that go on to form the superficial dorsal vein. This drains into the external pudendal vein.

Peripheral Innervation

The penis receives innervation from parasympathetic, sympathetic, and somatic efferents (see Fig. 2.3). The parasympathetic penile innervation comprises the major excitatory input to the penis responsible for vasodilation of the penile vasculature and erection. Preganglionic fibers originate in the sacral parasympathetic nucleus [4, 7]. These fibers travel to the pelvic plexus via the pelvic nerve, which also carries sympathetics [7, 8]. After synapsing in the pelvic plexus, postganglionic parasympathetic fibers emerge as a part of the cavernous nerve [9]. The cavernous nerve travels along the posterolateral aspect of

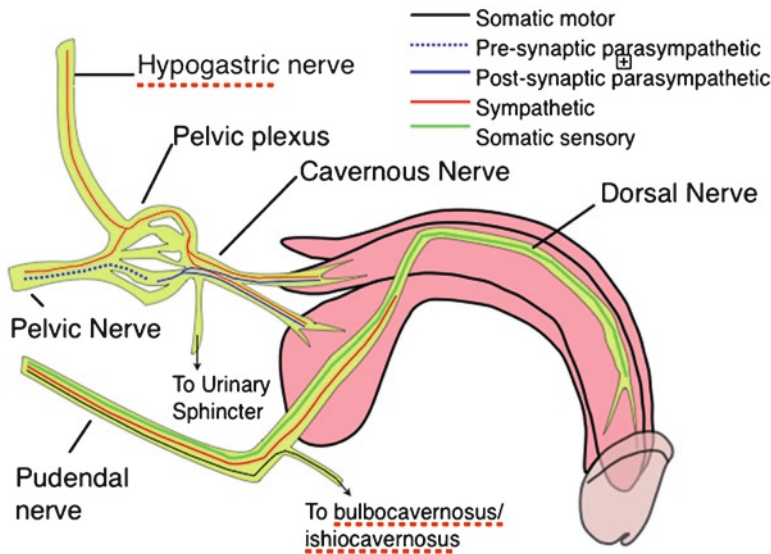


Fig. 2.3 Innervation of the penis. Presynaptic parasympathetic fibers travel via pelvic nerve to synapse in pelvic plexus, postsynaptic fibers emerge within cavernous nerve and travel to corporal bodies as well as urinary sphincter. Sympathetic fibers travel via hypogastric and pelvic nerves to join cavernous nerve as it emerges from

the pelvic plexus. Sympathetic fibers also travel to penis via pudendal nerve. Somatic motor fibers to the bulbocavernosus and ischiocavernosus travel via pudendal nerve. Somatic sensory afferent signals travel from the penis via the dorsal nerve which goes on to join the pudendal nerve

the prostate within the pelvic fascia that fuses with the prostatic capsule [10]. The cavernous nerves then exit the pelvis as two groups of fibers [10]. The first group travels to the urethral sphincter to modify urinary function. The second group travels to the penis. This group branches further as it reaches the penis with a portion of the fibers heading for the corpus spongiosum and the remaining fibers entering the penile crura along with the deep penile artery and cavernous veins [10].

Sympathetic pathways begin in the intermediolateral cell column and intercalated nucleus at spinal levels T9-L2 [8, 11]. Preganglionic fibers emerge and travel to synapse on sacral and caudal lumbar ganglion cells within the sympathetic chain [12]. Postganglionic sympathetics to the penis exit the sympathetic chain via three routes. The first carries sympathetic fibers via the hypogastric nerve to the pelvic plexus where they join the cavernous nerve for the remaining distance to the penis. In the second path, postsynaptic sympathetic outflow from paravertebral ganglia

joins the pelvic nerve, which travels to the pelvic plexus to join the cavernous nerve to the penis. Finally, a portion of the sympathetic outflow is carried on a direct route to the penis from the sympathetic chain ganglia via the pudendal nerve [9]. The role of these sympathetic neurons appears to be primarily one of antierectile function. They stimulate vasoconstriction and appear to have spontaneous activity that produces an antierectile tone [9, 13]. However, total eradication of sympathetic input leads to diminished erectile function demonstrating that the sympathetic input is not entirely antierectile [9, 11, 14]. Opinions differ on the reason for this effect, however, some authors have suggested that due to the vital role of sympathetic input for arterial tone and regulation of blood distribution, a sympathetic lesion may disrupt routing of blood to the penis [14].

Somatic motor efferents arise from the ventral sacral spinal cord (Onuf's nucleus). They travel via the pudendal nerve to innervate the bulbospongiosus and ischiocavernosus muscles [9].

Neural input to these muscles in the presence of an erect penis leads to increased penile rigidity [15]. Additionally, contraction of these muscles in a rhythmic manner assists in the expulsion of ejaculate [9].

Somatosensory input from the penis arises primarily at free nerve endings and corpuscular receptors. The input is carried via C- and A-delta fibers [16]. These fibers coalesce to form the dorsal nerve of the penis, which extends into the pelvis to join the pudendal nerve. The pudendal nerve carries sensory signals to the spinal cord via spinal roots S2-S4 and terminates in the gray matter of the lumbosacral cord [17].

Hemodynamics of Erection

Flaccid State

The flaccid state of the penis is characterized by blood flow sufficient to meet nutritional and other physiologic needs, but insufficient for penile erection. During this state, sustained partial contraction of smooth muscle cells in the walls of arteries, arterioles, and in the corporal trabeculae is essential for the limitation of blood flow. The molecular mechanisms leading to this tonic smooth muscle contraction are discussed below.

Tumescence and Erection

With sexual stimulation and subsequent release of proerectile mediators onto corporal smooth muscle the erectile response is initiated. Within the corpora cavernosa there is dilation of arteries and arterioles and thus increased inflowing blood. The trabecular smooth muscle additionally relaxes allowing corporal sinusoids to expand as they become engorged with blood. This cavernosal expansion begins to compress the subtunical venules decreasing venous outflow. With further engorgement, the tunica is stretched occluding the

emissary veins between the two tunical layers leading to minimal venous outflow [18]. This leads to an increase in intracavernosal pressure to approximately 100 mmHg that raises the penis to the fully erect position [18].

During heightened sexual activity, the penis enters the rigid-erection phase. The ischiocavernosus muscles contract, as a result of the bulbocavernosus reflex, compressing the base of the corpora cavernosa leading to temporary cessation of inflow and outflow of blood and increasing intracavernous pressures up to several hundred mmHg [18].

The corpus spongiosum and glans behave somewhat differently in tumescence and erection. Arterial flow increases in these locations just as in the cavernosa. Due to differences in the tunica albuginea, thin in the spongiosum and absent in the glans, venous occlusion is less in these locations. This leads to pressures in the spongiosum only one third to one half of that of the cavernosa [19]. The glans and spongiosum thus act essentially as arteriovenous shunts during erection. Similar to the corpora cavernosa, during the rigid erection phase contraction of the ischiocavernosus and bulbocavernosus muscles compresses out-flowing veins leading to further pressure increase in the spongiosum and glans. The deep dorsal vein is compressed between the engorged cavernosa and Buck's fascia contributing to rigidity of the glans [18].

Detumescence

With cessation of sexual stimulus and subsequent decrease in erection inducing neural activity, the erectile response ends. Antierectile neural input leads to vasoconstriction of penile arteries and contraction of the trabecular smooth muscle resulting in reduced arterial inflow and collapse of the trabeculae [20]. With decreased arterial inflow and subsequent corporal decompression, occlusion of venous drainage subsides allowing efflux of corporal blood and return to flaccid state physiology [21].

Local Mechanisms of Erection

As previously mentioned, partial contraction of trabecular, arterial, and arteriolar smooth muscle and subsequent limitation of blood flow is essential for maintaining penile flaccidity. Sympathetic adrenergic signaling and the activity of substances derived from vascular endothelium (endothelins and prostaglandin $F_{2\alpha}$) appear to play a crucial role in this process [22, 23]. These substances activate G-protein coupled receptors that initiate a cascade leading to the increased production of inositol triphosphate and diacylglycerol. In turn, these substances lead to an increase in intracellular $[Ca^{2+}]$ via releasing intracellular stores or opening cell membrane channels to allow influx of Ca^{2+} [19, 23, 24]. The resultant elevated intracellular free Ca^{2+} binds to calmodulin changing its conformation to expose sites that bind and activate myosin light-chain kinase [19]. The now activated myosin light-chain kinase phosphorylates myosin light chains, allowing them to initiate smooth muscle contraction [25].

This rise in intracellular Ca^{2+} is only a transient event, and further mechanisms, most notably calcium sensitization, appear to play a significant role in maintaining contraction of smooth muscle during the flaccid state. The RhoA, Rho-kinase pathway is important to calcium sensitization [26, 27]. G-proteins expressed in penile smooth muscle activate RhoA which activates Rho-kinase. Rho-kinase, in-turn, phosphorylates the regulatory subunit of smooth muscle myosin phosphatase, inhibiting its activity. This inhibition prevents dephosphorylation of smooth muscle myofilaments allowing them to maintain their contractile tone [28, 29]. The sum total of this pathway is the maintenance of smooth muscle contraction during the flaccid state without a significant change in intracellular $[Ca^{2+}]$ [29]. RhoA is expressed at a 17-fold higher concentration in rabbit cavernosal smooth muscle when compared to other vascular smooth muscle sites supporting its important role in erectile physiology [30].

During the erectile response, a drop in intracellular Ca^{2+} is important for the relaxation of vascular and corporal smooth muscle. The release

of nitric oxide (NO) from nonadrenergic, noncholinergic nerve terminals and the endothelium is a major mediator of this response [31, 32]. NO works in the smooth muscle cell to activate a soluble guanylyl cyclase. This enzyme leads to an increase in the production of the second messenger cyclic guanosine monophosphate (cGMP). Increased cGMP concentration activates protein kinase G (PKG). The activated PKG phosphorylates multiple intracellular proteins to cause: sequestration of intracellular Ca^{2+} in the endoplasmic reticulum, inhibition of cell membrane calcium influx channels, and opening of potassium channels with resultant myocyte hyperpolarization [18]. The resultant decrease in intracellular calcium concentration and hyperpolarization leads to smooth muscle relaxation via what is essentially a reversal of the process for smooth muscle contraction described above. In brief, intracellular calcium levels fall, deactivating the calcium-calmodulin complex. This allows myosin light-chain kinase to become inactive facilitating resultant dephosphorylation of the myosin light chains deeming them unable to initiate muscle contraction (see Fig. 2.4).

During the return to flaccid state physiology phosphodiesterase type 5 (PDE-5) hydrolyzes cGMP to the inactive guanosine monophosphate. As cGMP concentration falls intracellular $[Ca^{2+}]$ rises and the vascular and corporal smooth muscle cells again contract [31].

Spinal Control of Erection

Erection can originate from both tactile stimulation of the penis (reflexive erection) and supraspinal stimuli (psychogenic erection). The sacral spinal cord appears to integrate and coordinate the excitatory and inhibitory neural inputs from both peripheral and supraspinal sources. Complete destruction of the sacral spinal cord or its outflow eliminates erectile function [33, 34]. However, patients with suprasacral spinal cord transection have shown erectile function to be at least partially maintained in response to tactile stimulation of the penis [8, 33–35]. This has led to

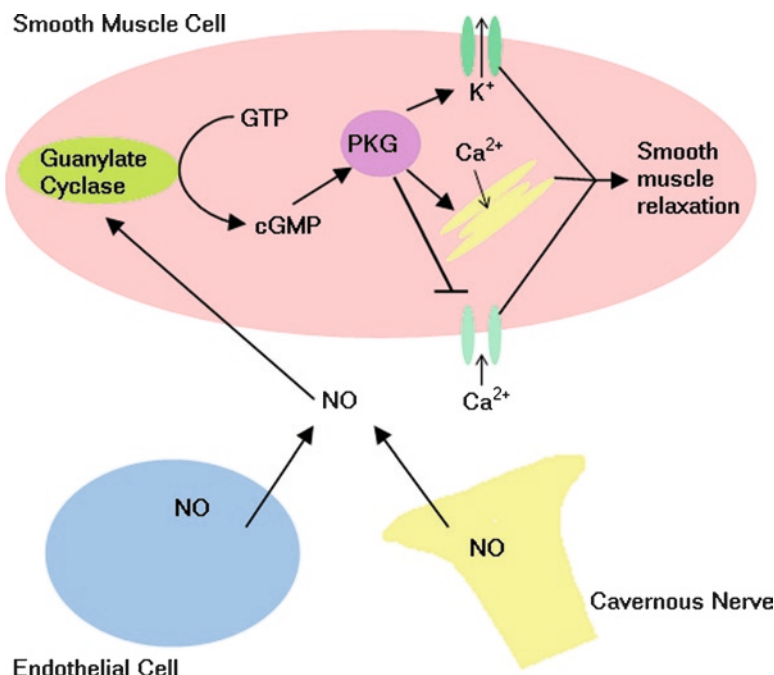


Fig. 2.4 Smooth muscle relaxation – Nitric oxide (NO) released from endothelium and cavernous nerve terminals stimulate guanylate cyclase within smooth muscle cell leading to the production of cyclic guanosine monophosphate (cGMP) from guanosine triphosphate (GTP). cGMP activates protein kinases (PKG)

which phosphorylate proteins leading to potassium efflux, calcium sequestration in the endoplasmic reticulum, and blockage of calcium membrane channels. Calcium sequestration and hyperpolarization lead to smooth muscle cell relaxation via inactivation of myosin contractile units

postulation that sacral centers are essential for erection regardless of origin (i.e., reflexive or psychogenic) [12]. The sacral spinal reflex, which can function in the absence of suprasacral signals, coordinates sensory input from the dorsal nerve of the penis and proerectile output via sacral parasympathetics facilitating erection in response to direct penile stimulation. Additionally, sacral centers are vital to the integration of psychogenic erectile stimuli from supraspinal origins and the resultant erectile response, as evidenced by the absence of psychogenic erection in patients with sacral destruction.

Supraspinal Control of Erection

Supraspinal control of erection is poorly understood with almost all evidence being from

experimental animal models. Erections in response to imaginative, visual, tactile, and olfactory stimuli are thought to originate from supraspinal centers. Hypothalamic and limbic pathways have been shown to play a key role [9].

Paraventricular Nucleus

The hypothalamic paraventricular nucleus (PVN) contains premotor neurons that project from the parvocellular layer directly into the spinal cord [36–38]. These neurons have been shown to contain a variety of neurotransmitters: oxytocin, vasopressin, enkephalins, and dopamine [39, 40]. In rat models injection of a variety of neuromediators (oxytocin, glutamate, nitric oxide, dopamine agonists) into the PVN has been shown to elicit penile erection [39, 40]. Additionally, in both rats and monkeys, stimulation of the PVN

elicits erection [41]. Lesion of the parvocellular layer of the PVN causes longer latencies and fewer noncontact erections in rats [42]. Parvocellular PVN neurons have been shown to respond to stimulation of the dorsal nerve of the penis in rats, suggesting that the PVN may be a supraspinal reflex center for erections [43]. The PVN also receives input from the medial preoptic area (MPOA) suggesting that the PVN serves to integrate MPOA input before sending it downstream via autonomic pathways selectively activated within the PVN [9, 44].

Medial Preoptic Area

The MPOA of the hypothalamus is key to sexual behavior [45, 46]. In rats and monkeys, MPOA stimulation elicits erection [41, 47]. In monkeys, increases in MPOA neuronal activity have been recorded during erection [48]. Interestingly, MPOA lesions do not affect reflexive or noncontact erections [49, 50]. All of this has led to debate as to the role of the MPOA in erectile function. The emerging theory is that the MPOA likely serves as an integration center of hormonal and sensory inputs for sexual behavior and redistributes these signals to the hypothalamic and brainstem structures thought to be more directly linked to erectile control, such as the PVN [17, 44, 51].

Other Supraspinal Centers

Many other supraspinal areas have been shown in animal studies to be related to erectile function. In monkeys, isolated stimulation of the medial dorsal nucleus of the thalamus, ventral tegmental area, precallosal cingulate gyrus, and subcallosal and caudal gyrus led to erections [41]. Hippocampal stimulation in anesthetized rats increased intracavernous pressures as did desynchronization of the somatosensory cortex following cocaine administration [52, 53]. A center for descending the inhibition of spinal sexual reflexes has been localized

to a group of neurons in the paragigantocellular reticular nucleus of the ventral medulla [54]. The exact role each supraspinal area plays in mediating erection is currently unclear. However, it is apparent that there are extensive interconnections between many supraspinal centers that contribute to descending pathways and exert powerful control, both inhibitory and excitatory, on the spinal responses driving erection [51].

Central Neurotransmission

Oxytocin

Proerectile projections from the supraoptic area of the hypothalamus and the PVN travel to the spinal centers for erection and oxytocin has been shown to be a key neurotransmitter in these neurons [1, 55, 56]. In lab animals, intracerebroventricular or intrathecal injection of oxytocin antagonists blocks the induction of erection that is seen with intrathecal oxytocin injection. Additionally, antagonist injection into the lateral ventricles leads to a dose dependant reduction in noncontact erections [57]. This has led to the belief that oxytocin plays a role in facilitating nonreflexive erections.

Dopamine

Dopaminergic neurons project to the MPOA and PVN [58] and also have been discovered to travel from the caudal hypothalamus to the lumbosacral spinal cord [59]. Dopamine is thought to participate in central regulation of the autonomic and somatic penile reflexes. The dopamine receptor agonist, apomorphine, induces penile erection in rats when administered systemically [60]. Additionally, apomorphine injection into the MPOA facilitated erections while dopaminergic antagonist injection into the MPOA decreased penile reflexes [60–62]. In the PVN, dopaminergic neurons appear to stimulate oxytocinergic

neurons, which then more directly account for the erectile response. This is supported by the prevention of apomorphine-induced erections in the presence of oxytocin receptor antagonists [63].

Serotonin

In experimental animal models, bulbospinal neurons containing serotonin (5-HT) project to the lumbar spinal cord [22]. Serotonergic fibers have been demonstrated in close proximity to retrogradely labeled sacral preganglionic neurons [64]. One study showed 5-HT in general had an inhibitory effect on male sexual behavior [65]. However, there have been conflicting reports with another study showing that the stimulation of 5-HT_{2c} receptors mediated the erectile response [66]. Thus, the full function of 5-HT in erectile function has not been fully elucidated. It appears to serve various functions likely acting as a major modulator of the central control of erection [22].

Nitric Oxide

NO is emerging as an essential neurotransmitter within the CNS for erectile response. NO appears to act in several regions of the brain, including the MPOA and PVN [67–70]. Injection of NO-synthase (NOS) inhibitors into the PVN prevents penile erection induced by dopamine agonists and oxytocin [71]. NO production increased in the PVN of rats during noncontact erections, confirming the role of NO production during erection [72].

ACTH and α -MSH

Adrenocorticotrophic hormone (ACTH) and its related peptide α (alpha)-melanocyte stimulating hormone (α -MSH) have been shown to elicit erectile responses in addition to increased

grooming, stretching, and yawning behaviors when given intracerebroventricularly to lab animals [73]. This proerectile effect appears to be due to the stimulation of melanocortin-3 (MC₃) receptors which are prevalent in the hypothalamus and limbic system [74]. The role of these peptides in erectile response is not entirely known, but they appear to induce erection by acting at sites distinct from those in the PVN stimulated by dopamine and oxytocin [75]. Additionally, Melanotan II, an α -MSH synthetic analog, has had proerectile effects in humans with psychogenic impotence [76].

Other Neurotransmitters

Excitatory amino acids, such as l-glutamate, N-methyl-d-aspartate (NMDA), amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA), and trans-1-amino-1,3-cyclo-pentadecarboxylic acid (ACPD) have been shown to have proerectile effects when injected into the MPOA or PVN of lab animals [77–79]. Gamma-amino butyric acid (GABA) appears to function as an inhibitor in the reflex pathways for penile erection [80]. Stimulation of opioid μ receptors appears to centrally prevent penile erection and impair copulation likely through the prevention of the increased NO production in the PVN during sexual activity [81].

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Chapter 3

Psychological Aspects of Erectile Dysfunction

Richard A. Carroll

Abstract Because the brain is intimately involved in the control of erections, a wide variety of psychological factors impact erectile response and may lead to erectile dysfunction (ED). This chapter reviews the assessment of psychological factors in ED, the immediate and underlying psychological conditions involved, and the development of ED over time. Outcome research on psychological treatments for ED is also reviewed. The goal of the chapter is to help health care providers to conduct a comprehensive evaluation of ED that is sensitive to psychological factors.

Keywords Sexual dysfunction • Medical intervention • Psychological intervention • Couple therapy • Cognitive interference • Reflexogenic input • Psychogenic input

Introduction

A comprehensive understanding of erectile dysfunction (ED) must incorporate both the physical and the psychological aspects of erectile response. An erection is best characterized as a psychophysiological phenomenon that depends on a complex interplay of biological and psychological factors.

Impairment in any of these aspects may lead to erectile dysfunction. The focus of this chapter is on the assessment of psychological factors that contribute to erection difficulties. The evidence regarding the outcome of psychological treatments and the integration of medical and psychological treatments are also reviewed.

The definition of psychological factors to be used here encompasses a variety of mental aspects of sexuality. First are the behavioral aspects, which primarily involve who does what to whom in the sexual encounter. Second are the emotional aspects of the sexual response, that is, feelings during sex, as well as the emotional needs associated with sex. Third are the cognitive aspects of sexual response, which include knowledge, beliefs, and attitudes about sexuality. Fourth are the interpersonal aspects, i.e., the couple's interaction and the quality of the relationship, both sexual and emotional. Fifth are the cultural aspects of sexuality, which entail the expectations and norms that shape sexual behavior. It is also important to note that, while most of these aspects of sexuality are either observable or may be described by the patient, much of what is referred to as psychological is either unconscious or inaccessible to the individual himself.

The Brain–Penis Connection

Understanding the psychological aspects of ED requires understanding the connection between the brain and the penis. There are two basic inputs leading to sexual arousal and, therefore, erections.

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One is physiological and results from direct stimulation of the penis. This reflexogenic input is centered in the sacral regions of the spinal cord and is primarily under parasympathetic nervous system control. The other is psychological and results from mental experiences in the brain which are transmitted to the penis. This psychogenic input is mediated in the cerebral cortex.

The brain is the source of both excitatory and inhibitory influences on erections [1]. The inhibitory pathway is under serotonergic control, while the excitatory pathway is under the influence of the neurotransmitter oxytocin. The medial parieto-occipital region of the limbic system has a primarily inhibitory role, such as in the fight-or-flight response. The sexual centers of the brain, particularly the midbrain, hypothalamus, and amygdala respond to gonadal hormones and, thus, are part of the hormonal feedback system that shapes sexual behavior. The reticular activating system has an important triage role through its connections between higher and lower brain structures as they process sexual stimuli. These connect to one of two coordinating nerve centers along the spinal cord.

More simply stated, erections are the result of friction and fantasy. An implication of these two inputs to erectile response is that mental experiences, i.e., thoughts, feelings, memories, and fantasies, have a central role in normal sexual response and are crucial factors in the development of sexual dysfunctions.

Bancroft and Janssen [2] have proposed a dual control model of erectile function that includes both excitatory and inhibitory influences on sexual response, which is similar to the model of CNS control over erections described above. This model emphasizes that higher brain functions (e.g., thoughts and feelings) can impact erectile response positively or negatively. For example, a common manifestation of ED is the man who, while experiencing sexual arousal, becomes anxious about his performance and loses his erection. The inhibitory influence of sympathetic nervous system arousal on erectile response is the biological basis to many of the psychological origins of ED.

Everhard and colleagues [3] have posited a complex feedback process for sexual arousal

that incorporates physiological response, the immediate situation or context, emotional arousal, and cognitive appraisal. This understanding of the neurological control involved in sexual response highlights the interdependence of psychological and physiological aspects of ED.

The Assessment of Psychological Factors in ED

Organic Versus Psychogenic ED

For many years, ED was classified as either organic or psychogenic. As recently as 1999, the International Society for Impotence Research maintained the organic–psychogenic separation at the core of its taxonomy [4]. Physicians generally took the approach that if a clear medical cause was identified, it was an organic condition requiring a medical solution. Likewise, if a physical cause could not be identified, it was assumed that there was a psychogenic cause and that psychological treatment was indicated.

However, research has demonstrated that this distinction is neither clear nor helpful. LoPiccolo [5] found that most cases of ED are the result of a combination of physical and psychological etiologies. Buvat and colleagues [6] found that, in two-thirds of cases of ED, two or more etiological factors were implicated. Critiques of the organic–psychogenic split have argued that the concept is based on an outdated model of the mind–body separation and that even supposedly psychological causes of ED have biological underpinnings (e.g., depression, anxiety, stress) [7].

Developments in the understanding of both physical and psychological factors have demonstrated that, rather than defining a patient's ED as organic or psychogenic, the goal of a comprehensive evaluation of ED is to identify the various physical and psychological factors involved in order to tailor treatment to the individual case. We have moved from an either/or model to a detailed checklist model in which the clinician considers all the possible etiological factors that might be involved.

The Assessment Process

It is not expected that most medical or mental health clinicians have the time or expertise to complete the detailed assessment outlined here. This overview hopefully sensitizes the physician to the complexity of ED and its various etiologies. The suggested assessment process outlined below is based on a comprehensive evaluation typically conducted by a mental health specialist in sexual disorders, i.e., a sex therapist (See Table 3.1). Maurice [8] provides a detailed description of assessment and treatment of sexual dysfunctions in a medical practice setting.

The ideal team for assessing and treating ED is a health care provider and a mental health care provider. The health care provider (physician, nurse) may be a generalist or a specialist as long as he or she has expertise in sexual dysfunctions. Likewise, the behavioral health care provider may come from a variety of disciplines (e.g., psychologist, psychiatrist, or social worker), but has specialized training in the psychological aspects of sexual disorders. These individuals typically label themselves as sex therapists.

The collaboration between the medical and the behavioral halves of the team may take a variety of forms. It may be as simple as cross-referral of patients for evaluation and treatment. It could be as integrated as both clinicians working in the same setting, seeing the patient and his partner together and jointly developing a

treatment plan. In general, the closer the collaboration between these two members of the ED team, the better the clinical care.

Most of the evaluation is relatively straightforward. What is likely to be unfamiliar to the nonspecialist in sexual disorders is the “sexual script”. Sexual script refers to the internal mental aspects of the sexual situation that direct behavior [9]. It also includes the individual’s expectations of the sexual encounter. Sexual scripts have several levels, including the intrapsychic, the interpersonal, and the sociocultural dimensions of sexuality. The script connects the mind to the act of sexual activity. Analyzing the sexual script involves not only examining the process of the sexual encounter, i.e., who does what to whom, but also the affective, cognitive, and interpersonal aspects of the encounter. Examination of the sexual script for both members of the couple often identifies where the obstacles to sexual response are occurring. For example, a man may become anxious whenever his girlfriend initiates sex because he believes that he should be the initiator of sexual activity.

Talking to Patients about Sexual Problems

Patients are often reluctant to address their sexual concerns with their health care provider. In one study, medical patients were asked, “If you went to your doctor about a sexual problem you were having, how concerned would you be that each of the following might happen to you during your doctors’ visit?” [10]. Seventy-six percent of patients reported they were concerned that there would be no medical treatment for their problem, 71% were very concerned that their physician would tell them that the problem is “just in your head,” and 69% of patients believed that their doctor would be uncomfortable discussing a sexual problem.

Talking to patients about sex requires that the clinician be comfortable with the topic. Clinicians often have not had specific training in addressing sexual issues. They also bring their own discomfort

Table 3.1 Comprehensive assessment of ED: medical and psychological factors

Medical factors
Medical history
Current medical conditions
Medication and substance use
Medical tests
Psychological factors
Current sexual response
Premorbid sexual function
Psychological history
Current psychological health
Current relationship function
Partner’s health, mental health, and sexual response
Sexual script

Table 3.2 How to talk to patients about sexual problems

Delay asking about sensitive areas until later in the interview
Emphasize confidentiality
Use a common language
Normalize experience and problems
Be nonjudgmental
Provide information on normal function by way of explanation
Ask questions about feelings, thoughts, behavior, as well as physical function
Convey a belief that sexual problems can be solved

and embarrassment about sex into the clinical setting. Preparation for work with sexual disorders should include a careful examination of one's own attitudes about sexuality. Table 3.2 outlines ways to approach sexual issues with patients in order to obtain the most accurate and complete understanding of the problem.

Unless the patient is already presenting with a sexual problem, the process begins by asking the most basic question, "Do you have any sexual concerns?" This should be a standard part of any general medical evaluation. It helps to ask this question after establishing rapport with the patient through other parts of the medical history. Reminding the patient of the confidential nature of the evaluation increases the patient's openness about his or her concerns. While it is important to talk openly and directly about sexual issues, it is not generally helpful to make jokes about sex, since this may be misinterpreted by the patient.

Discussion of sexual issues is aided by using common language that avoids both technical jargon, such as "coitus" or "cunnilingus", as well as street slang, such as "cunt" or "prick". The use of standard terms (e.g., penis, vagina, intercourse, oral sex penetration, or orgasm) increases the patient's comfort with the process. It will be helpful, however, if the clinician understands sexual slang, such as "a top" referring to the person who penetrates, or "bare-backing", meaning unprotected sexual intercourse. Often it is necessary to further inquire to understand what the patient means by their description of sexual behavior. For example, it is often uncertain what a person is referring to when he or she says,

"We had sex." For most people, this refers only to intercourse, while for others it may include oral sex, or any genital contact.

The patient will be more open to admit to problems if the clinician points out that sexual difficulties are common concerns (e.g., "Men often report that they have problems with erections as they get older. Has this been a concern for you?"). It is very helpful for people with sexual concerns to know that they are not the only one with the problem, since these difficulties are often associated with feelings of shame, inadequacy, and anxiety.

A crucial aspect of addressing sexual problems is approaching sexuality in a nonjudgmental fashion. This begins with the clinician being aware of his or her own values and attitudes regarding appropriate and inappropriate sexual behavior. Work with sexual disorders requires clinicians to be tolerant of a wide range of common and uncommon sexual behavior and impulses. Clinicians who possess narrow views of acceptable behavior may not be able to work with certain patients (e.g., women, unmarried people, or gay men) or sexual problems of any kind. While it is important to respect the patient's values or cultural differences, it is also critical not to presume to know what they are.

The assessment of sexual dysfunction also provides an opportunity to provide information about normal sexual responses. For example, in asking whether a man has erections at night in order to assess his complaint of erection difficulties, a clinician could explain that men normally have several erections each night, and this is a part of the physical state of REM sleep. Similarly, when asking about a woman's sexual response, it may help to point out that many women are often not routinely orgasmic through intercourse. This information helps to correct common myths about sexual response.

The assessment of sexual problems should also inquire about the patient's feelings about the problem. The clinician should ask the man presenting with ED about his feelings about and reactions to his problem. The response may range from anxiety or depression to relief or indifference. Some men may not view the dysfunction as a problem at all.

Finally, the assessment process should convey a realistic sense of hope that sexual difficulties can be resolved by addressing them directly. As noted earlier many patients assume that effective treatments do not exist for sexual dysfunction.

While it is not standard practice in most medical settings, involving the patient's partner in the evaluation of any sexual dysfunction is the most effective way to obtain a comprehensive understanding of the problem. One reason for this is that the patient's partner may provide additional information and/or a different perspective on the history and current manifestation of the problem. An entirely different picture often emerges about the ED once the partner has been involved in the assessment. For example, the partner may point out that the erection problem started just after beginning a new medication, after the development of relationship problems, or was associated with stressful events.

A second reason to involve the partner in the evaluation is that the partner may be contributing significantly to the ED. For example, it may be revealed that the partner has lost sexual desire, is experiencing sexual pain, or is so angry with the patient that she or he is engaging in sabotage of the sexual relationship. As described later in this chapter, there are many ways that the partner may contribute to a patient's ED.

A third reason to involve the patient's partner in the initial evaluation is that she or he may be a necessary part of the treatment. If psychological treatment is indicated, most often this will include the partner in some phase of treatment. Even if the partner is not directly involved in the treatment, her or his support for the treatment, medical or psychological, may be crucial for success. Efforts to gauge the partner's acceptance of the treatment plan should be part of the evaluation, even if she or he is not present. Many medical and psychological treatments for ED have been subverted by a partner who was threatened by the treatment or resented not being part of the decision-making process.

Because erectile disorder is usually a dysfunction in a dyadic interaction, involvement of the partner almost always increases the likelihood of accurate evaluation and successful

treatment outcome. This may not be possible for the primary care provider or the medical specialist, but should be incorporated at some point, usually by the mental health specialist.

Assessment by History

Though most clinicians do not have the luxury of a detailed assessment of sexual dysfunction, a simple and quick assessment of erectile function is possible. The first step is to ask about sexual problems of any kind. Many patients may not volunteer information about their sexual difficulties, unless they are presenting with such a complaint. Studies have found that patients still face obstacles in addressing these concerns with their health care provider, often as a result of the clinician's avoidance of the issue [10]. Research indicates that patients with sexual dysfunctions wait, on average, 4 years before they receive appropriate treatment for their problems [11]. Therefore, a general question about sexual problems should be a standard part of any medical or mental health evaluation.

Once a patient has identified a sexual concern, the next step is to determine if he indeed has a sexual dysfunction. Despite society's apparent openness about sexuality, ignorance and misinformation about sexual function still abound. One important intervention that clinicians are often called upon to provide is accurate information about normal sexual response. Simple education and reassurance are sometimes the only treatment necessary. This depends on a clinician having both the requisite knowledge and the appropriate attitude to discuss sexual issues with his or her patient.

If the patient is experiencing ED, the next step is to describe the problem more specifically. The most important distinction to be made is between "generalized" ED and "situational" ED. Generalized ED is defined as a problem that occurs on all occasions of sexual arousal. This can be determined most simply by asking one question, "Do you ever have a full erection?" A patient who answers "No" manifests a generalized form

Table 3.3 Key questions in the assessment of erectile dysfunction

-
1. Are you experiencing any sexual difficulties?
 2. How often do you have the urge for sex with a partner? (By yourself?)
 3. How often do you have any type of sexual activity with a partner? (By yourself, e.g., masturbation?)
 4. When you are engaged in sexual activity with a partner, how mentally aroused do you feel (on a 10-point scale)? (By yourself?)
 5. How full and firm are your erections with a partner (on a 10-point scale)? (By yourself?)
 6. How often do you lose an erection involuntarily?
 7. How often do you wake at night or in the morning with an erection?
 8. How full and firm are these erections (on a 10-point scale)?
-

of ED. Usually, more detailed questioning is required to accurately categorize the problem by asking the patient about: (1) sexual activity with any partner, (2) self-stimulation (i.e., masturbation), (3) nocturnal erections, and (4) spontaneous sexual arousal (see Table 3.3). The goal of all of these questions is the same, i.e., to determine if the patient is ever capable of a full erection. If the patient is able to obtain a full erection in any of these situations, the problem is labeled a situational case of ED.

Of particular interest are the patient's nocturnal erections. Surprisingly, most patients are not aware that healthy men experience 4–5 erections every night during periods of REM sleep. It is therefore helpful to explain this when asking about nocturnal erections. The presence of at least occasional normal nocturnal erections is strong evidence that “the plumbing works” and is often a relief to patients.

In assessing erectile dysfunction, a central distinction should be made between mental sexual arousal, (e.g., “excited” or “turned on”) and physical sexual arousal (the erection). It is helpful to ask the patient to rate both the level of mental arousal and the fullness/firmness of the erection on a 10-point scale. This helps to identify the common situation in which the individual is not experiencing a full erection, but is not attuned to the fact that he is also not sexually excited.

All of this information is crucial to be able to gauge the relative presence of physical and

psychological factors in ED. If it becomes clear that the patient is able to experience full erections in some situations (e.g., at night, with self-stimulation, or with one partner versus another), it will strongly suggest that the problem is not likely to have a primarily organic etiology. This then allows a more focused examination of the salient aspects of the situations that are associated with ED. The clinician would explore what is unique about the situations in which the patient experiences ED (e.g., feeling anxious, a different partner, or heavy alcohol use).

Inquiring about mental arousal as well as physical arousal allows the clinician to make a valuable distinction between ED that occurs when sexual arousal is low or absent, and ED that occurs in the presence of what seems to be adequate sexual arousal. It is difficult to determine the presence of organic factors in ED when the individual is not experiencing sexual excitement. If the patient reports normal sexual excitement and diminished erections, one can still postulate both organic and psychological factors. If the patient reports, both that he is able to achieve full erections on some occasions of sex or at night, and that he experiences little or no sexual excitement, there is strong *prima facie* evidence that psychological factors are involved. One can then inquire about what may be contributing to the lack of sexual arousal or about the occasions during which he experiences ED.

Another important distinction to make in the description of ED is whether it is a life-long problem (primary ED) or an acquired problem, i.e., it developed after a history of normal erectile response (secondary ED). Primary ED in adult males is less frequent than secondary ED and is more likely to have significant psychological origins, often an anxiety disorder.

The various physical factors that cause ED are reviewed elsewhere in this volume. It is helpful to organize the many possible psychological contributions into two broad categories (immediate and underlying factors) and two sub-categories (individual and interpersonal factors) under each of these (see Table 3.4). Immediate factors in the origins of ED are those conditions or situations that are occurring at the time of the sexual activity itself. Underlying factors are

Table 3.4 Psychological factors in erectile dysfunction (patient and partner)

Immediate
Individual
Lack of arousal
Performance anxiety
Inappropriate conditions for sex
Other sexual dysfunction
Interpersonal
Inadequate sexual behavior
Partner's response (including possible sexual dysfunction)
Lack of feedback
Underlying
Individual
Avoidance of sex
Ambivalence about sex
Excessive need to please one's partner
Unrealistic expectations
Feelings of sexual inadequacy
Stress
Paraphilia
Comorbid mental health problems
Interpersonal
Anger
Avoidance of intimacy
Communication problems
Relationship dysfunction

generally those issues that the person brings to the sexual encounter or may be the cause of the immediate factors. For example, if one identifies the presence of performance anxiety as contributing to a person's ED, one would then want to examine what has led to the development of the performance anxiety. Individual factors are those that are experienced by the patient himself. Interpersonal factors include those that may be experienced by the partner, or are manifest in the dyadic interaction or the relationship.

Immediate Factors

Individual

Lack of arousal. One of the most overlooked causes of ED is the lack of mental sexual arousal on the part of the patient. Often the patient

himself may not be aware of this. Men often expect that they will experience an automatic erection when in a sexual situation and may be alarmed when it does not happen. Simply asking the patient about his level of sexual excitement may serve to pinpoint the cause of the problem. Once a lack of arousal is identified, further questions can focus on the reasons for the lack of sexual excitement.

Performance anxiety. The experience of performance anxiety takes a variety of forms. Most often, it is worry about having an erection problem. It may also be fear of displeasing the partner or of negative reactions by the partner. It may include fear that the erection problem will never go away or that it will lead to embarrassment or the loss of a relationship. Sometimes, it expands into a sense of failure as a man. Research has demonstrated that, for men with erectile dysfunction, anxiety results in decreased sexual arousal and erections [12]. Similarly, Bancroft and Janssen's "dual control model" of sexual arousal has shown that anxiety serves as the primary source of inhibitory control [2]. It is important to note that performance anxiety can be either a cause or an effect of ED. Most men with ED will experience some amount of performance anxiety, even if there is a clear organic cause. Likewise, performance anxiety may not be the original cause of the ED, but may be a secondary cause once the ED has started.

Inappropriate conditions for sex. Patients with ED may not recognize that they are trying to be sexual when the conditions are not right. Therefore, asking about the patient's physical and mental state before and during sex may identify obstacles to erectile response, such as feeling stressed, ill, tired, or preoccupied. Timing, the partner's physical or mental state or other elements of the situation may not be conducive to a good sexual response.

Other sexual dysfunction. Other sexual dysfunctions are often present in men with ED. Results from a study of sexual dysfunction found that two-thirds of men with hypoactive sexual desire had ED as well [11]. Likewise, men with ED frequently also have premature ejaculation.

These two conditions should always be assessed in men with ED. If there are co-occurring sexual dysfunctions, the question becomes which condition may be primary. A temporal ordering of the onset of the problems may make this clear. For example, many men with ED subsequently develop inhibited desire as a result of the frustration and distress of the ED. Conversely, the ED may be the result of a loss of sexual desire. At other times, the sexual problems appear develop simultaneously. These cases highlight the possibility of a more pervasive sexual inhibition.

Interpersonal

Inadequate sexual skills. Sometimes, people just do not know how to have good sex. Whether the result of ignorance or unrealistic expectations, a patient may not be aware of the kind of stimulation that he requires for sustained sexual excitement. Problems of this type may be identified through the examination of the couple's sexual script.

Partner's response. In assessing the sexual interaction for clues to the obstacles to an erection, one should not forget the other person who may be present. A frequent problem noted by men with ED is that their partner is not aroused, which decreases their own arousal and increases their anxiety. This may be the result of a sexual dysfunction on the part of the partner (e.g., inhibited arousal, pain, or anorgasmia). The partner may also be experiencing her or his own sexual anxiety or anger about the problems in the sexual relationship.

Lack of feedback. A satisfying sexual encounter usually requires a process of feedback between partners about their experiences of pleasure or displeasure. Individuals learn what works for the other person sexually and what to avoid. The absence of feedback can lead to continuing unproductive ways of seeking arousal or to missing the sexual activities that would produce arousal.

Underlying Factors

Individual

Negative attitudes about sex. There may be multiple reasons for a man's negative attitudes or beliefs about sex, and these should be identified for a complete understanding of his ED. Possible reasons include: sexual abuse history, ambivalence about sex, negative attitudes about sex from cultural or social sources, negative feelings about one's partner, and expectation of problems.

Excessive need to please one's partner. A man's excessive preoccupation with his partner's satisfaction or response may create performance anxiety as well. The effect of this excessive focus is that he does not attend to his own sexual arousal, and he is not able to experience enough sexual arousal to produce and maintain an erection.

Unrealistic expectations. Performance anxiety is also often created by a man's unrealistic expectations of himself. Given that inaccurate information and unrealistic images of sexual behavior are common, many men have irrational beliefs about their sexual response. Often these assumptions about sex are unconscious. The partner may bring her or his own unrealistic expectations to the sexual encounter as well.

Feelings of sexual inadequacy. A frequent underpinning to impaired erectile response is a man's internal sense of sexual inadequacy, which leads to expectations of sexual failure. This sense of inadequacy may be recent or have lasted for many years. It may stem from or predate experiences of ED.

Stress. Stress may have both an immediate and an underlying role in ED. At the time of sexual activity, acute stress may make it difficult for the man to relax and attend to appropriate sexual stimuli, due to the interference of intrusive worries. Over longer periods of time, stress may serve to inhibit sexual desire and arousal, leading to performance anxiety and avoidance.

Paraphilia. Another cause of insufficient sexual arousal during a sexual encounter is the presence

of competing or interfering sexual fantasies. On occasion, the evaluation of ED identifies the presence of predominantly homosexual fantasies in men who present as heterosexual and vice versa. An underlying paraphilia, i.e., sexual arousal to nonconventional fantasies, may be also identified. Examples include fetishism, transvestism, and pedophilia. If such fantasies are a man's predominant sexual interest, he may simply not be aroused by his partner or their sexual activity.

Comorbid mental health problem. Other mental health problems in either the man with ED or his partner may lead to ED. (See below.)

Interpersonal

Anger. A common interpersonal cause of ED is anger, especially unresolved anger toward one's partner. Such anger may lead to a phenomenon of "sexual sabotage," in which the man consciously or unconsciously attempts to deprive his partner of sexual pleasure. The man's partner may also manifest such sabotage, such that she or he is frustrating the man's desire for sexual pleasure. There is a wide variety of possible sources to such anger, which often require a careful examination of the current relationship.

Avoidance of intimacy. Another common pattern seen in men with ED is the situation in which the man experiences problem-free sex during the courtship phase of relationship but suddenly develops ED when the relationship requires a more serious commitment. Men who experience mistrust or fear of rejection in the context of a relationship may also manifest this conflict about sexual intimacy through ED.

Communication problems. Obstacles in healthy communication may lead to ED in several ways. First, conflicted communication frequently leads to resentment and withdrawal. Second, poor communication may lead to a lack of understanding about the sexual needs or wants of the man's partner.

Other relationship dysfunction. A wide variety of other relationship difficulties may negatively impact erectile response, including mistrust, struggles for control, and conflict about the sexual relationship. For this reason, most sex therapists also have expertise in couple therapy.

Comorbid Mental Health Problems in ED

In addition to the psychological issues noted earlier, a thorough evaluation of ED should identify any underlying mental health problems. These mental health problems range from mild (e.g., temporary depression) to serious (chronic schizophrenia). Not only are mental disorders related to increased incidence of ED, but medications for mental conditions may also contribute to the development and/or maintenance of ED.

Research on the comorbidity of sexual dysfunctions in men with a variety of mental health problems indicates that they are more likely to present with ED than men without such conditions [13].

Anxiety has been associated with ED for many years, beginning with Masters and Johnson [14]. As discussed earlier, anxiety during the sexual encounter is a major cause of ED. Individuals with a variety of anxiety disorders, including social phobia, obsessive-compulsive disorder and posttraumatic stress disorder, manifest higher rates of sexual disorders, including ED [13].

Depression has long been associated with sexual problems. In fact, the loss of sexual desire is considered one of the most common symptoms of depression. In men with serious depression, the incidence of ED can be as high as 90% [15]. Depression has also been shown to be associated with reduced nocturnal erectile capacity, highlighting an underlying biochemical connection between depression and ED [16].

Psychiatric treatment of depression, however, is also frequently associated with ED. A large-scale study found that 37% of patients on antidepressant medications manifested a sexual disorder [17]. While the most common sexual

side effects of antidepressants are inhibited orgasm and decreased libido, the prevalence of ED is also higher in men taking these medications. All classes of medications for depression have been implicated in ED, but it is most common for selective-serotonin reuptake inhibitors (SSRIs). It is often unclear, however, whether the ED is the result of the illness or the treatment, so both must be considered.

Both treated and untreated men with schizophrenia demonstrate increased incidence of ED and those on antipsychotic treatment show greater difficulties [18]. It is difficult to separate the various possible factors that may link schizophrenia to ED, which include the disorder itself, the medications used to treat it, and the psychosocial impact of the illness on the ability to develop sexual relationships. Unfortunately, men on antipsychotics may discontinue their use because of the perceived sexual side-effects.

The Development of ED

A thorough understanding of a patient's ED should involve a formulation of the development of the disorder (see Table 3.5). It is helpful in this effort to identify the chronological ordering of: (1) vulnerability factors, (2) triggering factors, (3) exacerbating factors, and (4) maintaining factors [6]. Each of these categories may contain either

physical or psychological factors, which includes both individual and interpersonal factors. Some of the factors noted above may fit into more than one of these categories. Further, it should be noted that these factors may be present in the partner of the man with ED as well.

Vulnerability factors are those conditions that predate the onset of ED, but which are causally connected to it. The physical or medical factors that predispose a man to ED are well known (e.g., age, diabetes, or atherosclerosis). Less well-known, though no less important, are the psychological factors that lead to increased susceptibility to ED. These could be mental conditions of the patient, such as stress, an anxious personality style, or feelings of sexual inadequacy. They may also be conditions of the sexual relationship, primarily some form of relationship strain or dysfunction (e.g., conflict, lack of emotional intimacy, or mistrust).

Triggering factors are those events that precipitate ED. Physical triggering events may be an illness, injury, or medication change. The most common psychological precipitant to erectile dysfunction is a single episode of erection difficulty. Whether this one event develops into a condition of ED depends on the presence of vulnerability or exacerbating factors. A change in the man's mental or emotional state can trigger ED, such as changes in stress levels or the onset of a depressive episode. A common relationship event that may lead to the onset of ED is the start of a new relationship, which is often associated with increased anxiety and fears of rejection.

Exacerbating factors are conditions that follow the onset of the ED and increase the likelihood that isolated occasions of erection difficulty generalize into a persistent period of ED. These are typically the individual's and the partner's response to the lack of an erection at times it is expected. Performance anxiety is the most common response on the part of the man that causes an exacerbation of normal fluctuations in erectile response. This is commonly seen in men who are predisposed to performance anxiety due to an underlying personality trait, unrealistic expectations of their own sexual response or feelings of sexual inadequacy.

Table 3.5 The development of erectile dysfunction

Vulnerability factors	
	Psychological (e.g., anxiety, relationship difficulties)
	Physical (e.g., diabetes, atherosclerosis, age)
Triggering factors	
	Psychological (e.g., new relationship, one episode of erection difficulty)
	Physical (e.g., new medication, illness)
Exacerbating factors	
	Psychological (e.g., overreaction to occasional ED, partner's negative reaction)
	Physical (e.g., meds, illness)
Maintaining factors	
	Psychological (e.g., avoidance, partner's withdrawal)
	Physical (e.g., meds, illness, age)

Even one occasion of less than optimal erectile response can quickly mushroom into persistent ED because performance anxiety then interferes in subsequent sexual situations.

The partner's response to the onset of an erection problem is also crucial. If the partner responds in a relaxed and supportive fashion, the man is less likely to develop performance anxiety. Occasional lapses in erections are overlooked and the couple is able to continue to enjoy the sexual relationship. However, if the partner reacts negatively to the onset of an erection problem, the man will be at greater risk of escalating frequency of ED. Most often the origin of the partner's overreaction is her or his own fear of the meaning of the sexual problem. Most partners, at first, worry that the cause of the lapsed erection is the man's lack of attraction or affection for them. If she or he is already feeling insecure about herself or himself or the relationship, this may manifest as anxiety and/or anger at the man, which may then exacerbate his anxiety and the ED.

How the partner responds typically depends on his or her own psychological health. Partners who have a healthy sense of self-worth and the maturity to address the sexual problem typically get past these doubts and may be able to help the man with ED overcome his performance anxiety. Other partners, however, may be threatened by the ED and respond with their own anxiety. Such partners often have underlying negative body images, exaggerated fears of rejection, or doubts about their own sexual response. This is another reason why it is valuable to have the partner of a man with ED involved in the evaluation. Assessing the degree to which the partner is threatened, anxious, or angry about the ED contributes to a better understanding of the development of the problem. It also helps in developing a more effective treatment plan.

Maintaining factors are the situations that keep the ED going. The most frequent form that this takes is the vicious cycle of erectile difficulty and performance anxiety. Frequently, men report that they had never experienced performance anxiety before their first occasion of a problem with an erection. However, after experiencing a

problem, sometimes only once, they develop performance anxiety. This anticipatory anxiety then leads to further erection problems, usually as a result of being unable to relax and to attend to the appropriate sexual stimuli necessary for normal sexual response. Continued difficulties with erections then lead to heightened performance anxiety and the cycle escalates. Very often this vicious cycle leads to the avoidance of sexual activity all together. One of the goals of treatment of ED is to intervene in this process and to stop the continuation of the cycle.

Being aware of the many psychological factors that may be involved in ED allows clinicians to identify them, even if they cannot carefully assess them or treat them. Another value of being aware of the full range of factors that contribute to ED is that it helps determine the treatment plan and the prognosis. The clinician wants to categorize the case of ED as simple or complex. Simple cases of ED would include those that are acquired (i.e., not life-long), and do not have significant medical factors or psychological factors associated with them. Complex cases are those that have multiple physical and psychological etiologies. These are more likely to require the involvement of a sex therapist.

Outcome of Psychological Treatments for ED

It is beyond the scope of this chapter to describe in detail the various psychological treatments for ED. Table 3.6 outlines the various strategies that are typically used to treat ED from a psychological perspective. The essential goals of psychological treatment are: (1) to increase sexual arousal and (2) to decrease obstacles to sexual arousal. These impediments to erectile response are summarized above. Psychological treatment of ED should also be integrative, meaning that the treatment should incorporate various approaches (behavioral, cognitive, insight-oriented, or systems oriented) and treatment modalities (individual, couple or group) depending on the underlying etiology of the disorder.

Table 3.6 Psychological treatment of erectile dysfunction

Behavioral techniques
Self-stimulation: to increase awareness of sexual response and decrease anxiety
Sensate focus: graduated steps to decrease anxiety and increase sexual feedback between partners
Stimulus control: to identify conditions for a positive sexual encounter
Cognitive techniques
Identify and diminish negative thoughts and expectations
Address assumptions about partner's thoughts
Enhance focus on appropriate erotic stimuli
Insight-oriented psychotherapy: to identify and resolve intrapsychic obstacles to sex
Couple therapy: to increase intimacy, decrease conflict and improve communication
Relapse prevention: to identify possible causes of relapse and to prepare for them

Research, beginning with the work of Masters and Johnson [14] has examined the outcome of psychological interventions with ED. Their early studies found high success rates with intensive treatment programs that focused on decreasing sexual anxiety and enhancing sexual response through education, guided exercises, and feedback. In an outcome study, they reviewed 792 patients through up to 5 years posttreatment and found an 85% success rate. These studies, however, were not controlled clinical trials.

Subsequent research, using more rigorous empirical approaches, has examined both specific aspects of the treatment for ED and integrative forms of sex therapy. Auerbach and Kilmann [19] found that systematic desensitization, conducted in a group therapy format, with single men experiencing ED was more effective in increasing erectile response than an attention-only placebo group. Treatment gains were maintained at a 3-month follow-up assessment.

Munjack and colleagues [20] used a rational-emotive therapy (RET) approach which focused on changing unrealistic expectations and cognitive distortions about sexual performance in single men with ED. They found that RET was more effective than a wait-list control group in decreasing sexual anxiety and increasing successful

attempts at intercourse. They noted that treatment gains diminished over time for about half of the treatment group.

Takefman and Brender [21] compared two components of ED treatment that were hypothesized to be effective, (1) a ban on sexual intercourse and (2) enhancing communication about preferred sexual activity. They worked with couples in conjoint treatment, rather than group treatment. They found that both groups improved over the 1-month treatment phase and at a 1-month follow-up. Improvement was seen in both successful occasions of intercourse and measures of marital adjustment.

Price et al. [22] used a comprehensive group ED treatment with men without partners that included a ban on intercourse, education about sexual response, sensate focus techniques, and other strategies to enhance sexual arousal and communication. They found improvement in erectile response, as well as enhanced "sexual self-image." Treatment gains were maintained at a 6-month follow-up. Another study by this group [23] examined the effectiveness of a group treatment that included education, group discussions, and communication skills training for men without partners who presented with ED. They also found a statistically significant decrease in reported erectile difficulties.

In a study of men with ED and their partners Goldman and Carroll [24] used a group format that focused on: (1) education about normal sexual response, (2) enhancing the couple's comfort and communication about sex, and (3) increased acceptance of the partner's sexual difficulties. The couples in the treatment group showed greater increases in sexual satisfaction than the control group.

A review of psychological treatments for ED involved a reexamination and meta-analysis of controlled studies over the past 30 years [25]. The review included eleven studies that met the criteria for empirically sound clinical trials. Melnik and colleagues drew several conclusions based on the results of the review. First, groups receiving sex therapy-focused treatment showed greater efficacy for the treatment of ED than did the control groups receiving no treatment. Second, there were no clear differences in the

outcome based on age, relationship status, or severity. However, men with secondary ED, i.e., those who had developed ED after a period of normal erectile function, tended to respond better to treatment than did men with primary (i.e., life-long) ED. Third, studies that compared psychological treatment with vacuum pump devices and intracavernosal injections did not show clear differences between the two treatments, though both the medical and psychosocial treatments were found to be effective.

Finally, the reviewers also examined several studies which compared psychological treatment in combination with sildenafil with medication alone [25]. The meta-analysis showed that men with ED randomized to the combined treatment showed significantly greater improvement and lower dropout rates than men with the medication alone.

A small study by Melnik [26] compared the standard sex therapy approach to the treatment with sildenafil alone. This study found a statistically significant greater improvement in erectile function in the sex therapy group, which continued at the 3-month follow-up. There was also a significantly lower dropout rate in the psychological treatment group.

A number of studies of the outcome of sex therapy have included bibliotherapy, i.e., books that provide education and self-treatment strategies [23]. Results suggest that book-based, self-help forms of treatment are a beneficial adjunct to medical or psychological treatment. There are several recommended books that have been written by respected sex therapists [27–29]. Most therapists have found that treatment outcome is enhanced if both members of the couple are involved, though treatments for single men have also been found to be effective [25].

In sum, psychological treatments for ED have been demonstrated to be effective in group, couple, and individual treatment formats. Most of the studies have used an integrated sex therapy model that combines education, anxiety reduction, a temporary ban on sexual intercourse, enhanced communication and graduated steps of sexual activity. Heiman and Meston's review of empirically validated treatment for sexual

dysfunction offers support for some of the long-standing approaches to these disorders [30]. Using the criteria of the American Psychological Association Task Force on empirically validated treatments, they found that psychological treatments were “well established” for erectile disorder in men. It remains unclear, which of these components of treatment is most effective, though most components have been shown to be effective by themselves. More research is needed to identify the most effective and efficient psychological approaches to the treatment of ED.

Integration of Medical and Psychological Interventions for ED

As discussed previously, there is evidence that a combination of medical and psychological interventions is the most effective treatment strategy for ED [25]. Just as the etiology of ED has been shown to be both biological and psychological, the treatment for ED has moved beyond an either/or model to an integrative model that incorporates both medical and psychological treatments. The field of sex therapy can point to a long history of such integration beginning with Masters and Johnson's earliest theoretical and clinical work and continuing to the present. Indeed a major focus of the past 10 years has been to develop models of how medical and psychological interventions can be integrated to increase effectiveness [31, 32].

The common themes in these approaches include: (1) appreciation of the heterogeneity of disorders, (2) a comprehensive view of etiology that considers the full range of biological, psychological, interpersonal, and cultural factors, (3) appreciation of how the disorder impacts psychological well-being, as well as how psychological well-being impacts sexual function, (4) assessment of the relative “psychosocial complexity” involved in the problem, (5) the important role of the partner in understanding and treating sexual problems, and (6) a flexible treatment approach that can incorporate medical interventions into the

solution. Research demonstrates the value of such an integrative approach for ED, but more research is required to better establish its efficacy and to refine the methodology of the treatment [31].

Key Points

1. The CNS has both excitatory and inhibitory control over erections.
2. Both physical and psychological causes of ED must be evaluated.
3. Questions about sexual dysfunction should be asked in a direct, nonjudgmental fashion.
4. Involvement of both the patient and the partner in the evaluation yields the best understanding of the etiology of ED.
5. The development of ED involves several stages: vulnerability, onset, exacerbation, and maintenance.
6. The single most useful question to identify whether a case of ED has a prominent physical etiology is whether the man is ever able to have a full erection (including nocturnal erections or through self-stimulation).
7. The presence of comorbid mental health problems is an important part of the assessment of ED.
8. Psychological treatment for ED has been shown to be effective, and combined medical and psychological treatments appear to be most effective.

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Chapter 4

Epidemiology of Erectile Dysfunction and Key Risk Factors

Ray C. Rosen and Varant Kupelian

Abstract Erectile dysfunction (ED) is a common, age-related disorder in men, which has been associated with multiple medical and psychosocial risk factors. In addition to the well-known association with age, cardiovascular risk factors have been associated with ED in multiple studies. Based upon these findings, ED has been proposed as a sentinel event or harbinger of future cardiovascular risk for younger or older men with ED. Other studies have shown an association between ED and depressed mood or loss of well-being in many men with the disorder. Based on recent analyses of the Massachusetts Male Aging Study, we have shown that approximately one third of men with ED show improvement in their symptoms over time (remission), whereas 2/3 show progression or no change over time. Progression was most evident in older men with other health risks. Recent findings from the Boston Area Community Health (BACH) study have shown that apparent associations between ED and race/ethnicity are due primarily to differences in socioeconomic status between the groups. The role of medical comorbidities, concomitant medications and lifestyle factors have also been highlighted in these studies. Future studies will investigate mechanisms associated with these effects and the broader psychosocial impact of ED.

Keywords Aging and ED • Race/ethnic disparities in ED • Socioeconomic diversity • Cardiovascular disease and ED • Endothelial dysfunction in ED

Background and Overview

Erectile dysfunction is a significant and common medical problem. Epidemiologic surveys in the past 20 years suggest that approximately 30–40% of men over 40 have ED to one degree or another. Data from the Massachusetts Male Aging Study (MMAS) have shown that ED is a common occurrence among aging men with a prevalence rate of 34.8% of moderate to complete ED (Feldman et al. *Journal d’Urologie*, 151, 54–61, 1994). The disorder is highly age-dependent, as the prevalence rises from 2% for men aged 40–49, 6% for men aged 50–59, 17% for men aged 60–69, and 39% for men aged 70 and older (Inman et al. *Mayo Clinic Proceedings*, 84, 108–113, 2009). Recent reports from the National Health and Nutrition Examination Survey (NHANES III) and the Males Attitude Regarding Sexual Health Survey (MARSH) show similar prevalence estimates (Saigal et al. *Archives of Internal Medicine*, 166, 207–212, 2006; Laumann et al. *Archives of Sexual Behavior*, 35, 145–161, 2006). NHANES data suggests that Hispanics are more likely to report ED especially at younger ages (<50 years) (Saigal et al. *Archives of Internal Medicine*, 166, 207–212, 2006), a pattern not observed in the MARSH study (Laumann et al. *Archives of Sexual Behavior*, 35, 145–161, 2006).

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The role of aging in ED has been investigated in several studies. In a large national sample of men ($N=1,455$) between the ages of 57 and 85 years of age [5], 37% of men in the overall sample had problems with ED, increasing to 44% in the 75–85 year age group. Men were asked whether or not they had “difficulty achieving or maintaining an erection for several months or more during the past year.” Of note, 90% of men with ED reported being bothered by the problem. Fourteen percent of men in the sample reported the use of medications to improve sexual function. As in previous studies, age and diabetes were significant independent risk factors for ED in this study [5], in addition to overall health and well-being. Previously, Laumann et al. (1999) had shown that ED increases from 7% in men under 30 to 18% in men aged 50–59 [6]. Taken together with the recent findings from the Lindau et al. [5] study, it appears that ED increases about 400-fold from less than 10% of men under age 30, to almost 50% of men aged 50 and above. However, we should note that almost 50% of men aged 50 and above *do not* develop ED, and thus it should not be viewed as a natural or inevitable consequence of aging. The role of medical comorbidities and risk factors has been shown to be increasingly important.

Findings from multiple epidemiological studies have also shown convincingly that ED impacts mood state, interpersonal functioning, and overall quality of life (2–8). ED is associated with a wide range of psychosocial consequences and risk factors, such as decreased quality of life (QoL), poor self-esteem and increased incidence of depression and interpersonal relationship problems [7–10]. Numerous studies have demonstrated that ED can undermine a man’s QoL; for example, Jønler et al. [11] have shown that patients with the loss of erectile function within the past year had significantly lower QoL than men without ED. Similarly, in other recent studies, men with a complaint of ED had poorer QoL than age-matched men from the general population [12, 13]. QoL was also shown to be impaired in men with ED and diabetes [14] who showed significantly higher levels of diabetes-specific health distress, worse psychological adaptation to and acceptance of diabetes, and a less satisfactory sexual life. Moreover, these men were more easily frustrated and discouraged by their diabetes, which translated into worse metabolic control and higher levels of depressive symptoms. Although not a life-threatening condition, ED is thought to have a profound effect on the quality of life of aging men [15]. Moreover, ED is viewed increasingly as a harbinger or signal of future cardiovascular events.

The role of comorbidities has been recognized since the MMAS and other early epidemiologic findings [1]. Among the major comorbidities and risk factors for ED are diabetes, depression, and cardiovascular disease [8, 16–20]. This classic trio of risk factors has been implicated in multiple epidemiologic studies, across multiple populations and research settings. Medications for diabetes, hypertension, cardiovascular disease, and depression may also cause erectile difficulties [21]. In addition, there is a substantially higher prevalence of erectile dysfunction among men who have undergone radiation or surgery for prostate cancer, or who have a lower spinal cord injury or other neurological diseases (e.g., Parkinson’s disease, multiple sclerosis). Life style factors, including smoking, alcohol consumption, and sedentary behavior are additional risk factors [20]. Despite its increasing prevalence

among older men, erectile dysfunction is not considered a normal or inevitable part of the aging process. It is rarely (in fewer than 5% of cases) due to aging-related hypogonadism, although the relationship between erectile dysfunction and age-related declines in androgen remains controversial.

One recent review [22] highlighted four major areas of epidemiologic contribution: (1) ED is highly prevalent in aging men, affecting approximately 50% of all men older than 60. For many men, ED manifests in their 40s and 50s, increasing in frequency and severity after age 60 [1, 23–25]. (2) The degree of bother associated with ED is inversely related to aging, as men older than 70 typically report a somewhat lower degree of bother than their younger counterparts. The level of bother and treatment-seeking are typically higher in younger and middle-aged, compared to older men [14, 19, 26]. (3) The prevalence and incidence of ED are highly correlated with the presence of known risk factors and comorbidities, which have a linearly increasing effect on ED. Specifically, cardiovascular comorbidities (e.g., hypertension, hypercholesterolemia), diabetes mellitus, and the metabolic syndrome have all been associated with the increasing prevalence of ED in multiple cross-sectional and longitudinal studies [10, 14, 27, 28]. Additionally, depression and lower urinary tract symptoms (LUTS) have been associated with ED in a number of recent studies [13, 29–31]. (4) Lifestyle factors, including smoking, obesity, and exercise, are also significant predictors of ED [10, 32, 33].

Is ED predictive of cardiovascular disease (i.e., a sentinel or harbinger of future cardiovascular events)? Accumulating evidence of a pathophysiologic and epidemiologic association between ED and cardiovascular risk factors and disease has led to the hypothesis of ED as a possible marker for CVD [17, 34–38]. The association between cardiovascular risk factors and ED was first demonstrated longitudinally in the MMAS [28] and has been subsequently confirmed in other large epidemiologic studies [10, 39, 40]. The hypothesized pathophysiological link between ED and CVD is firmly based in a growing body of epidemiological data and could

have profound public health significance. The onset of ED (to the degree that it reflects systemic arterial compromise, as has been repeatedly demonstrated) may be interpreted as a sentinel of subclinical cardiovascular disease.

Several studies have documented a strong cross-sectional association between ED and clinical manifestations of CVD. Smoking, physical activity, hypertension, hypercholesterolemia, and diabetes, which are all related to endothelial injury leading to atherosclerosis, are important risk factors for both ED and CVD [3, 4, 18, 32, 41–51]. In the MMAS study, cigarette smoking (both active and passive) and unfavorable lipid levels were associated with ED [1]. Additional studies have shown a dose-response relationship between pack-years of smoking and risk of ED [41, 49]. Obesity and physical activity have also been related to ED. Esposito et al. have shown that weight loss and increased physical activity were associated with improved sexual function in about one third of obese men with ED at baseline [52].

Longitudinal data, from a historical cohort study based on medical records data [53] and from the Prostate Cancer Prevention Trial [54], provide the strongest evidence to date of ED as an *independent predictor of CVD*, with an associated increased risk of CVD similar to the effect of smoking or family history of myocardial infarction. The clinical importance of ED as a marker of CVD has been underscored by the Princeton Consensus Conference [55] and the International Consultation in Sexual Medicine [56]. Strong recommendations were made by both of these guidelines committees for the proactive cardiovascular assessment and specific assessment of cardiovascular risk in *all* men presenting clinically with ED.

Inman et al. [2] most recently published longitudinal data from the Olmsted County Study from January, 1996 to December, 2005 consisting of a sample of 1,400 community-dwelling men with regular sexual partners. Results showed a highly significant three-way interaction between age, ED, and new-incident coronary artery disease. Specifically, the rate of new-incident coronary artery disease nearly doubled in the men with ED compared to the

men without ED, controlling in the model for age and effects of other comorbidities. Controlling for the effects of other comorbidities only slightly decreased the strength of this relationship ($OR=1.8$; 1.2–2.6). In the 70 and older age group, the unadjusted odds ratio was 5.5 (3.4–9.7). This latest study provides additional, independent confirmation in a well-characterized longitudinal sample of men of the strong association between ED and clinically relevant aspects of cardiovascular health, including new-incident coronary artery disease. Undoubtedly, clinicians should routinely enquire about sexual function and ED in all men over 40, and symptomatic men should be proactively investigated for their overall cardiovascular health, including any symptoms of angina or coronary artery disease.

In reviewing results from multiple epidemiological studies, we can conclude for the importance of medical comorbidities (e.g., hypertension, diabetes, lower urinary tract symptoms) and lifestyle factors (e.g., obesity, sedentary lifestyle) as key determinants of ED. By assessing the impact of specific risk factors and comorbidities, we aim to identify suitable targets for future treatment and prevention. Current medical or surgical therapies for ED may be viewed as symptomatic or palliative treatments [26], which fail to address the underlying pathophysiological mechanisms involved [57, 58]. Findings from population-based studies should be used to guide clinical prevention or education efforts. These should be directed to those patient groups or individuals most likely to benefit from early intervention (e.g., men without major illnesses or comorbidities) [33].

ED Progression and Remission

What factors account for early onset and progression of ED in some men, but not others? Despite the overall association with aging, a number of older men in their eighth and ninth decades continue to enjoy sexual activity and adequate penile erections [20, 59, 60].

The increased incidence of ED and progressive decline in testosterone levels in aging men is

well documented [7, 8, 23, 61]. Recent findings, in particular, from the MMAS study has demonstrated the remission of ED in a significant proportion of men over time, even without specific intervention or the use of oral medications or other ED treatments [62]. Analyzed data from the MMAS to investigate the natural history of ED, including both progression and remission. 401 men of the original MMAS sample were followed who reported minimal, moderate, or complete ED at T1 (1988–1992) [62]. These men were eligible for remission, defined as a lessening of severity by at least one category of ED from T1 to T2 (1996–1998). Of the 401 men included in this analysis (Fig. 4.1), 141 subjects (35%) exhibited ED remission by T2 (95% CI: 30%, 40%). Of 323 subjects with minimal or moderate ED at T1, 107 (33%) exhibited ED progression (95% CI: 28%, 38%). The proportion of men with ED experiencing progression, remission, and remaining stable is roughly equivalent (Fig. 4.1) [9, 62]. Age and BMI were associated in this analysis with both progression and remission, while smoking and self-assessed health status were associated with progression only. These observations (which predate development of PDE-5s) suggest that the likelihood of natural remission of ED and its symptoms is more common than previously believed. Furthermore, it provides positive support for the use of lifestyle modification or other nonpharmacological treatments for ED. These new findings have important clinical implications, particularly given the fact that increasing numbers of patients prefer nonpharmacologic means of treatment.

ED Findings From the Boston Area Community Health Survey

Recent findings from the Boston Area Community Health (BACH) Survey have provided further evidence of the association of ED with prevalent comorbid conditions and modifiable risk factors in a large population-based epidemiologic study, as well as new insights on the role of socioeconomic status (SES) and race/

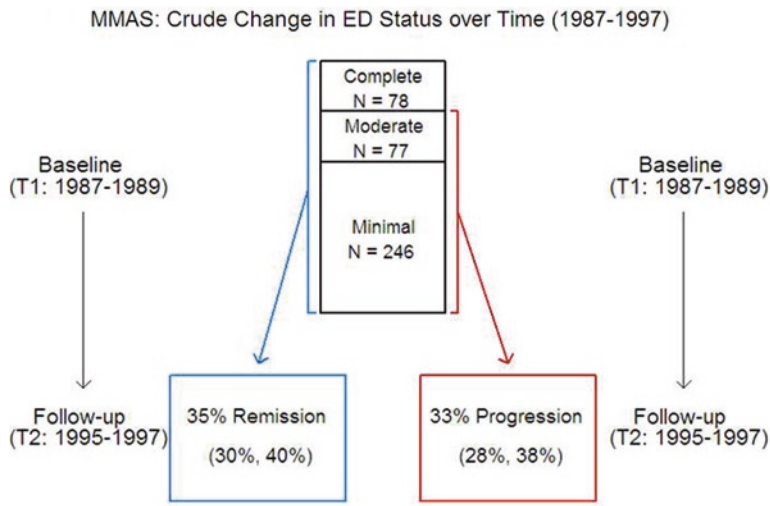


Fig. 4.1 MMAS: Progression and remission of ED with time [62]. A substantial number of men experience remission without intervention

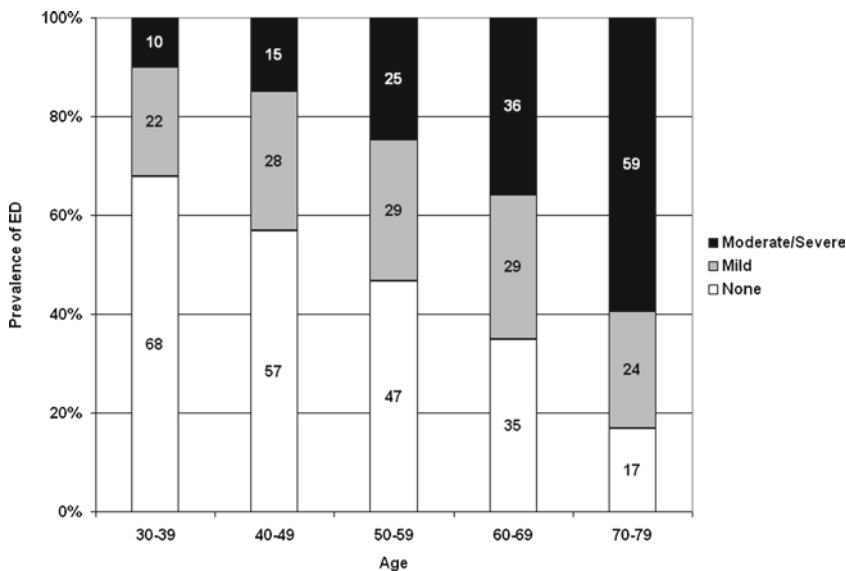


Fig. 4.2 Prevalence of erectile dysfunction by age. Boston Area Community Health (BACH) Study 2002–2005

ethnic disparities in ED, as well as the complex interaction between ED, chronic illnesses, and prescription medication use.

BACH is a community-based epidemiologic study of a broad range of urologic symptoms in a random sample of over 5,500 adults, including 2,301 men age 30–79 years. The BACH study used a multistage-stratified design to recruit

approximately equal numbers by age decade, gender, and race/ethnicity, resulting in a population representative, diverse sample. Multidisciplinary data collected through an extensive in-home interview include a wide range of covariates, including anthropometric and blood pressure measurements, venous blood sample collection, self-reported medical history,

sociodemographic characteristics, and lifestyle and psychosocial factors as well as administration of an extensive sexual questionnaire, including the International Index of Erectile Function (IIEF-5). Medication use was collected using a combination of drug inventory and self-report with a prompt by indication [63].

Consistent with findings from previous studies, results of the BACH study show a strong association between ED and major chronic illnesses, such as heart disease, diabetes, and depression with an approximately twofold increase in risk of ED [64, 65]. A comparable association between hypertension and ED disappeared only after adjusting for heart disease and diabetes. While the association between overall obesity, assessed by BMI and ED was weak, a much stronger association was observed when considering abdominal obesity measured by waist-to-hip ratio. Similar to the association of ED and hypertension, the effect of abdominal obesity was nonsignificant only after controlling diabetes and heart disease. Overall, these results were consistent across race/ethnic groups, with only minor observed differences between groups.

Results from the BACH study also contribute to the growing body of evidence showing an association between ED and LUTS. We further investigated the contribution of urinary incontinence and prostatitis which are common voiding symptoms not included in the AUA symptom index. The observed association in BACH between ED and LUTS, both conditions with increasing prevalence in aging men, is consistent with findings from previous studies, BACH data shows that this association is primarily due to nocturia, and symptoms of urinary incontinence and prostatitis, with results again consistent across race/ethnic groups [66]. Similar results were recently observed when investigating the association between urinary symptoms and low sexual desire and sexual inactivity [67].

In addition to the role of comorbid medical conditions, BACH findings also provide support for the contribution of potentially modifiable behavioral risk factors, such as physical activity, smoking, and alcohol consumption in their effects on ED. Results show a weak association between

alcohol consumption and ED, in particular, with no evidence for a linear trend, as moderate alcohol consumption was associated with a slight decreased in risk while increased amounts were associated with very slightly higher risk of ED. On the other hand, a *clear trend* in decreased risk of ED was observed with increased physical activity [65]. BACH data also provide further evidence of the increased risk of ED associated with smoking with a strong dose-response pattern in between duration and intensity of smoking and increased risk of ED with a significant increase in ED risk with exposure to 20 pack-years or more. BACH data also permits the assessment of the impact of exposure to second hand smoke (passive smoking) and shows a moderate, statistically nonsignificant, increase in the risk of ED comparable to the effect observed for 10–19 years of smoking [41]. These results highlight the importance and opportunity for the intervention on modifiable behavioral factors, such as *smoking cessation* and increased *physical activity* in prevention or improvement in erectile function as well as the possibility of adverse effects of long-term chronic exposure to passive smoking [41].

Although differences in prevalence and risk of ED by race/ethnicity have been reported previously, findings have not been consistent and have seldom taken into account the separate contributions of SES and other background variables to apparent race/ethnic disparities [3, 6, 68]. The strength of the BACH study is the race/ethnic and socioeconomic diversity of the sample and balance, with the SES index calculated as weighted sum education and income and categorized as low, middle, and high SES based on the 25th and 75th percentiles of the distribution of the SES index. Prevalence estimates of ED by race/ethnicity show that ED is more common among Black and Hispanic men with a prevalence rate of 25% compared to a prevalence rate of 18% among White men. These differences persisted after adjusting for age, comorbid conditions, and lifestyle factors. However, there were significant differences in the SES composition of the three race/ethnic groups and differences in ED prevalence were even larger across SES categories, with a prevalence rate of 36%

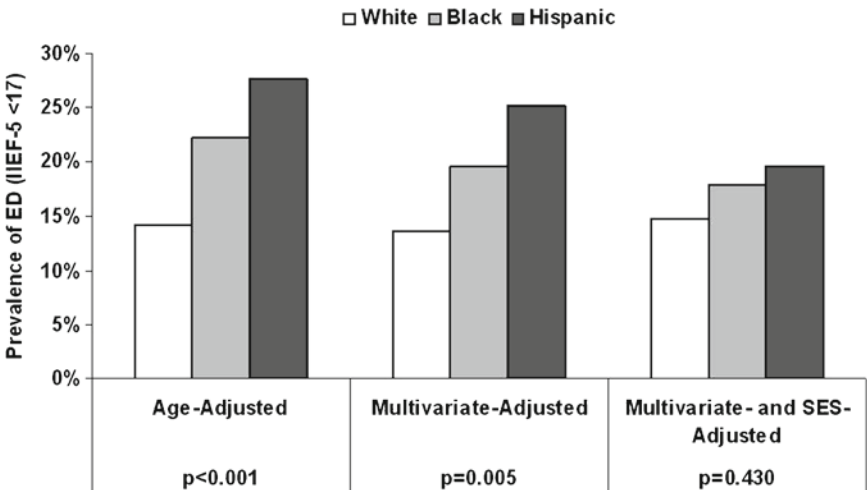


Fig. 4.3 Association of race/ethnicity and erectile dysfunction disappears after adjusting for socioeconomic status

for the low SES category, in particular. Once we controlled SES in the subsequent multivariate analyses, the differences between the race/ethnic groups was lost (Fig. 4.3), while the low SES group remained at more than twofold increased risk of ED, independent of the effects of age, comorbid medical conditions (heart disease, diabetes, depression), and lifestyle risk factors (smoking, physical activity). These finding point to a need for further research to understand the potential role of SES-dependent factors and variables – such as occupational health, nutrition, and access to health care – that may contribute to the increased risk of ED in our low SES group.

Inventory-based medications data collected in the BACH study also presents the opportunity to investigate effects of common medications on ED. An analysis of lipid-lowering medications, including statins and nonstatin antilipemics, shows a complex interaction between the use of medications, presence of comorbid chronic illnesses and age. An association between statin use and increased risk of ED was observed only among younger men (age <55 years) who had diabetes or cardiovascular disease, while the association essentially disappeared or was obscured in older men in the BACH sample. Additionally, no association was seen in our cohort between untreated hyperlipidemia and

ED in multivariate analyses. These findings suggest that lipid-lowering agents may be associated with some increased risk of ED in some men. However, this potential adverse effect of statins and other antilipemic medications should be weighed against the well-established benefits of lipid-lowering therapy in the reduction of major coronary events and mortality. Further research is needed to determine whether other classes of medication contribute to interaction with lipids and resulting changes in prevalence rates of ED across samples [21].

Discussion

Conceptual and methodological issues need to be addressed. First, the definition and measurement of ED varies from study to study. All definitions of ED, however, are based on patients’ self-report, which is typically assessed by single-item scales or questionnaire measures [69–73]. Some differences are evident among these scales, although studies show overall concordance in the prevalence rates and association with well-known comorbidities and risk factors. Early landmark studies, such as MMAS and National Health and Social Life Survey (NHSLs) used single-item

scales, which assessed erection difficulties over several months or in the past year [69, 70]. Subsequent studies used 5- or 15-item versions of the IIEF, a multidimensional, self-report scale that assesses male sexual function over a 4-week period [73]. Single-item instruments have the advantage of high completion rates and low patient burden. On the other hand, multidimensional scales provide broader and more complete assessment of disease severity. Despite such differences, largely similar results have been obtained across studies using these different measures.

A second, and potentially more challenging issue, concerns the complex and often bidirectional interactions between variables. For example, depression may be a cause or a consequence of ED in many studies [8, 9, 31, 74]. These studies support a direct association between ED and mood. In other studies, the causal relationships among the major risk factors for ED are less evident. Biomedical, psychosocial, and lifestyle factors may interact in complex ways. Separating the effects of one risk factor or comorbidity from another and determining the direction of causality among these factors, can be difficult if not impossible to ascertain in cross-sectional studies alone [20, 59, 72, 75]. More research is needed to elucidate these associations.

The increased evidence of a link between ED and CVD with the potential for ED to serve as a sentinel marker of subclinical vascular disease has led to an increased awareness of ED as a “barometer” of vascular health and the early opportunity for primary prevention in at-risk men. The 2nd Princeton Consensus Conference has called for the routine assessment of cardiovascular risk in all ED patients and subsequent classification of ED patients into low, moderate, or high risk of CVD and recommendation for aggressive lifestyle modification in patients with ED and CV risk factors [70]. However, further understanding is needed of the link between endothelial dysfunction and ED and the specific role of endothelial dysfunction in the progression and remission of ED to: (1) refine our understanding of pathophysiological processes of ED in human subjects; (2) improve the identification of ED patients at higher risk of CVD who would benefit most from preventive interventions, such

as statin therapy, perioperative beta blocker therapy, etc.; (3) establish the primacy of endothelial dysfunction in ED incidence and progression and relationship to other predictors.

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Chapter 5

Etiology and Risk Factors of Erectile Dysfunction

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Abstract A wide variety of risk factors contribute to erectile dysfunction (ED). Many of these risk factors are treatable yet go unrecognized. Further, many of the treatments of these risk factors have also been implicated in causing the disease. Thus, the treatment of ED may be a complicated issue for the general practitioner. The majority of this chapter focuses on the correlation between cardiovascular disease and erectile dysfunction. A major benefit of screening for ED is that it may lead to early diagnosis of subclinical cardiovascular disease, alerting the clinician to potential treatment intervention in these patients.

Keywords Cardiovascular disease and ED • Etiology of ED • Atherosclerosis • Obesity and ED • Diabetes and ED • Depression and ED

Introduction

The physiology of penile erections and derangements of this physiology are such that it may be the reason for consultation to a variety of specialists (urologist, endocrinologist, psychiatrist, neurologist, etc.). Thus, an understanding of the

etiology of erectile dysfunction (ED) falls within the purview of generalists as well as the gamut of medical and surgical specialists. The multiple etiologies of ED are generally classified as being either organic or psychogenic. Psychogenic etiologies of ED are further compartmentalized into generalized and situational.

Epidemiology and Risk Factors

Risk factors for ED have been delineated in large prospective studies, such as Massachusetts Male Aging Study (MMAS), Boston Area Community Health Survey (BACHS), and Health Professionals Follow-up Study (HPFS). The MMAS study reported on males between ages 40 and 70 years and found that erectile function declined precipitously with age. Overall, the study found that 52% of men within this age range suffered from some degree of ED. Diabetes, heart disease, and hypertension increased the risk of ED significantly in this study [1].

Erectile dysfunction was studied in men aged 45–70 years with a 14-year follow-up in the HPFS. Excluding men who developed prostate cancer, the relative risk (RR) of development of ED as per self-assessment was 1.5 for current smokers and 1.9 for obese men. In contrast, moderate exercise decreased the risk of ED. Interestingly, these risk factors produced greater effect in men 55 years or younger [2].

The BACHS was created specifically to assess urologic symptoms in a diverse cohort. This study found a dose-response effect of tobacco

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cigarettes on ED, although there was not a significant increase in the odds of developing ED until over 20 pack-years of the habit. They also found that low socioeconomic status, independent of other risk factors, including race, was a risk factor for ED [3].

Erectile Physiology

A successful male penile erection requires two processes. Cavernal smooth muscle relaxation and increased venous outflow resistance. In order to sustain an erection one must achieve and maintain a high arterial inflow and a low venous outflow.

Cavernal arterial smooth muscle relaxation is an active process and the initial event of an erection. Smooth muscle relaxation leads to arterial dilation which results in increased penile blood flow that in turn causes radial and longitudinal cavernal expansion. This process is mediated by nitric oxide released through stimulation of nonadrenergic, noncholinergic nerves (NANC). Nitric oxide binds to smooth muscle cells stimulating the production of cyclic GMP, which then decreases intracellular calcium and causes relaxation. Cyclic AMP, a second minor messenger, acts in a similar manner to decrease intracellular calcium and causes muscle relaxation.

Venous outflow resistance, in contrast to arterial smooth muscle relaxation, is a passive process. As the cavernal tissues engorge and expand, they compress the subtunical venous sinuses and cause the outflow resistance necessary to maintain an erection.

Cardiogenic and Vascular Correlates with ED

Over the past decade, there has been an increased interest and focus of urologic research on the field of ED. Particular focus has been on ED and its correlation with cardiovascular disease. Many

disease states already known to be associated with ED are also associated with cardiovascular disease. These disease states include hypertension, atherosclerosis, diabetes, peripheral vascular disease, obesity, sedentary lifestyle, and myocardial infarction [1]. The latest research has been aimed at verifying a direct correlation between ED and cardiovascular disease. There has even been suggestion that ED is often the first clinical manifestation of underlying cardiovascular disease in up to 30% of men presenting with erectile dysfunction [4]. If so, it would be increasingly important for men to disclose symptoms of ED to their primary care providers, as ED might represent an opportunity to evaluate these men for cardiovascular disease. Unfortunately, a reported 90% of men with ED do not discuss this information with their primary provider [5]. It can be speculated that the reason for underreporting ED is due to patients' embarrassment in addressing sexual issues with a health-care provider. Other possibilities are that patients believe the issue resolves without intervention, or that ED is just a normal symptom of aging. Doctors caring for these patients may then be missing the opportunity to prevent cardiovascular morbidity and mortality [6].

The MMAS of the early 1990s opened the door to increased awareness of the correlation between ED and cardiovascular disease [1]. This study was the first large scale, population-based study investigating ED, revealing that increased prevalence of ED correlated directly with increasing age. The study evaluated 1,290 randomly selected men and found a clinically significant correlation between ED and other medical comorbidities independent of age. These comorbidities included hypertension, hypercholesterolemia, diabetes, and cardiovascular disease. Patients treated for hypertension had a 15% likelihood of also having complete ED and those with cardiac disease had a 39% likelihood of ED [1].

Schouten recently conducted a longitudinal, population-based study focused specifically on erectile rigidity as an independent indicator for upcoming cardiovascular events. They found that severely reduced erectile rigidity had a hazard ratio of 3.8 for the presentation of cardiovascular

disease within 6 years. They agreed that a single question focused on the presence of ED should be incorporated into cardiovascular risk assessment in men. They also stated that men presenting only with the complaint of ED should be evaluated for cardiovascular risk [7].

Atherosclerosis

The most common recognized cause of ED is atherosclerosis. Atherosclerosis is known to be associated with such cardiovascular diagnoses as hypertension and dyslipidemia, which produce oxidative stress and damage to the endothelial cells [8]. The underlying pathophysiology seems to stem from endothelial cell dysfunction, which would be a common factor between general cardiovascular disease and ED [8]. Failed vasodilation seen in ED is a direct effect of the inability of smooth muscle cells lining the arterioles to relax. Atherosclerosis has been found to be associated with up to 40% of cases of ED in men over age 50 [9].

Cholesterol

One group looked at cavernous biopsies of rabbits after three months of a cholesterol-rich diet versus controls. The control group showed normal muscle cells on biopsy while the high cholesterol group showed muscle cell degeneration. This tangible evidence of direct effect of high cholesterol diet on cavernous muscle cells suggests that abnormalities in lipid metabolism has a direct effect on cavernous smooth muscle cell degeneration, thus contributing to ED [10].

Hypercholesterolemia is a known direct risk factor for cardiovascular disease. Erectile dysfunction in association with hypercholesterolemia was documented in a group of healthy men with no known cardiac risk factors. These otherwise healthy men with ED were found to have abnormal cholesterol levels at a rate of 60%. In addition, over 90% of

these men with abnormal cholesterol levels were also noted to have penile arterial disease on Doppler ultrasound [11].

Saltzman et al. evaluated men with ED in which their only known risk factor was hypercholesterolemia. They were able to meet their treatment goals of total cholesterol less than 200 mg/dl and LDL less than 120 mg/dl. They found that ED improved in men with hypercholesterolemia when treated with a statin drug [12]. The resulting decreased cholesterol levels improved ED while also decreasing overall cardiovascular risk. Primary care physicians may theoretically have more success with patient compliance of statin drugs for current improved sexual function than for future cardiovascular risk. Of note, there is also contradicting evidence, based on literature review, that statins and fibrates may actually cause or worsen ED [13]. Should this be the case, it would be very difficult to determine the effect of cholesterol on ED, as in order to treat a known risk factor of ED, we may be in effect worsening ED with the use of medication [14].

Hypertension

Erectile dysfunction has a high prevalence among patients with both treated and untreated hypertension. Large studies have confirmed that, not only was ED more prevalent in patients with elevated blood pressure than controls, but also that the degree of ED that experienced by patients with hypertension was also more severe in nature than in the general population [15]. One study highlighted the specific penile vascular effects of hypertension through the use of rat models [16]. The study found that hypertensive rats demonstrate impairment in endothelial-mediated relaxation of corporal cavernosal strips in response to acetylcholine. This finding suggested that a defect exists in endothelial-dependent reactivity as well as a reduction in nitric oxide in the presence of hypertension [16]. It is somewhat more difficult to evaluate the exact effect of hypertension on erectile function in humans. Patients are

often being treated for their hypertension with medications that are themselves known to cause ED, such as beta blockers and thiazides. It is likely that the ED experienced in hypertensive men is caused by penile vascular arterial changes including atherosclerosis [17].

Coronary Artery Disease

Beyond hypertension, ED may also predict the presence of occult coronary disease. One study evaluated 50 men with ED and no clinical signs of cardiovascular disease. The men were age 40–60 years and underwent cardiac stress testing and coronary angiography [18]. Eighty percent of the men demonstrated significant cardiovascular risk factors. Stress testing showed myocardial ischemia in 56% of these men. Coronary angiography was performed in 20 of the men with ischemia. Angiography revealed left main stem or severe three-vessel disease in 6 of 20, with some degree of significant coronary artery disease (CAD) in 40% of the total. It is important to note that none of these 50 men showed any clinical signs of ischemic heart disease prior to this testing that was prompted only by the presence of ED [18].

Thompson et al. reported a secondary finding in a randomized study of almost 10,000 men age 55 or older enrolled in the Prostate Cancer Prevention Trial [19]. The secondary finding was a direct association between ED and subsequent cardiovascular disease. Eighty-five percent of the men had no cardiovascular disease at the start of the study, with 47% of these men having ED at that time. Incident ED that occurred during the first 5 years of the study was associated with a 1.25 increased risk of subsequent cardiac event during follow-up. In reference to subsequent cardiovascular events, the risk was 0.015 per person-year among those without ED at study entry, and was 0.024 per person-year for those with preexisting ED at the time of study entry. These authors stated that this increased associated risk was similar to the risk associated with smoking or a family history of myocardial infarction, thus clearly

echoing the concept that ED should prompt cardiac investigation in these patients [19].

A smaller investigation using 285 patients looked at the specific extent of CAD in relation to ED. They divided patients into age-matched groups based on acute single vessel disease, acute two or three vessel disease, or chronic coronary syndrome. A control group included those with normal angiography but with suspected CAD. They found that both multiple vessel disease and chronic coronary syndrome were independent predictors of ED. They also found that, in patients with established CAD, clinical presentation of ED comes before CAD in the majority of these patients by an average of 2–3 years [20].

Although ED has been found to affect about 75% of patients with chronic CAD, the topic is not generally an accepted part of cardiologists' patient evaluation. Reportedly 25% of these patients experience severe ED. The same study also delved into specific cardiac disease states and their association with various degrees of ED. They found that ED had a prevalence of about 60% in men with a history of prior myocardial infarction or coronary artery bypass surgery [14]. These authors echoed the assumption that these outcomes were related to endothelial dysfunction and atherosclerosis. They also theorized that the endothelial damage that occurred as a result of smoking, hypertension, lipid disorders, and diabetes diffusely affected vasculature of the body, including the arterial blood supply to the corpora cavernosa of the penis. They warned that ED may be the warning sign for undiagnosed CAD [14].

Obesity

Obesity, which is an independent risk factor for cardiovascular disease, is also associated with ED. Esposito et al. showed that intervention with the modification of lifestyle behaviors that led to weight loss and decreased cardiac risk also led to the improvement in erectile function [21]. A decrease in body mass index may reduce the risk of both ED and endothelial dysfunction in

obese men [21]. If obesity is positively associated with endothelial dysfunction and increased serum concentrations of vascular inflammatory makers, with what has been previously aforementioned, it would appear that a common pathway exists – patients suffer from both increased cardiovascular risk and ED per similar physiologic pathways [21].

In a more recent publication, Esposito et al. stated that obesity increases ED risk by 30–90% compared to controls. The authors again agreed that lifestyle changes aimed at reducing body mass index improves both erectile and endothelial function in men. In addition, they mentioned that Mediterranean-style diet may aid sexual function [22]. A separate literature review in 2006 was completely dedicated to the topic of the Mediterranean-style diet and its relation to sexual function [23]. They found that sexual function can improve in as little as 2 years through exercise and adoption of the Mediterranean-style diet [23, 24]. Specifically, men consuming more fruits, vegetables, nuts, whole grain, and olive oil as compared with controls were found to have an improved endothelial function score and improved levels of inflammatory markers [24].

Cardiac Risk Association with Severity of ED

A cohort of nearly 30,000 men evaluated through a screening questionnaire reaffirmed the previous concepts – patients with ED are more likely to suffer from cardiovascular disease. But the study also suggested that it is important to take into account the degree of ED. Authors stated that the greater the severity of ED, the greater the risk of presence of a medical comorbidity in the patient. Degree of ED severity can therefore be used as a prognostic marker for overall health risk, particularly cardiovascular disease risk [25]. Specific degrees of ischemic coronary disease and their association with ED in male patients were researched in a group of men with an average age of 56. These men underwent coronary angiography for the purpose of documentation of the

specific extent of coronary disease in order to compare this with sexual function. Sexual function was evaluated using an extensive questionnaire focused on sexual desire, erectile function, and ejaculation. A statistically significant correlation was made between ED and the number of coronary vessels involved. Those patients with one-vessel coronary disease were much more likely to achieve erection than those with two- or three-vessel disease [26].

It is well understood that only a small fraction of men with ED seek treatment. With the positive correlation between ED and cardiovascular risk, this underreporting by male patients to their healthcare providers should be taken seriously. Perhaps all men over a particular age should be screened for the presence of ED, much like the current recommendations for prostate cancer screening. If ED is present, it could be argued that these men should then undergo investigation for underlying subclinical cardiovascular disease. Endothelial dysfunction appears to be the link between the two disease entities. Increased awareness of the association between ED and cardiac disease should lead general practitioners to inquire as to the presence of ED symptoms in their male patients.

An important issue in patients with cardiac risk and ED is the safety of ED treatment. Topics including the risk of sexual activity eliciting a cardiac event and risk of drug interactions were addressed in an algorithm developed by the First Princeton Consensus Panel. They designated patients to low, intermediate, or high risk for the treatment of ED and participation in sexual activity. They support lifestyle interventions in patients with ED, including weight loss and increased physical activity [27].

Diabetes

The pathophysiology of ED in men with diabetes mellitus (DM) is complex and multifactorial. Men with DM, even those without significant comorbidities, suffer from a wide range of sexual dysfunction, including decreased desire and

sexual satisfaction [28]. Prevalence of ED among diabetic men that has been reported in the literature ranges widely. Unfortunately, many studies either have not differentiated between DM Type 1 and Type 2, or were not done in Type 1 diabetics. The prevalence of ED among men with DM in the MMAS was reported at three times the general population, or 28% versus 9.6%. A more recent study evaluated self-reported ED in males with DM Type 1 and found a prevalence of 20% overall and 47.1% in those 43 years of age or older [29]. Along with objective factors, such as decreased libido, men with DM Type 2 demonstrate organic causes with a decreased nocturnal penile tumescence [30].

Several cellular and molecular derangements have been described in diabetic men that contribute to the increased risk of ED in this population. Vascular injury is an important cause of ED in this population. At gross anatomical level, men with diabetes have an increased prevalence of cavernosal arterial insufficiency, thus impaired arterial response, on ultrasound [31]. An early study reported impaired endothelial-mediated vasodilation upon exposure to acetylcholine, a parasympathetic agent, in cavernosal tissue of diabetic men with ED [32]. Since this study, endothelial dysfunction in cavernosal tissue of diabetic men has been characterized by abnormalities including, but not limited to, increased apoptosis, oxidative stress, and overactivity of protein kinase C [33–36]. Thus, the effect of DM on penile vasculature is mechanically similar to its effect on other vascular structures throughout the body. Although advanced glycation end-products have been demonstrated in cavernosal tissue, their significance remains unclear [37]. While a majority of research has focused on diabetic ED as vascular phenomenon, there is at least correlational evidence that autonomic neuropathy plays a role in the development of ED in diabetics (53). The existence of ED in men with diabetes is also predicted by age and other complications of diabetes, such as retinopathy and depression [38].

A large national epidemiologic study was able to review a very large database of the diabetic male population through the use of managed care

claims [39]. The study used this database to determine the prevalence of diabetes in men with and without ED. The prevalence of diabetes in men with ED was found to be much higher than the general population. Twenty percent of men suffering from ED were also found to have been diagnosed with diabetes; this is in comparison to only 7.5% in men without ED [39]. Given this finding that men with ED are twice as likely to have diabetes as those without ED, the diagnosis of ED may indeed serve as a useable marker for diabetic screening. A similarly large national study in 2005 evaluating men with ED found four specific comorbidities to be significantly prevalent among men carrying the diagnosis of ED. The authors even suggested that ED may be used as an observable marker for all four: hypertension, hyperlipidemia, depression, and diabetes [40].

Treatment of ED in Diabetics

Although treatment of ED is discussed later in the book, it is prudent to mention here that certain trials in the past decade have been specifically dedicated to the treatment of ED in diabetic males. A retrospective analysis of data from twelve placebo-controlled trials evaluated the efficacy and safety of tadalafil for the treatment of ED in diabetic males. They confirmed that diabetic men have more severe ED than controls at baseline. Interestingly, they also found that baseline erectile function in the diabetic males correlated inversely with baseline HbA(1)c levels. They concluded that although ED was found to be more severe in the diabetic population, response to tadalafil was only slightly lower than controls for the treatment of ED [41].

Metabolic Syndrome

An estimated 47 million people in the USA have metabolic syndrome [42]. Metabolic Syndrome is a combination of medical disorders that

increase an individual's risk for CAD and diabetes. Components of the syndrome include abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance, prothrombotic states, and proinflammatory states [42]. Correlation between metabolic syndrome and ED has been well established and mirrors the association of CAD or diabetes with the syndrome. Reported prevalence of ED in patients with metabolic syndrome falls between 26.7% and virtually 100%, and this prevalence increases as the number of components of the metabolic syndrome increases [43, 44].

Of mention, hyperhomocysteinemia is an emerging risk factor for the development of ED in diabetic men. Further studies are needed to evaluate the exact mechanism by which this metabolite exerts its effect.

Respiratory Disease and Erectile Dysfunction

Chronic Obstructive Pulmonary Disease

There is a clear association between respiratory diseases and ED independent of comorbid conditions, such as peripheral vascular disease or coronary artery disease. Chronic obstructive pulmonary disease (COPD) is a common chronic disease in men. Dyspnea and hypoxemia diminish a patient's functional capacity and can lead to ED. The prevalence of ED in patients with respiratory disease has been reported as high as 75% [45]. Several investigators have demonstrated that as pulmonary function tests (i.e., FEV1, FRC, PaO₂) worsen, so does a man's erectile function [45].

Pathophysiology of ED in patients with COPD is multifactorial. Disruption of the hypothalamic–pituitary–gonadal axis has been reported in patients with COPD [46]. Reversal of hypoxemia with long-term oxygen has been shown to be effective in improving impotence [47].

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is also a common chronic disease. It has been reported in as many as 10% of men over 40 years old [48]. Recurrent intermittent hypoxemia and transient increases in sympathetic tone during apneic episodes result in an increased risk of daytime somnolence, hypertension, and ischemic cardiovascular events. Erectile dysfunction has also been found to be associated with OSA [49]. This association appears to be strongest in the most severe cases of OSA [50]. Causes for ED in these patients include hypoxemia-driven neural damage, microvascular endothelial damage from increased sympathetic tone and hypertension, low gonadotropin secretion, and psychosocial abnormalities, including daytime somnolence and depressed mood [51, 52].

Neurogenic Factors

The proportion of ED that is currently attributed to pathophysiology of the neurological system is likely underestimated. In the central nervous system, the amygdala, medial preoptic area (MPOA) and periventricular nucleus (PVN) of the hypothalamus, and the hippocampus are all involved libido and erection [53].

Parkinson's Disease and Alzheimer's Disease

The prevalence of ED in men with Parkinson's disease (PD) exceeds that of age-matched controls [2]. The pathophysiology of ED in patients with PD is multifactorial, as PD is characterized by significant psychiatric comorbidities and dysautonomia in addition to the destruction of dopaminergic cells in the substantia nigra [54]. The specific pathophysiology of ED in Alzheimer's disease has not been elucidated but appears to be independent of concomitant risk factors such as age [55].

Multiple Sclerosis

One case-controlled study found ED to occur five times more often in men with Multiple Sclerosis (MS) compared to those with other chronic diseases [56]. Over 50% of men with MS report either one or more of altered genital sensation, decreased libido, decreased intensity of orgasm, and increased time for arousal [57].

Epilepsy

Epileptic men also have an increased prevalence, with 15–57% experiencing ED [58, 59]. Temporal lobe epilepsy, specifically, may exert its effects on erectile function through a derangement in the hypothalamic–pituitary axis (HPA). More pronounced in times of epileptic discharge, this derangement results in hypogonadotropic hypogonadism and hyperprolactinemia [59].

Spinal Cord Injury

The nature of ED caused by spinal cord injury (SCI) is dependent on the acuity and location of the injury. Estimates of the preservation of erectile function vary widely, and are as high as 95% for reflexogenic erection [60]. Erections in men with SCI are characterized as reflexogenic when the stimulus is tactile or psychogenic when visual, auditory, or memory serve as the stimulus [61]. Since erections are the result of parasympathetic output to the penis arising from S2 to S4, reflexogenic erection is maintained in suprasacral injuries or those not involving the lower motor neurons (LMN) [62].

Cerebrovascular Accidents

Cerebrovascular accidents (CVA) are another important cause of sexual dysfunction and, specifically, ED. As with other neurological diseases, the pathophysiology of ED in these patients is

multifactorial and related to the physical, psychological, and social consequences of stroke. Sexual complaints in stroke patients include the loss of libido, frequency of sexual intercourse, ED, and sexual satisfaction [63]. These complaints are most attributable to interpersonal variables, such as the inability to discuss sexuality with a spouse or changed attitude toward sex, but the fear of impotence is a significant variable. Erectile dysfunction increases from 36% pre-stroke to 76% poststroke, and is associated with the degree of depression poststroke [63]. In a study that specifically assessed ED in stroke patients, approximately half of stroke patients reported ED [64]. A more important finding in this study was that preexisting diabetes, hypercholesterolemia, obesity, and smoking increased the prevalence of ED after stroke [64].

The neurogenic component of ED in stroke patients is complex due to the various central structures involved in erectile physiology and the complexity of stroke distributions. Only one study to date has attempted to associate lesions on MRI with sexual dysfunction. Erectile dysfunction was only weakly associated with lesions involving the right pons [65]. While the specific nature of neurological insults that determine ED in stroke patients is yet to be determined, it is evident that psychosocial factors are an important determinant of sexual dysfunction after stroke.

Peripheral Nerve Injury

Peripheral nerve injury is another important cause of ED, especially in patients undergoing prostatectomy. Other causes of peripheral nerve injury include bicycle riding and acute pelvic trauma. Several authors have reported genital numbness and increased the incidence of ED among cyclists. The pathophysiological basis for ED in cyclists is thought to be neurogenic as well as vasculogenic [66–68].

A recent systematic review of the literature found that the reported incidence of ED after radical prostatectomy with nerve sparing technique varies widely due to methodology.

In 14 studies, the mean incidence of ED was 50% and 34% for bilateral and unilateral nerve-sparing surgery, respectively [69]. Nerve-sparing techniques are based on the seminal study by Walsh and Donkers in which they identified the path of the nerves to the corpus cavernosa [70]. They identified the branches of the pelvic plexus traveling through the urogenital diaphragm adjacent to the prostatic capsule and then adjacent to and through the wall of the membranous urethra. Not surprisingly, they found that men with tumors that did not invade the prostatic capsule and were amenable to salvage of this structure had reduced rates of ED [70]. Recovery and improvement in erectile function after radical prostatectomy has been reported to continue up to and beyond 2 years postoperation, perhaps indicating healing of injured nerves [71, 72]. Loss of erectile function is also related to anatomical changes in the penis, specifically fibrosis of the penis due to prolonged lack of tumescence. In animal models, histological changes occurring after nerve injury are prevented by regular pharmacologically induced erections [73].

Psychogenic Risk

The number of cases of ED attributed purely to psychogenic etiology have greatly declined in the past several decades. Younger men who complain of ED are more likely to have a psychogenic component than older men. Psychogenic ED is generally classified into generalized and situational pathologies and further subclassified (Table 5.1) [74].

This classification scheme has been criticized as it fails to account for advances in neurobiology that have linked certain psychiatric

illnesses with neurochemical and neurohormonal derangement [75].

Depression

Depression and ED are often comorbid conditions. Several epidemiologic studies report men with ED are more likely to report depression, and that this association is independent of associated comorbidities, demographic factors and medications [76]. In a study of men diagnosed with Major Depressive Disorder but not yet treated, almost half had trouble sustaining an erection and reported decreased sexual desire [77].

Endocrine Risk Factors

Testicular Failure

In recent years, there has been increasing interest in the study of aging males. Testicular failure increases with age as serum testosterone levels gradually decline. This process is not universal. When it does occur, there is significant variability in the age at the onset and the degree of the androgen decline associated with age.

Androgen Deficiency

The estimated prevalence of androgen deficiency among men 40–70 years of age ranges from 12% to 45%. Approximately 481,000 new cases of androgen deficiency are diagnosed yearly in the USA. Physiologic levels of testosterone support several critical processes involved in penile erectile response, including the maintenance of libido and energy levels, in addition to the cascade of events mediated by nitric oxide leading to arteriolar dilatation and relaxation. Screening for hypogonadism in men initially presenting with ED can help identify these men.

Table 5.1 Classification of psychogenic ED

Generalized psychogenic erectile dysfunction	Situational psychogenic erectile dysfunction
Unresponsiveness	Partner-related
Inhibition	Performance-related
	Psychological stress or adjustment-related

Hypogonadism

In cases of ED and hypogonadism, recent randomized controlled trials suggest that patients who are initially refractory to type V phosphodiesterase (PDE5) inhibitors (sildenafil, vardenafil, and tadalafil) can be rescued by the concurrent administration of testosterone with PDE5 inhibitors. The administration of testosterone alone, without PDE5 inhibitors, has also been shown to improve erectile function in hypogonadal men. Androgen deficiency has been shown to result in penile tissue atrophy, increased adipose tissue within the subtunical region, and severe venous leak resulting in ED. All of these effects can potentially be reversed by the administration of testosterone.

A number of distinct pathways of the endocrine system lead to ED when functioning abnormally. Several studies show that hypogonadism of any cause is an uncommon cause of ED [78, 79]. The role of testosterone and other androgens in the achievement and maintenance of penile erection is controversial due to the lack of standardization in defining low testosterone. A recent study found that the prevalence of “low testosterone” in men with ED was largely dependent on the accepted definition of this disease state. Reported prevalence increased from 7% to 47% for definitions of testosterone level less than 200 ng/dL versus less than 400 ng/dL, respectively [80].

The role of androgens in erectile physiology as demonstrated in the animal model is to potentiate the effects of neurologic and vascular/endothelial mechanisms of erection. Although tumescence is possible with decreased testosterone, the quality of the erection may be diminished. Importantly, the efficacy of PDE5 inhibitors is greatly diminished in the absence of androgens [81, 82]. Furthermore, in rats, dihydrotestosterone is the primary androgen responsible for erectile physiology at the level of the endothelial cell [83]. This decline in serum testosterone level can be age-related or the result of hypogonadism of any cause.

A recently published study evaluated the prevalence of both hypogonadism and depression in men presenting to an ED clinic. They also tested the correlation of hypogonadism and the

presence of depressive symptoms. They indeed found hypogonadal men to be more likely to have overt depression scores compared to eugonadal controls. The authors derived the conclusion that depression symptoms are strongly associated with hypogonadism and that physicians should consider the evaluation of testosterone levels in men with overt symptoms of depression [84].

Hyperprolactinemia

While hyperprolactinemia is often clinically associated with the existence of ED and hypoactive sexual desire, the prevalence and pathophysiology of this association are debated in the literature. The prevalence of hyperprolactinemia in men with ED or sexual dysfunction ranges from 1.5% to 10% in recent literature [85, 86]. While several studies support the classic hypothesis that hyperprolactinemia causes ED through the suppression of GnRH, there is no consensus as of yet [87–89]. While severe hyperprolactinemia is a risk factor for sexual dysfunction, the role of moderate hyperprolactinemia in the pathophysiology of ED is unclear [85]. Thus, as with androgens, it is unclear if pathophysiologic findings from clinical studies and animal models are applicable to the clinical evaluation of ED. There is also evidence that prolactin may have a dichotomous role in erectile physiology. A recent study found that men with prolactin levels below 5 ng/mL had increased prevalence of arteriogenic ED, while men with hyperprolactinemia only had an increased prevalence of hypoactive sexual desire [90].

Thyroid Disease

Both hypothyroid and hyperthyroid states are associated with ED, though the specific pathophysiology remains elusive. A recent study compared men with thyroid dysfunction to controls and reported that men with both hypothyroidism and hyperthyroidism had significantly increased the

prevalence of and more severe ED. Overall, 79% of men with thyroid dysfunction had ED compared to 34% of controls. Both hyperthyroid and hypothyroid men had a prevalence of ED that exceeded the prevalence of ED in the control group. Additionally, both groups had significant response to treatment [91]. While extrapolation of specific physiologic mechanisms from clinical treatment is limited, these findings suggest that thyroid dysfunction acts at multiple sites to cause ED. There is some evidence that hypothyroidism causes a decline in both testosterone and steroid hormone binding globulin (SHBG) [92].

Drug-Induced ED

Erectile dysfunction is a common adverse effect of a number of drugs, and it often has a great effect on patient compliance [93]. This subject as a risk factor is lightly discussed here and further discussed in more detail later in the textbook. It is important to recognize that many of the drugs associated with ED are used to treat conditions that are themselves risk factors for ED, thus the interpretation of ED in the setting of pharmacological therapy is often difficult in the clinical setting.

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) have gained notoriety as a common cause of several manifestations of sexual dysfunction. SSRI-induced ED rather than sexual dysfunction, though, is rarely reported in the literature and is limited mostly to case reports [94, 95].

Antihypertensive Agents

Several antihypertensive agents have been implicated in ED, yet the evidence is limited. Older thiazide diuretic treatments have been associated with mild effects on erectile function [96, 97].

Many of these studies have limited clinical implications as they were conducted with chlorthalidone, a thiazide-like diuretic. A recent study suggested that beta-blocker-induced ED is likely psychogenic rather than organic [98]. Clonidine is reported to cause ED in both human and animal studies through agonism of central alpha-2 adrenoreceptors [99, 100].

Statins

Statins are HMG-CoA reductase inhibitors that are a commonly used medication for the treatment of hyperlipidemia. Do et al. conducted a study to investigate the association between exposure to statins and the occurrence of ED. The study was limited to males age 18–30. They found a statistically significant association for statins with induction and worsening of ED. Further studies are needed to distinguish the severity of the effect on ED between the many different statin drugs that are currently in use [101].

Antipsychotics

Antipsychotic medications are also implicated in ED. These drugs exert their effects primarily by antagonism of dopamine receptors but have effects on several other receptors [102]. In addition, dopamine antagonism causes hyperprolactinemia which contributes to the sexual dysfunction associated with these drugs [103].

Antiandrogens

Antiandrogens are a well-known cause of sexual dysfunction and ED. In recent studies, finasteride has been shown to cause minimal ED at higher doses (5 mg) for prostate cancer prevention, and almost no effect on erectile function at low doses (1 mg) for the treatment of alopecia [104].

Illicit Substances and Nicotine

Several illicit substances cause ED. In addition, men on methadone maintenance therapy for heroin dependence have been reported to have significant impairment of erectile function [105]. The use of tobacco products, and specifically nicotine, is associated with ED in both chronic and acute exposure. Nicotine produces vasoconstriction through its actions on endothelial cells through a likely underproduction and degradation of nitric oxide [106, 107]. A recent study of healthy men between the ages of 18 and 27 reported that the use of nicotine gum immediately decreased erectile response to visual stimuli despite unchanged subjective measurements of sexual arousal [108]. This study may imply an immediate neurogenic and hemodynamic response of the penile tissue to nicotine. Furthermore, chronic cigarette smoking is also associated with an independently increased risk of ED and clinically significant damage to penile vasculature [1, 109].

Ethanol

The role of ethanol, while classically thought to impede erectile function, has been less clear in the literature. Despite the association of alcohol consumption and sexual activity, very little objective evidence exists on the effect of acute ethanol intoxication on erectile function. The data on chronic ethanol exposure is also mixed. Ethanol exposure in an animal model showed histologic evidence of both endothelial damage and metabolic dysfunction. Impairment of smooth muscle relaxation due to endothelial dysfunction was pronounced while neurogenic smooth muscle relaxation remained intact [110].

Age and Chronic Illness

There is no consensus as to whether ED is a non-pathologic, natural aspect of aging in healthy males, though older males do have higher rates

of ED [111]. The association between naturally declining testosterone level in older males, so-called andropause, and ED, is complex, but no clear association is found to date [112]. Interestingly, penile vibrotactile sensation of the penis decreases significantly with age, but this has not been directly linked with ED [113].

Approximately 82% of men with chronic renal failure (CRF) on hemodialysis have some degree of erectile function, with 45% having severe ED [114]. Additionally, regardless of treatment, patient with CRF have significantly decreased mean nocturnal penile tumescence when compared to both normal and chronically ill controls [115]. The pathophysiology of ED in patients with CRF is complex. A majority of men with CRF have hyperprolactinemia [116]. Uremia also interferes with the HPA such that oligospermia, azoospermia, and impaired steroidogenesis with elevations in LH are common in uremic men [117, 118]. Zinc deficiency has also been postulated as a potential cause of ED in uremic men and has been targeted for possible therapeutic interventions [119].

Benign Prostatic Hypertrophy and Lower Urinary Tract Symptoms

Lower urinary tract symptoms (LUTS), the classic symptoms of benign prostatic hypertrophy (BPH), were present in 72% of males with ED versus only 38% of males with normal erectile function in a broad epidemiological survey of men [120]. A later study identified overflow urinary incontinence and incomplete emptying of the bladder as the most important LUTS in predicting the presence of ED [121]. Recently, a longitudinal analysis of the Health Professional Follow-up Study supported that men with LUTS are at an increased risk for developing ED. Thus, this was the first study to develop a temporal relationship between ED and LUTS, and possibly a causal link [122].

Key Points

- Many of the risk factors for ED are easily treatable.
- Lifestyle modifications, including smoking cessation, increased physical activity, decreased obesity, and lowering cholesterol can all lead to the improvement of ED.
- Risk factors for ED and for cardiac disease are greatly overlapping.
- There is documented correlation between the degree of cardiovascular disease and the severity of ED.
- Screening for ED may lead to early diagnosis of cardiovascular disease.

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Chapter 6

Making the Diagnosis of Erectile Dysfunction

Edgardo Becher and Amado Bechara

Abstract When we speak about diagnosing ED we refer to two major aspects of this diagnostic approach: diagnosis of the condition and diagnosis of the cause. Unfortunately, many physicians still consider ED a low priority during their patient's medical evaluation; due to the ignorance of the relationship this condition has with different risk factors. This situation is worsened by possible patient misinformation and sometimes embarrassment to seek help for this symptom. From the epidemiologic point of view, ED is related to several major diseases: hypertension, cardiovascular disease, dyslipidemia, diabetes, and depression (Seftel et al. *Journal d'Urologie* 171, 2341–2345, 2004). This implies that ED is part of the presentation of those prevalent diseases, and the concept of asking about ED, especially in the higher risk populations, should be encouraged among physicians.

Keywords Hypertension and ED • Cardiovascular disease and ED • Diabetes • Dyslipidemia

Introduction

Sildenafil's launch in 1989 set a landmark not only on the treatment, but also on the assessment of patients with erectile dysfunction (ED).

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Detecting the symptoms of ED, frequently its cause or risk factors and the indication *d'amble* of a phosphodiesterase type 5 inhibitor (PDE5-I), is a typical scenario during medical consultation. Hence, specialized diagnostic tests almost routinely performed in the past are currently limited to special cases, as discussed later in this chapter.

When we speak about diagnosing ED, we refer to two major aspects of this diagnostic approach:

1. *Diagnosis of the condition*: The diagnosis of the inability to achieve or maintain an erection rigid enough for satisfactory sexual intercourse rises mainly from patient complaint and physician evaluation.
2. *Diagnosis of the cause*: The diagnosis of the cause/s generating ED, which can arise from medical history, a psycho-physic evaluation and relationship issues.

Unfortunately, many physicians still consider ED a low priority during their patient's medical evaluation; due to the ignorance of the relationship this condition has with different risk factors. This situation is worsened by possible patient misinformation and sometimes embarrassment to seek help for this symptom. Some aspects which influence the screening of this condition, and the low consultation rate related to its high prevalence, are patient-related issues (shame, fear, ignorance, prejudices, lack of knowledge of sexual function, acceptance, and lack of interest), or physician-related issues (lack of exposure to sexual medicine in medical school, prejudices towards the patient's age, personal values, physiologic misconceptions [such

as sexual activity augments cardiovascular risk], lack of interest, lack of time, and socioeconomic factors).

From the epidemiologic point of view, ED is related to several major diseases: hypertension, cardiovascular disease, dyslipidemia, diabetes, and depression [1]. This implies that ED is part of the presentation of those prevalent diseases, and the concept of asking about ED, especially in the higher risk populations, should be encouraged among physicians.

Even among specialists such as urologists, who are frequently consulted for ED, there is a need to understand the strong relationship ED has with serious risk factors like the metabolic syndrome and cardiovascular disease. This condition is defined by the ATP-III guidelines as including one of the following components in males: abdominal obesity (waist circumference greater than 102 cm in men), elevated triglycerides (greater than 150 mg/dL to 1.69 mmol/L), low levels of HDL cholesterol (less than 40 mg/dL to 1.04 mmol/L in men), arterial hypertension (blood pressure greater than 130/85 mmHg), and fasting glucose greater than 110 mg/dL to 6.1 mmol/L [2].

Diagnosis of ED: Basic Diagnostic Tools

Medical and Sexual History

The first step in diagnosing ED is to confirm the symptom, since frequently the patient might confuse difficulty to maintain an erection with premature ejaculation or other sexual dysfunctions. It is important to establish the duration of the symptom (onset), as well as its severity and frequency (once, always, situational) to help confirm the dysfunction and help identify the diagnosis. The interviewer should use clear and simple language and make the patient feel as comfortable as possible to discuss his situation. Language too technical and distant will jeopardize the patient's understanding and expression. Frequently, the patient needs *permission* to talk

about ED with his physician, since he may think his doctor could feel uncomfortable with the discussion. This is easy to overcome by *allowing* the patient to discuss the issue, asking direct questions about the patient's sex life [3]. History-taking should follow a formula allowing the interviewer to identify the different risks and predisposing factors, with the intention to act on each of them with a clear therapeutic purpose (Fig. 6.1). Also, a thorough review of the patient's current medications is mandatory to rule out etiology and potential treatment contraindications.

One important aspect to explore during the interview is the patient and partner's degree of knowledge regarding the normal sexuality changes with aging, such as the progressive decrease of testosterone levels. This decrease may be due to a lower number of Leydig cells, a decrease of the LH peaks, an impaired tissue perfusion, and/or an increase of the serum sex-hormone binding globulin (SHBG).

The concept that sexual dysfunctions are a part of the normal sexual changes accompanying aging is a common myth. It is important to explain to the patient that while the sexual responses may change with aging, they do not disappear. There are many reports supporting the concept of a continuing sexual interest and activity in the elderly, which could represent even a larger proportion of subjects if non-coital sexual activity were considered.

The Massachusetts Male Aging Study showed a clear relationship of ED with age and reported a prevalence of ED as 52% of men over 50 years old [4].

A decrease of sexual interest with age may reflect a hormonal imbalance. Also, there may be an adrenergic over-sensibility or hyperactivity, and a decrease of penile smooth muscle resulting in a lower intensity arousal phase, thus translating into difficulty to obtain and maintain an erection. The ejaculatory volume and orgasmic intensity is lower, and with a decrease of ejaculatory contractions, the detumescence phase is faster and the refractory period is longer.

These changes need to be discussed with the patients as they often result in a lower sexual frequency, a longer time needed to achieve a

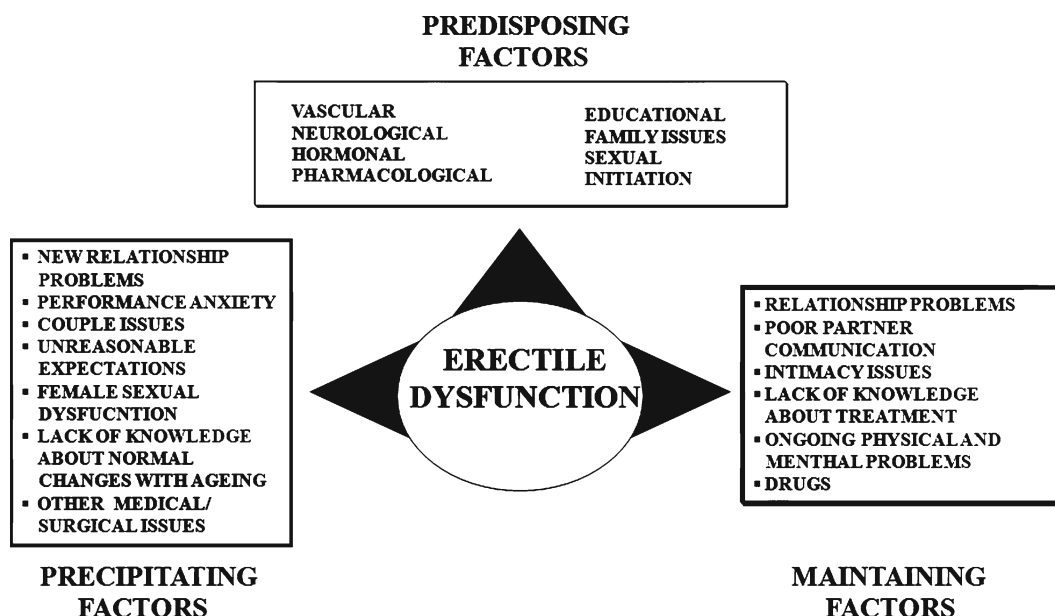


Fig. 6.1 Risk factors for erectile dysfunction [15]

rigid erection, a need of a greater stimulus to obtain a similar response, lower penetration rigidity, lower ejaculatory volume, and faster detumescence. It is also important to discuss the normal physiologic changes which occur in their female partner, such as the physical and psychological changes occurring during menopause and female sexual dysfunction.

Physical Examination

A focused physical examination is mandatory in assessing the patient complaining of ED. Although not always revealing the exact etiology, it will certainly help in determining risk factors such as gynecomastia, hair distribution, abdominal circumference, peripheral pulses and measurement of the blood pressure and weight. Special attention should be given to external genitalia including penile size, consistency, presence of penile plaques, foreskin retraction, pre-pubic fat, and testis shape and consistency. Rectal exam is important to assess rectal tone and reflexes as well in men over 50 years old who have a risk for prostate cancer [5]. One important

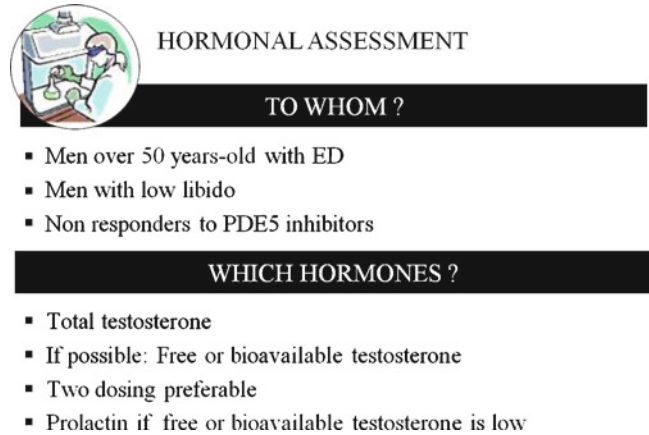
aspect when evaluating a patient with ED is to consider the degree of cardiovascular risk.

Laboratory Tests

In view of the strong relationship of ED with vascular risk factors, it is important to dose fasting glucose and lipids in every patient consulting for ED if these have not already been performed.

Serum testosterone needs to be dosed, especially in those subjects with low libido and/or poor response to PDE5-Is, although many clinicians consider it mandatory in every patient with ED, since sexual function could be a marker for hypogonadism [6]. This controversy rises from many factors: clinical manifestations of hypogonadism is diverse and rarely complete, severity is also variable, and more than one laboratory measurement is required as there is a 40% rate of false positive results. If this test is not part of the initial assessment, a more complete hormonal evaluation could be ordered when considering additional testing (Fig. 6.2).

Since the majority of the circulating testosterone is bound to the SHBG and to the albumin

Fig. 6.2 Hormonal assessment

(bioavailable testosterone), the free portion of circulating testosterone is most important in terms of function, though a reliable laboratory dosing is very expensive and not widely performed. Calculated free testosterone (CFT) is a safe and reliable method to assess free testosterone using the values of total testosterone and SHBG on a table designed by Vermuelen [7]. Another option for finding free and bioavailable testosterone is to use a formula through the ISSAM webpage entering albumin, SHBG, and total testosterone values, found at: <http://www.issam.ch/freetesto.htm>.

Gonadotrophins (LH and FSH), dehydroepiandrosterone (DHEA) and its sulfated form (DHEAS), prolactin, and thyroid hormones are only part of advanced hormonal assessment in special endocrine situations and treatment monitoring; routine use of these studies should be discouraged.

Establishing Cardiovascular Risk

It is not uncommon to find risk factors unknown by the patient such as diabetes, dyslipidemia, or hypertension [8, 9]. In 1999, a panel of experts elaborated the guidelines for cardiovascular evaluation in patients with ED [10], then revised and published them for the second Princeton consensus. These guidelines recommend an evaluation for ED patients, and establish three levels of cardiovascular risk [11]:

Low-risk category: Asymptomatic; <3 risk factors for coronary artery disease ([CAD] excluding gender); uncomplicated past myocardial infarction (MI); left ventricular dysfunction (LVD)/congestive heart failure (CHF) (New York Heart Association [NYHA] class I); mild, stable angina (evaluated and/or being treated); post-successful coronary revascularization; controlled hypertension; mild valvular disease.

Intermediate-risk category: >3 risk factors for CAD (excluding gender); recent MI (>2, <6 weeks); moderate, stable angina; LVD/CHF (NYHA class II); non-cardiac sequelae of atherosclerotic disease (e.g., stroke, peripheral vascular disease).

High-risk category: High-risk arrhythmias; unstable or refractory angina; recent MI (<2 weeks); LVD/CHF (NYHA class III/IV); uncontrolled hypertension; moderate-to-severe valvular disease; hypertrophic obstructive, and other cardiomyopathies.

Additionally, each level has corresponding management recommendations [10]:

Low-risk category: Primary care management, consider all first-line therapies, reassess at regular intervals (6–12 months).

Intermediate-risk category: Specialized CV testing (e.g., exercise treadmill test [ETT], Echo), restratification into high risk or low risk based on the results of CV assessment.

Fig. 6.3 Sexual Health Inventory for Men (SHIM) questions

Over the past 6 months:

1. How do you rate your confidence that you could get and keep an erection?
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?
5. When you attempted sexual intercourse, how often was it satisfactory for you?

High-risk category: Priority referral for specialized CV management, treatment for sexual dysfunction to be deferred until cardiac condition stabilized and dependent on specialist recommendations.

function related to the prior 6 months, and has a total score ranging from 5 to 25 (Fig. 6.3): a score of 22–25 means normal erectile function, 17–21 mild ED, 12–16 mild to moderate ED, 8–11 moderate ED, and <7 severe ED [13].

Scales (Self-Administered Questionnaires)

Although not mandatory, questionnaires might be helpful to assess the presence or severity of ED, especially in those settings where the interviewer is not familiar with the condition and when a measurable clinical response is needed. Although questionnaires are a subjective tool with information from the patient's interpretation and self-response, it can serve as objective data to assess treatment response or disease progression. One of the most widely used questionnaires is the International Index of Erectile Function (IIEF) [12]; this is a 15-item questionnaire covering five domains including desire, erection, orgasm, ejaculation and satisfaction, with scores ranging from 1 to 5 per question. A lengthy questionnaire, it is often used in clinical trials, but might be a tedious task during consultation. An abbreviated version of this questionnaire is the IIEF-Erectile Function Domain, one comprised of six questions focused on the erection domain and sexual satisfaction with a maximum score of 30. Men with a normal erectile function will have a score of ≥ 25 .

Another short questionnaire derived from the IIEF is called the Sexual Health Inventory for Men (SHIM) includes five questions on erectile

What Do We Get from the First Consultation for ED?

An integrated approach looking beyond the symptoms might detect diabetes, dyslipidemia, hypertension, hormonal imbalance, Peyronie's disease, cardiopathy, phobic disorders, depression, and female sexual dysfunction, among other conditions. It may also be the first opportunity to educate the patient and his partner on sexual function. This approach will help many patients find treatment for ED and potentially detect life-threatening diseases.

Additional Diagnostic Tools

This section examines those tests performed to establish an etiological diagnosis of ED. The broader knowledge of the physiology and pathophysiology of erectile function, the variable specificity and sensibility of the current diagnostic tests, the availability of effective oral treatment, and the current trend to evaluate and treat patients while considering patient quality of life, has changed the paradigm of finding the ultimate cause of ED. A more goal-oriented

approach to diagnosing ED is currently used, after evaluating risk factors and modifiable negative habits and initiating a first-line therapy likely including PDE5-Is [14, 15].

A thorough evaluation of a specific cause of ED is limited to certain situations in which a confirmed diagnosis or modified therapeutic decision is needed.

In general, candidates needing a more specific evaluation are:

1. Nonresponders to oral medication
2. Post-traumatic ED
3. Those considering a penile implant
4. Peyronie's disease patients considered candidates for surgery
5. Post-priapism ED
6. Life-long (primary) ED
7. Medico-legal situations
8. Per patient's request.

Nocturnal Penile Tumescence and Rigidity Test

Nocturnal and morning erections are physiologic events occurring during rapid eye movement (REM) sleep. Nocturnal erections provide oxygenation of the penile tissues which is necessary to preserve function and tissue trophism. A normal man will have between four and six erections during sleep. Evaluation of nocturnal erections has been performed since the early 1970s [16]. This evaluation can be done in conjunction with a full sleep lab (rarely indicated), or as a stand-alone ambulatory test using the RigiScan® device (Fig. 6.4). The RigiScan assessment should take place over the course of two nights, with the goal of an erectile event of at least 60% rigidity recorded on the tip of the penis lasting for 10 min or more; this outcome is considered indicative of

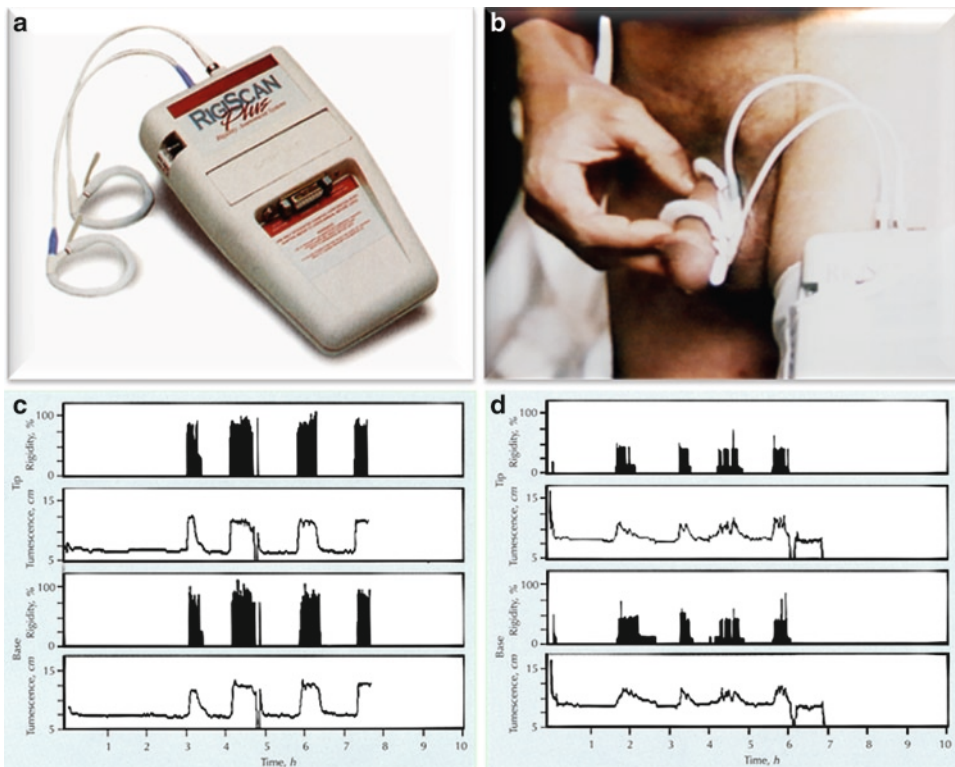


Fig. 6.4 The RigiScan® Test: (a) RigiScan® Patient Unit, (b) device on the patient, (c) normal tracing, and (d) abnormal tracing

a functional erectile mechanism [17]. In theory, a man who has normal erectile episodes during sleep and complains of ED could potentially be experiencing psychogenic ED; therefore the evaluation of nocturnal erections might distinguish organic from psychogenic ED [5].

Pharmacological Erection Test

The pharmacological erection test involves the intracavernosal injection of vasoactive agents. The test should be performed with the patient in a comfortable, private room, with or without visual and/or self-stimulation. It is a practical and simple office-based diagnostic tool, with normal response resulting in an erection lasting 30 min and rigid enough for penetration (Fig. 6.5).

Although it does not provide a direct vascular evaluation, it is useful in the following settings:

- Indirect evaluation of corporo-occlusive mechanism. A normal response (rigid erection) may still be obtained in the presence of arterial insufficiency; however, a normal response demonstrates the integrity of veno-occlusive function [18–20].
- Evaluation of penile curvatures either congenital or due to Peyronie's disease. It lets the clinician assess the degree of the curvature and plan a surgical correction if necessary.

- Evaluation of the erectile response and demonstration of a self-injection program. The titration phase will help determine the right dose and drug choice.

The most widely used drugs are papaverine, phentolamine, and alprostadil (semisynthetic prostaglandin E1); the latter is the most commonly used as a single drug, but mixtures of papaverine and phentolamine, or the three drugs together (known as *trimix*), are being used globally [21, 22]. There is no consensus on the standard drug or dose to use, although 20 mcg of alprostadil or 1 mL of trimix are the most frequently used [23].

Duplex/Doppler Penile Ultrasound

This test involves the hemodynamic evaluation of the cavernous arteries and penile structures through a color duplex/Doppler (DDPU) ultrasound using a high frequency linear probe (7.5–10 MHz). This gives the investigator insight on the arterial blood supply of the penis, the veno-occlusive mechanism, corporal and tunical fibrosis or plaques, and an evaluation of penile deformities. The examination is performed after an intracavernosal injection of a vasoactive drug as a pharmacologic erection test and followed by self-stimulation and/or redosing with multiple injections until an erection similar to the best at-home erection is achieved.

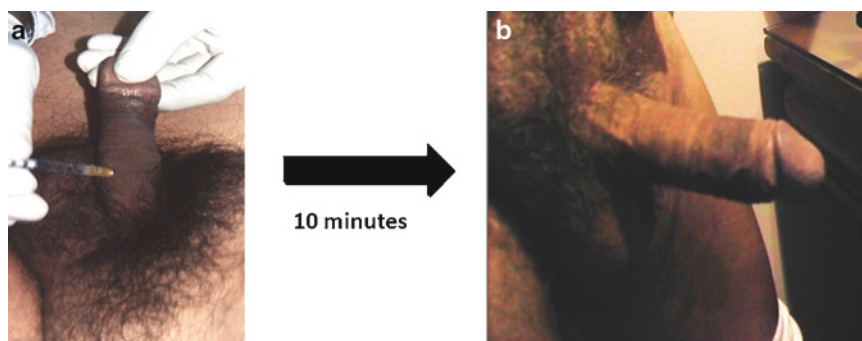


Fig. 6.5 Pharmacological erection test. (a) Vasoactive drugs are injected intracavernosally. (b) Full response at 10 min post-injection

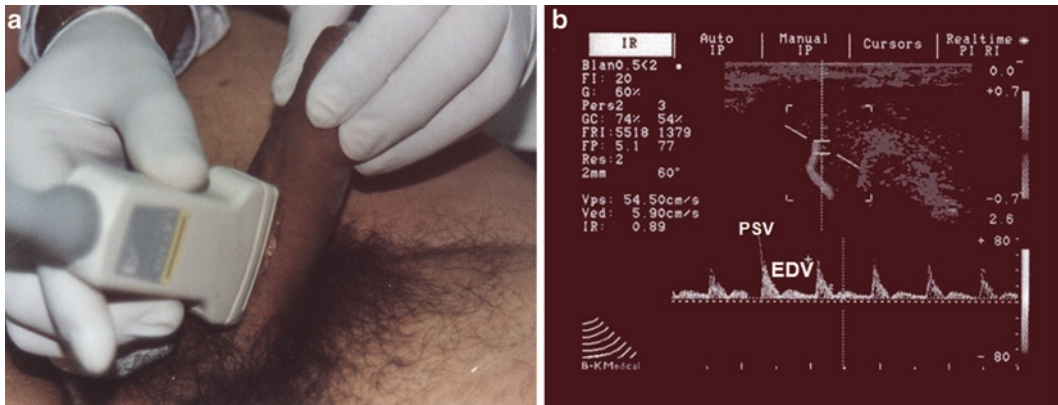


Fig. 6.6 Duplex/Doppler Penile Ultrasound. (a) High frequency probe on the dorsal aspect of the penis. (b) Cavernal artery tracing showing Peak Systolic Velocity (PSV) and End Diastolic Velocity (EDV)

Common indications of duplex/Doppler penile ultrasound (DDPU) are:

- Assessment of patients who do not respond to oral or intracavernosal vasoactive agents.
- Patients considered candidates for revascularization surgery.
- Priapism.
- Peyronie's disease patients considered candidates for reconstructive surgery.
- When an etiological diagnosis is necessary or requested by the patient.
- Medico-legal situations.

The original technique was introduced by Lue and Hricak in 1985 [24], and the following parameters are evaluated during DDPU at 5 and 20 min post-injection of the vasoactive agent [25–27] (Fig. 6.6).

- Peak systolic velocity – normal values: ≥ 30 cm/s
- End diastolic velocity – normal values: ≤ 5 cm/s
- Resistance Index – normal values: ≥ 0.85 – 0.9 .

Dynamic Infusion Cavernosometry and Cavernosography

This test was widely used until the late 1990s when a goal-directed approach was adopted and PDE5-Is became available. Now its indication is restricted to specific situations where revascularization, or more rarely, venous surgery are considered.

This is a dynamic test performed under high doses of intracavernosal vasoactive agents to maximize smooth muscle relaxation. This minimally invasive test involves the insertion of two intracavernosal butterfly needles (one for pump-infusion and one for pressure monitoring), with three phases recorded:

- *Phase 1*: recording of intracavernosal pressure curve after injection.
- *Phase 2*: recording of the cavernosal pressure decay curve from 150 mmHg in 30 s and/or flow to maintain a rigid erection with a pressure of 90–100 mmHg.
- *Phase 3*: Evaluation of the arterial Doppler signal when exposed to a suprasystolic intracavernosal pressure [5, 25, 28].

The last phase of the study is the cavernosography, which is performed under fluoroscopic monitoring using non-ionic contrast which will fill both corpora and assess the venous drainage systems (dorsal, cavernosal, and crural veins). Radiographs are then obtained in anterior/posterior and oblique/lateral projections (Fig. 6.6).

Phalloarteriography

The use of DDPU has replaced the penile angiography as the standard vascular evaluation in men with ED. This technique was widely used in the early 1980s, but is now only indicated in young

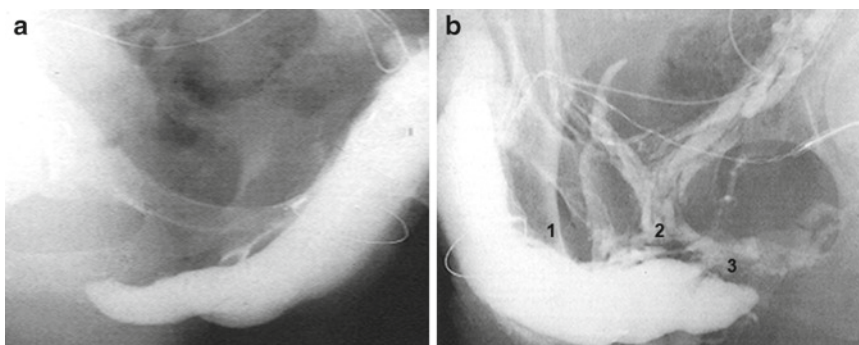


Fig. 6.7 Dynamic cavernosography. (a) Normal, no venous leak. (b) Abnormal venous leak. 1, dorsal vein; 2, cavernosal veins; 3, crural veins

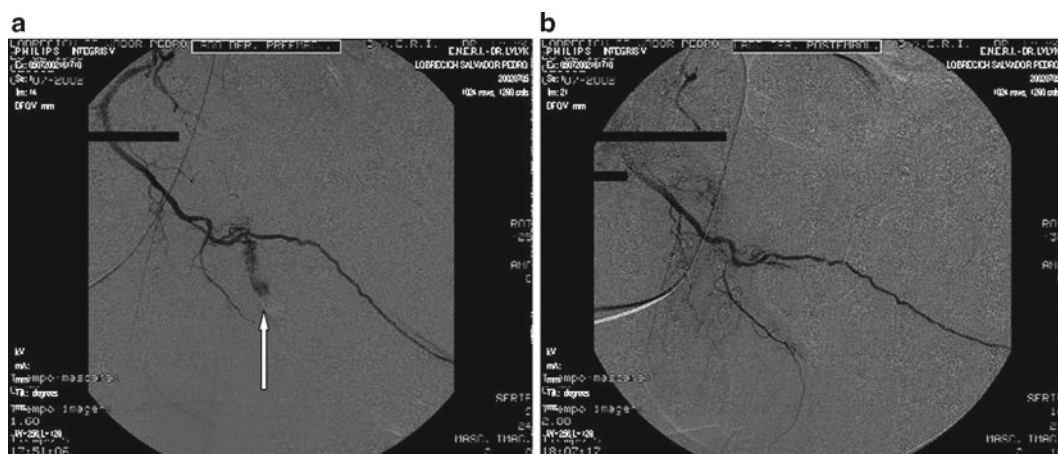


Fig. 6.8 Penile angiography. (a) Patient with a high flow priapism, arrow shows cavernous artery fistula. (b) Post-fistula embolization

men with suspicion of a single vascular lesion in the absence of general vascular risk factors, who may be considered candidates for a revascularization procedure, and to confirm and perform embolization in men with a high flow priapism [5, 15, 29] (Figs. 6.7 and 6.8).

Neurological Evaluation

A simple neurological physical examination can be performed during the initial consultation by evaluating the anal tone, bulbocavernous reflex, and penile and perineal sensitivity. More advanced neurological tests can be performed in select clinical situations where neuropathy is suspected and might influence the treatment choice or in rare medico-legal situations.

The purpose of the neurological tests is to evaluate the following pathways:

1. Afferent somatic pathways
 - (a) Bulbocavernous reflex latency
 - (b) Somatosensory evoked potentials
 - (c) Intrapenile dorsal nerve conductivity
 - (d) Biothesiometry
2. Efferent autonomic pathways through the corpus cavernosum electromyography [30, 31].

Working Toward a Diagnostic Algorithm

Each patient will present different and unique situations and expectations; thus, it would be utopian

to standardize the management of a patient with ED in a strict algorithm. However, we think the following approach might be useful in many cases:

The first step is always to compose a specialized history and try to isolate the main symptom, since frequently the patient fails to identify it properly and may indicate, for example, that he has difficulties maintaining an erection when he really suffers from a premature ejaculation. Once the presence of ED is established, the

interviewer should emphasize on when, how, where, and with whom he has difficulties. The patient and partner's expectations should be also explored. Psychological, social, marital, medical, pharmacological, and surgical factors are very important to explain the etiology of ED. The patient must be made to feel comfortable, *allowing* and giving *permission* to the patient to express his concerns and providing basic education on sexual function, if applicable.

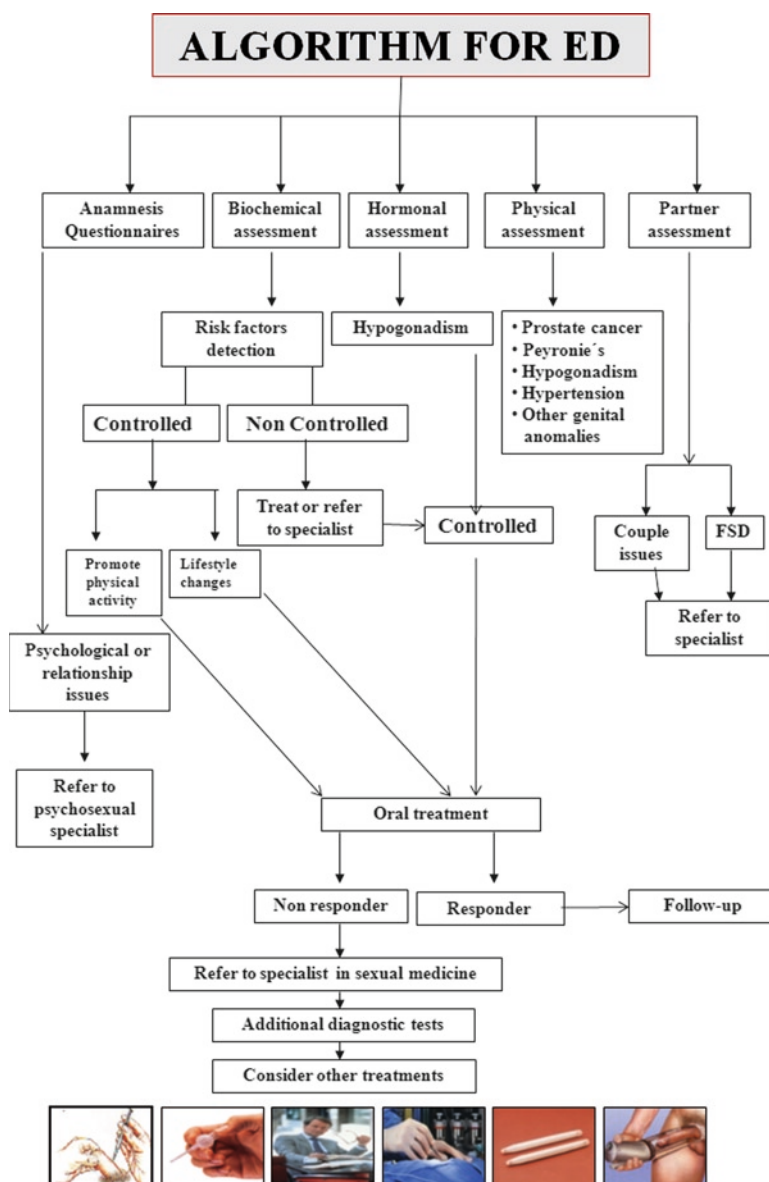


Fig. 6.9 Proposed diagnostic algorithm for ED

Physical examination will include basic urologic (genitalia and rectal exam), vascular (blood pressure and peripheral pulses), endocrine (secondary sexual characters, fat and hair distribution), and neurological assessment (bulbocavernous reflex and genital sensibility).

Routine laboratory tests with the intention of detecting diabetes, dyslipidemia, and kidney function are mandatory. Total and free or bioavailable testosterone is necessary when hypogonadism is suspected, the patient has low libido, or previous history of non-response to PDE5-Is. Prostate specific antigen (PSA) is ordered in men over 50 years old, or ≥ 40 years if family history of prostate cancer or testosterone supplement is considered.

First-line therapy with a PDE5-Is (unless contraindicated) with proper instructions is instituted after this basic evaluation, and a follow-up visit is scheduled to review the outcome and titration if necessary. For special situations and treatment failure when further specific evaluation is needed, additional diagnostic tests may be indicated (Fig. 6.9).

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Chapter 7

Drugs that Affect Sexual Function

Hannah H. Alphas and Kevin T. McVary

Abstract Multiple drugs are frequently assumed to induce sexual dysfunction as an unwanted side effect. In this chapter, we review the known mechanisms of sexual function and how the drugs hypothesized to cause sexual dysfunction are thought to interrupt these pathways. The management of drug-induced sexual dysfunction for physicians can be challenging; here, we discuss several management strategies for the treatment of drug-induced sexual dysfunction.

Keywords Detumescence • Ejaculation • Central and peripheral innervations • Sympathetic nervous system • Antihypertensives • Psychotropics • Hormone mediators • Hypolipidemics

Control of Erection and Male Sexual Function

It is necessary to establish a basic understanding of normal sexual function prior to the discussion of potential mechanisms for drug-induced pathology. Normal male sexual function requires (1) an intact libido, (2) the ability to achieve and maintain penile erection, (3) ejaculation, and (4) detumescence [1]. The major anatomic structures of the

penis that are involved in erectile function include the paired corpora cavernosa and the single corpus spongiosum that encloses the urethra. The tunica albuginea, a collagenous sheath, individually surrounds each corpus. The microarchitecture of the corpora is composed of a mass of smooth muscle which contains a network of endothelial-lined lacunar spaces. Penile tumescence leading to erection depends on the increased flow of blood into the lacunar network after complete relaxation of the arteries and corporal smooth muscle. Subsequent compression of the trabecular smooth muscle against the fibroelastic tunica albuginea causes a passive closure of the emissary veins and accumulation of blood in the corpora. In the presence of a full erection and a competent valve mechanism, the corpora become noncompressible cylinders from which blood cannot escape.

The central nervous system exerts an important influence by either stimulating or antagonizing spinal pathways that mediate erectile function and ejaculation. These interactions are mediated by a combination of central and peripheral innervation [1]. Sensory nerves that originate from receptors in the penile skin and glans converge to form the dorsal nerve of the penis, which travels to the S2-S4 dorsal root ganglia via the pudendal nerve. Parasympathetic nerve fibers to the penis arise from neurons in the intermediolateral columns of S2-S4 sacral spinal segments. Sympathetic innervation originates from the T-11 to the L-2 spinal segments and descends through the hypogastric plexus. Neural input to smooth muscle tone is crucial to the initiation and maintenance of an erection. There is also an intricate

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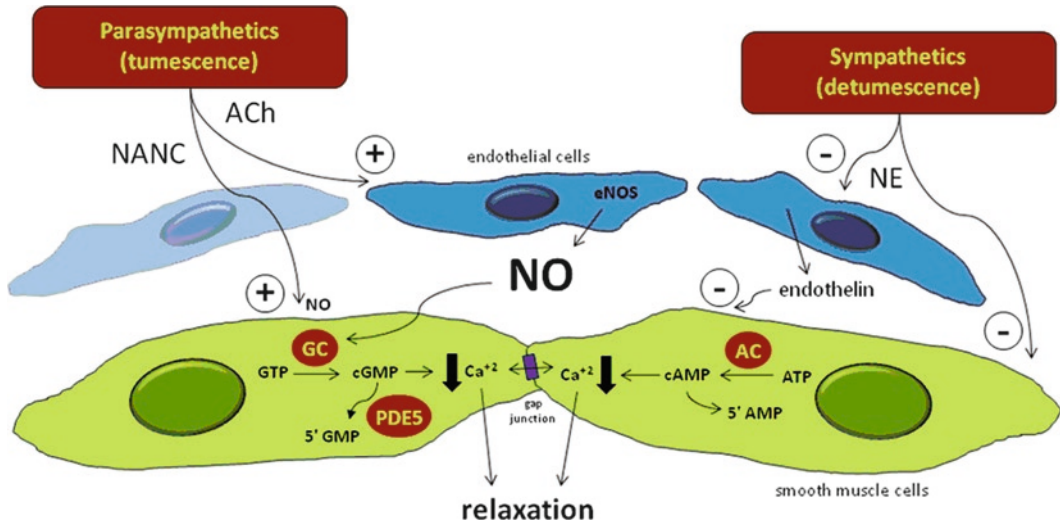


Fig. 7.1 Molecular mechanisms of erectile function. *ACh*=acetylcholine, *eNOS*=endothelial nitric oxide synthase, *GC*=guanylyl cyclase, *NANC*=nonadrenergic-

noncholinergic, *NE*=norepinephrine, *NO*=nitric oxide, *PDE5*=type-5 phosphodiesterase

interaction between the corporal smooth muscle cell and its overlying endothelial cell lining (Fig. 7.1).

Nitric oxide, which induces vascular relaxation, promotes erection and is opposed by endothelin-1 (ET-1), which mediates vascular contraction (Fig. 7.1). Nitric oxide is synthesized from L-arginine by nitric oxide synthase (NOS), and is released from the nonadrenergic, noncholinergic (NANC) autonomic nerve supply to act postjunctionally on smooth muscle cells. Nitric oxide increases the production of cyclic 3',5'-guanosine monophosphate (cyclic GMP), which interacts with protein kinase G and decreases intracellular calcium, causing relaxation of the smooth muscle. Cyclic GMP is gradually broken down by phosphodiesterase type 5 (PDE-5). Inhibitors of PDE-5, such as the oral medication sildenafil, maintain erections by reducing the breakdown of cyclic GMP. However, if nitric oxide is not produced at a basal level, the addition of PDE-5 inhibitor is not effective, as the drug facilitates but does not initiate the initial enzyme cascade. In addition to nitric oxide, vasoactive prostaglandins (PGE_1 , $PGF_{2\alpha}$) are synthesized within the cavernosal tissue and increase cyclic AMP levels, also leading to the relaxation of cavernosal smooth muscle cells.

Ejaculation is stimulated by the sympathetic nervous system, which results in contraction of the epididymis, vas deferens, seminal vesicles, and prostate, causing seminal fluid to enter the urethra. Seminal fluid emission is followed by rhythmic contractions of the bulbocavernosus and ischiocavernosus muscles, leading to ejaculation. Detumescence is mediated by norepinephrine released from the sympathetic nerves, the release of ET-1 from the vascular surface, and contraction of smooth muscle induced by the activation of postsynaptic α -adrenergic receptors [1]. These events increase venous outflow and restore the flaccid state. Venous leak can cause premature detumescence and is thought to be caused by insufficient relaxation of the corporal smooth muscle.

Erectile dysfunction (ED) may result from three basic mechanisms: (1) failure to initiate (psychogenic, endocrinologic, or neurogenic); (2) failure to fill (arteriogenic); or (3) failure to store (venoocclusive dysfunction) adequate blood volume within the lacunar network. The inability to initiate an erection may have psychogenic, vasculogenic, endocrinologic, or neurogenic etiologies. These categories are not mutually exclusive, and multiple factors contribute to ED in many patients. ED has also been

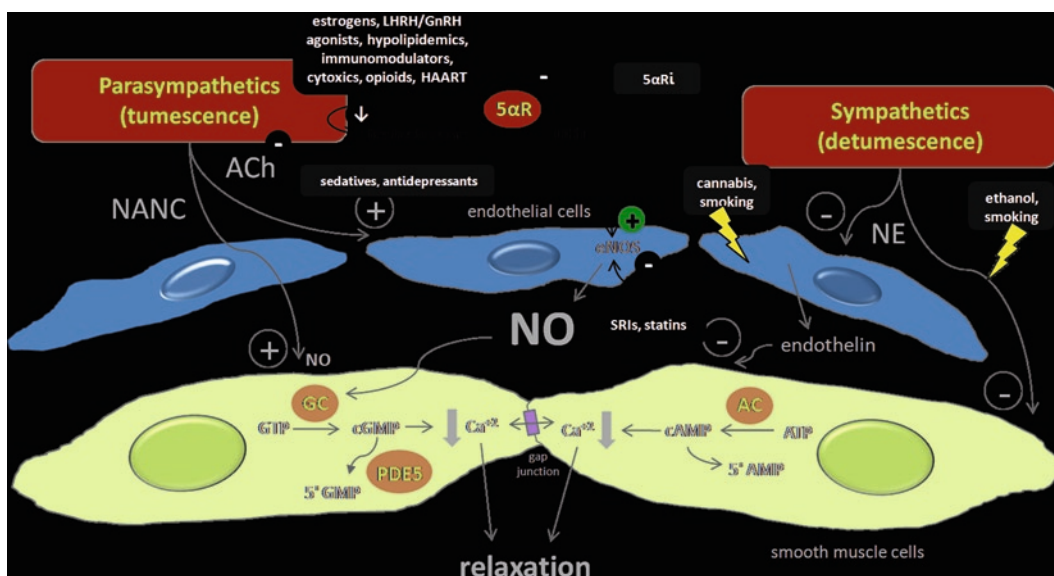


Fig. 7.2 Proposed mechanisms of drug-induced erectile dysfunction. $5\alpha R$ =5-alpha reductase, $5\alpha Ri$ =5-alpha reductase inhibitor, ACh =acetylcholine, $eNOS$ =endothelial nitric oxide synthase, GC =guanylyl cyclase,

$HAART$ =highly active antiretroviral therapy, $NANC$ =nonadrenergic-noncholinergic, NE =norepinephrine, NO =nitric oxide, $PDE5$ =type-5 phosphodiesterase, SRI =serotonin reuptake inhibitor

commonly associated with prescription and non-prescription medications. The remainder of this chapter focuses on the literature and the hypothesized mechanisms of dysfunction surrounding this relatively common clinical entity (Fig. 7.2).

Drug-Induced Sexual Dysfunction and its Mechanisms

Medication-induced ED is estimated to occur in 25% of men seen in general medical outpatient clinics [2]. The adverse effects related to drug therapy are additive, especially in older men. In this section, we review the existing literature on this subject. It is important to remember that virtually all data with few exceptions are largely subjective reports based on empiric observation, case series, physician and patient surveys, and pre- and postmarketing drug trials [3]. With all of the unvalidated information that exists regarding this subject, it is especially important for physicians to be aware of the disease process being treated and give strong consideration to whether or not the disease pathophysiology itself

is contributing to the sexual dysfunction [3]. In addition, physicians should pay particular attention to the presence of other risk factors for ED (i.e., the patient's psychosocial status) which exist outside of the disease being treated and the drug in question. The final section of this chapter addresses management strategies for the treatment of drug-induced ED.

Antihypertensive Agents

The most frequent organic cause of ED is a disturbance of blood flow to and from the penis. Atherosclerotic or traumatic arterial disease can decrease flow to the lacunar spaces, resulting in decreased rigidity and an increased time to full erection. In theory, any agent that decreases systemic pressure, subsequently altering the hemodynamics of pelvic blood flow, can potentiate ED [1]. Thus, it is not surprising that sexual dysfunction has been associated with nearly all available classes of hypertensive medication [3] (Table 7.1). These agents have been strongly correlated with

Table 7.1 Hypothesized mechanisms of drug-induced sexual dysfunction

	Drug class	Hypothesized mechanism of sexual dysfunction
Antihypertensives	β -blockers	Decreased corporal blood flow Suppression of CNS sympathetic outflow Inhibition of β_2 -mediated peripheral vasodilatation
	Thiazide diuretics	Decreased corporal blood flow
	Sympatholytics (methyldopa, clonidine)	Stimulation of α_2 adrenergic receptors in hypothalamus
	Calcium-channel blockers	Decreased corporal blood flow via altered calcium flux in penile smooth muscle cells
	α -blockers	Relaxation of the seminal vesicles leading to the absence of ejaculation
Psychotropics	Neuroleptics	Decreased dopaminergic-enhanced libido Stimulation of prolactin release from the hypothalamus Antagonism of α_1 -adrenergic receptors leading to ejaculatory dysfunction and priapism
	Antidepressants (tricyclics, SRIs)	Anticholinergic activity Stimulation of prolactin release from the hypothalamus Decreased dopaminergic-enhanced libido Sympathomimetic activity Alteration of nitric oxide synthesis (SRIs)
	Anxiolytics/tranquilizers	Centrally-mediated sedation Anticholinergic activity Decreased dopaminergic-enhanced libido Stimulation of prolactin release from the hypothalamus
	Hormone-mediators	Suppression of gonadotropin production
	Estrogens, GnRH agonists, LHRH agonists	
Hormone-mediators	H_2 blockers	Stimulation of prolactin release from the hypothalamus Competition with native testosterone for androgen receptor binding
	5α reductase inhibitors	Decreased nitric oxide synthase activity
	HIV therapy (protease inhibitors)	Increased aromatization of testosterone
	Statins (i.e., pravastatin)	Decreased nitric oxide synthase activity (statins)
Hypolipidemics	Fibrates (i.e., clofibrate, gemfibrozil)	Decrease steroidgenesis
Miscellaneous	Digoxin	Decreased corporal blood flow via altered calcium flux in penile smooth muscle cells
	Cytotoxic agents (methotrexate, thalidomide)	Destruction of gonadal tissue
	Immunomodulators (interferon, target of rapamycin inhibitors)	Decreased testosterone levels
	Cigarette smoking	Decreased nitric oxide bioavailability Ultrastructural damage to the vascular endothelium and peripheral nerves
Toxins/recreational drugs	Ethanol	Decreased nitric oxide bioavailability Ultrastructural damage to the peripheral nerves Impairment of hepatic estrogen metabolism Destruction of gonadal tissue
	Opioids	Decreased testosterone levels
	Cannabis	Ultrastructural damage to the vascular endothelium

new onset ED. While hypertension alone is considered a risk factor for ED, a population-based prospective study of over 1,000 randomly selected men in the Massachusetts Male Aging Study (MMAS), identified select antihypertensive treatments (specifically thiazide diuretics, spironolactone, β -blockers, methyldopa, and clonidine), and not the condition itself, as an independent risk factor [4]. However, logistic regression analyses with the adjustment for comorbidities and health behaviors attenuated these associations, finding that only nonthiazide diuretics and benzodiazepines were associated with ED to statistical significance. Studies like these make it difficult to interpret the previous literature surrounding antihypertensive-induced ED.

Among the antihypertensive agents, the β -blockers have been one of the most commonly implicated classes. The prevalence of β -blocker-induced sexual dysfunction has been reported to be anywhere from 5 to 43% [5]. ED has been reported with higher doses of propranolol [3] as well as with other, newer β -blockers as well [3, 5]. The proposed pathophysiology is via decreased corporal blood flow, suppression of CNS sympathetic outflow and in the case of non-specific blockers, inhibition of β 2-mediated peripheral vasodilatation leading to insufficient relaxation of the corpora [3, 5].

Thiazide diuretics are some of the most commonly used antihypertensives. This class is also commonly implicated as eliciting ED. The incidence of thiazide diuretic-induced ED has been reported to be anywhere from 4 and 32% [5]. Calcium channel blockers, angiotensin-converting enzyme inhibitors and vasodilators such as hydralazine are other antihypertensive agents linked to drug-induced ED. While the mechanism of action is not completely understood, it has been hypothesized that these drugs act directly at the corporal level (for instance, calcium channel blockers) or indirectly by reducing pelvic blood pressure, which is important in the development of penile rigidity.

Drug-induced ED is not limited to difficulties initiating and maintaining erections. Certain drugs have been reported to induce an absence of ejaculation [3]. Some α -blockers, tamsulosin

and silodosin, have been associated with this phenomenon, purportedly through relaxation of the seminal vesicles. While α -blockers have historically been used for hypertension, the practicing urologist is often more familiar with the use of this class of drugs in the treatment of benign prostatic hyperplasia (BPH). Epidemiologic evidence suggests that ED and BPH are conditions that often arise together. Because preliminary clinical data suggests that the addition of an α 1-blocker to a PDE-5 inhibitor can actually attenuate ED, multiple groups have investigated the effects of concomitant application of various α 1-blocker and PDE-5 inhibitor combinations on human [6, 7] and animal [8] cavernosal tissue as compared to each drug alone. In vitro studies on human tissue demonstrate that the combination of these two drugs exert an additive relaxant effect on cavernosal smooth muscle. In vivo models in the rat suggest that α 1-blockers can actually increase NO synthesis, alter sympathetic tone and augment blood flow in penile tissue when bladder-outlet obstruction and ED are present [8].

Psychotropic Medications

Psychotropic agents – particularly neuroleptics, tricyclics, and serotonin reuptake inhibitors (SRIs) – are associated with erectile, ejaculatory, orgasmic, and sexual desire difficulties (Table 7.1). Mental illness and the management of mental disorders are a significant cause of sexual dysfunction in men. A recent population study reported a fivefold increase in odds of self-reported complete ED among men who used selected antidepressant therapy (principally selective SRIs and tricyclics) which exceeded the risk of ED attributed to depression symptoms or diagnosis [4]. Antidepressant-associated ED is reported to occur with prevalence rates from 30 to 90% [9, 10]. Worsening or the initiation of sexual dysfunction has been reported with agents for all antidepressant classes, including monoamine oxidase inhibitors, tricyclic antidepressants, and SRIs. Bupropion, nefazodone, and

mirtazapine appear less likely to cause sexual dysfunction [9]. A number of molecular pathways have been implicated in antidepressant-induced sexual adverse events. Serotonin has been hypothesized to inhibit normal sexual response by decreasing dopamine-enhanced libido, arousal and erection and increasing prolactin release from the hypothalamus [10]. SRIs have also been shown to be potent inhibitors of NOS [11].

Given the high prevalence of antidepressant-induced sexual dysfunction, a prospective, parallel group, randomized, double-blind, placebo-controlled trial was undertaken to evaluate the safety and efficacy of PDE-5 inhibitors in the treatment of this disorder [12–14]. Ninety male outpatients at three different university medical centers with major depression in remission and sexual dysfunction associated with either selective or nonselective SRI antidepressant treatment were randomly assigned to take sildenafil at a flexible dose (50–100 mg) for 6 weeks. Multiple different validated and unvalidated questionnaires were administered, including the IIEF [12]. Based on several analyses, the authors concluded that sildenafil was well tolerated and significantly improved erectile function and overall sexual satisfaction in men with SRI-associated ED [12–14]. These data provide Level 1 evidence that a PDE-5 inhibitor may be successfully used to treat SRI-associated ED without the interruption of antidepressant therapy.

Antipsychotic medications are associated with both erectile and ejaculatory dysfunction in up to 50% of patients [5]. Certain antipsychotics, in particular the typical antipsychotics, can exhibit α_1 adrenergic antagonism and lead to the unwanted effects of retrograde ejaculation and priapism [15]. Atypical antipsychotics at high-doses have been implicated in retrograde ejaculation and priapism as well [16]. Dopamine is considered a key target of neuroleptic medications and is known to have multiple effects in the central nervous system. It is well established that dopamine inhibits prolactin release. Decreases in dopamine action thus lead to hyperprolactinemia. Increased serum levels of prolactin may decrease libido by suppressing gonadotropin-releasing hormone (GnRH) and decreased testosterone

levels, resulting in decreased libido, anorgasmia, and ED. In addition, many drugs that produce central nervous system sedation or depression, such as anxiolytics and tranquilizers, are also thought to lead to ED potentially via CNS antidopaminergic effects and increased prolactin release [1].

CNS sedatives are also known to have residual anticholinergic effects. While acetylcholine plays a significant role in normal erectile function, the use of anticholinergic agents has not been associated with ED as frequently as one might expect [3]. ED has, however, been reported with the anticholinergic antiarrhythmic drug disopyramide. In addition, many of the antidepressants, namely, tricyclics and select SRIs, maintain residual anticholinergic properties. It is possible that the sexual dysfunction from these medications is mediated in part by their anticholinergic properties.

Hormonal Agents

Androgens are known to increase libido, but their exact role in erectile function remains unclear [1]. Normal levels of testosterone appear to be important for erectile function, particularly in older males. It has been shown that androgen replacement therapy can improve depressed erectile function when ED is secondary to hypogonadism. As such, it is not surprising that any drug that interferes with testosterone production or action might lead to sexual dysfunction (Table 7.1). Estrogens, GnRH agonists, LHRH agonists, and corticosteroids can cause ED by suppressing gonadotropin production. Certain drugs like spironolactone, cyproterone acetate, ketoconazole, aminoglutethimide, and other similar drugs have also been shown to have anti-androgen activity and have each been linked to drug-induced sexual dysfunction [1, 3, 5]. These agents often resemble the molecular structure of testosterone and compete with native testosterone for binding to androgen receptors; they have also been shown to induce hyperprolactinemia. Multiple reports have linked H_2 blockers to sexual dysfunction. Ranitidine and cimetidine have

both been shown to increase prolactin levels and act as antiandrogens [1, 3].

5 α (alpha)-reductase inhibitors The potential sexual side effects, including ED, decreased libido and ejaculatory problems, which have been reported with 5 α -reductase inhibitors (dutasteride and finasteride) are of particular relevance to the urology patient. These drugs block the conversion of testosterone to the more potent androgen, dihydrotestosterone (DHT). Animal models have demonstrated decreased NOS activity with decreased DHT, and thus, it has been proposed that 5 α -reductase inhibitors elicit sexual dysfunction by indirectly attenuating NOS activity [17]. Sexual adverse events have been reported in clinical trials at rates of 2.1–38% [17, 18]. The most common complaint is ED, followed by ejaculatory dysfunction and decreased libido [17]. It appears that these effects occur early in the initiation of therapy and decrease over time. The results of these studies, however, have been questioned as the high incidence of drug-induced sexual dysfunction reported in some clinical trials does not seem to correlate with clinician experience. In a more recent study, two groups of blinded, randomized patients received 5 mg of finasteride with and without counseling regarding the potential for sexual side effects. The incidence of ED, decreased libido and ejaculatory problems were significantly reduced in patients who did not receive sexual side effect counseling [19]. The authors conclude that a “nocebo” effect, an adverse effect that is not a direct result of the specific pharmacological action of the drug, should be taken into account when managing patients with reported sexual side effects. This latter study elucidates a common problem encountered by any physician attempting to counsel their patients regarding the potential side effects caused by the drugs mentioned in this chapter. This psychological priming can be a particularly difficult challenge in the management of sexual dysfunction in the setting of drug use.

HIV therapy HIV and the polypharmacy standard in the care of HIV patients have been associated with sexual dysfunction. A recent cross-sectional study of HIV patients in England estimated the

prevalence of moderate to severe ED to be 33% and moderate to severe impairment of sexual desire to be 24% [20]. While multivariate analysis found sexual dysfunction to be common in both patients receiving antiretroviral therapy and those naïve to the drugs, ED was found to be associated with long duration of HIV therapy [20]. A survey among a different group of HIV patients from ten different European countries demonstrated decreased libido and potency in men receiving drug regimens containing protease inhibitors as compared to protease inhibitor naïve patients, specifically identifying protease inhibitors as a drug leading to sexual dysfunction among HIV patients [21]. Studies have shown that antiretroviral therapy is associated with increased aromatization of testosterone leading to increases serum levels of estradiol in men. It is hypothesized that the sexual dysfunction reported by patients taking antiretrovirals is secondary to these hormonal imbalances [22]. Various hormonal replacement strategies have recently been under investigation. While testosterone has been well studied in the treatment of HIV-related wasting syndromes [23] several more recent reports specifically address sexual function. Letrozole [24], an aromatase inhibitor, and both parenteral and topical forms of testosterone [25] have both been shown not only to increase serum levels of testosterone, but also to improve patient reported sexual function.

Lipid Lowering Medication

Fibrates (clofibrate, gemfibrozil, and less frequently bezafibrate and fenofibrate) are lipid-lowering medications that have long been associated with medication-induced sexual dysfunction [1, 3]. A case-control study of 339 age-matched men revealed that there were more impotent men in the group of patients treated with lipid-lowering medications (12% vs. 5.6%); and multivariate analysis showed that fibrates and statins were independent risk factors for erectile dysfunction [26]. A contemporary systematic review was recently carried out by a group in England evaluating the

evidence associating lipid lowering therapies, including statins, with the onset of ED [27]. While there are multiple trials that do not show and increased rate of sexual dysfunction in patients taking lipid lowering medications versus placebo, the authors report several studies in which the initiation of clofibrate, gemfibrozil, and multiple statins was associated with ED. While it remains unclear what the true rates of sexual adverse events with hypolipidemics, the mechanism in which this occurs is thought to be through decreased synthesis of sex steroid hormones derived from cholesterol, namely, testosterone [27]. In addition to their known effects on serum lipid levels, statins have been hypothesized to mediate anti-inflammatory effects through several different pathways, including the inhibition of NOS activity [28]. Thus, it is possible that statins might potentiate erectile dysfunction via decreased nitric oxide levels.

Miscellaneous

Case reports of sexual side effects from metoclopramide, baclofen, amicar (epsilon-amino-carpoic acid), disulfiram, and carbonic anhydrase inhibitors have been associated with ED [1, 3, 5]. Cytotoxic drugs have also been implicated in drug-related ED include methotrexate [29] and thalidomide [30]. Digoxin is yet another drug that has been suggested to induce ED. The mechanism it thought to be via blockade of the Na⁺, K⁺-ATPase pump, resulting in a net increase in intracellular calcium and increased corporal smooth muscle tone. Others have also suggested that the chemical structure of digoxin is similar to sex steroids leading to antiandrogen activity [3].

Immunomodulators Decreased libido and ED are commonly reported side effects experienced by male patients during antiviral therapy for chronic hepatitis C. This effect was studied in 34 male patients being treated with interferon and ribavirin [31]. Free and total testosterone decreased significantly during antiviral therapy while depression scores increased during therapy. Certain agents used in renal transplantation have been implicated in erectile function as well. The

immunosuppressive agents' target of rapamycin inhibitors (i.e., sirolimus and everolimus) have been shown to result in decreases in serum testosterone levels, increases in levels of luteinizing hormone, and a disruption of spermatogenesis [32]. The impairment of gonadal function is reported to elicit ED in patients receiving these drugs.

Toxins and Recreational Drugs

In theory, any process that alters the fibroelastic components of the corpora or of the associated vasculature may cause a loss of compliance and an inability to compress the tunical veins. While this may result from aging, increased cross-leaking of collagen fibers induced by nonenzymatic glycosylation, hypoxia, or altered synthesis of collagen associated with hypercholesterolemia, certain toxins have been implicated in the destruction of these fibroelastic structures and have been associated with erectile dysfunction. Arsenic exposure, for example, has been linked to ED via damage of peripheral vasculature [33]. Extensive work has also been done examining the relationship between cigarette smoking and ED [34, 35]. Chronic smoking has been identified as a major risk factor in the development of ED [34] and has been shown to have deleterious effects on vascular functioning through impairment of endothelium-dependent smooth muscle relaxation specifically by affecting NO production [34]. Animal models have demonstrated that long-term cigarette smoking is associated with impaired penile arterial flow, increased reactive oxygen species and decreased nitric oxide bioavailability, ultrastructural damage to the vascular endothelium, peripheral nerves and to the corporal tissue. The precise toxins found in cigarettes mediating these changes have not been fully elucidated. However, a recent randomized, double blind, placebo-controlled study evaluating the isolated effects of nicotine on sexual function has demonstrated that men, without significant prior exposure to nicotine, when administered nicotine gum 40 min prior to an

erotic film, showed significantly reduced erectile responses as compared to age-matched controls chewing placebo gum [36], suggesting that it may be the nicotine within cigarettes that plays a role in smoking-related ED.

Both acute and chronic ethanol abuse have been implicated as a potential cause of ED [4]. The incidence of sexual dysfunction within the chronic alcoholic population has been reported to range from 8 to 54% [3]. In addition, decreased sexual arousal, increased ejaculatory latency, and decreased orgasmic pleasure have all been noted to parallel the blood alcohol content of men. The hypothesized mechanism of these acute effects are thought to be secondary to central sedative action [3]. In mouse models, chronic ethanol exposure has been linked to the impairment of endothelial function in the corpus cavernosum through the reduction of NO release [37]. Chronic ethanol abuse has also been postulated to promote nerve damage via hormonal effects mediated through direct testicular damage and the impairment of the hepatic estrogen metabolism. Ethanol abuse is also notorious for producing nerve damage leading to global polyneuropathy [3]. As with any disorder that affects the sacral spinal cord or the autonomic fibers to the penis, nerve damage seen in alcoholism can preclude nervous system relaxation of penile smooth muscle, thus leading to ED.

ED has been associated with opioid use, including high-dose methadone regimens for men being treated for opioid dependence. Hypoactive sexual desire, ED and difficulty achieving orgasm as a result of opioid induced hypogonadism and testicular failure have been reported [38–40]. While the degree of sexual dysfunction appears to be less [38], buprenorphine, a newer drug used in the treatment opioid dependence, has also been shown to suppress levels of testosterone, luteinizing hormone, and estradiol [39, 40]. How androgen replacement improves sexual function in this group remains to be elucidated.

Recent evidence implicates the use of marijuana as a potential cause of ED in habitual cannabis users [41]. This study out of Italy looked at 64 men complaining of ED for at least 3 months. Patients were subjected to detailed

questioning regarding recreational drug use and subsequent dynamic penile duplex sonography. Using a peak systolic velocity cutoff of 35 cm/s as a marker for organic vasculogenic dysfunction, cannabis smoking was significantly more prevalent in the organic group (78% compared to 3% in the nonorganic ED group, $P < 0.001$) when no other vascular risk factors were present. While this study did not demonstrate a direct relationship between cannabis use and ED, based on these findings, the authors propose that cannabis use may promote early endothelial damage leading to subsequent difficulties with erections.

Management of Drug-Induced Sexual Dysfunction

Although many medications can cause ED, patients frequently have concomitant risk factors that confound the clinical picture. Because the etiology of ED may be multifactorial, successful treatment requires the management of underlying risk factors and concomitant medical conditions. The majority of the patients with ED also have coexisting obesity, coronary artery disease (CAD), hypertension, or diabetes. And in fact, as reviewed above, many of these patients also present with LUTS secondary to bladder outlet obstruction from BPH. Patients being treated for mental illness and experiencing sexual dysfunction can also be some of the most difficult patients to manage. Differentiating organic from psychogenic causes is highly challenging as depression is one of the most common causes of psychogenic ED and almost all patients in this population present with some overlap of psychogenic and organic factors. In any patient presenting with erectile dysfunction, psychogenic causes should also be given high consideration. Psychogenic causes are thought to mediate sexual dysfunction by inhibiting reflexogenic responses at the spinal cord level, thereby blocking the activation of vasodilator outflow to the penis. Excess sympathetic stimulation as is typical with generalized anxiety or performance anxiety can also increase penile smooth muscle tone.

If there is a strong association between the institution of a drug and the onset of ED, alternative medications should be considered. Otherwise, it is often practical to treat the ED without attempting multiple changes of medication choice, as it may be difficult to establish a causation. Depending on the drug, the nature of problem being treated by the drug, and the known pathophysiology of sexual dysfunction, various approaches have been previously suggested. What is becoming clear is that the treatment of this challenging problem often necessitates multidisciplinary planning and potential involvement of an urologist, especially when changes in medication therapy alone do not eliminate sexual dysfunction. While the utility of hormone replacement for drug-induced hypogonadism continues to be studied, various forms of androgen replacement exist and should be considered in the appropriate patient. PDE-5 inhibitors have been shown to attenuate drug-induced sexual side effects in multiple arenas. When pills do not provide relief, the urologist has an armamentarium of alternative therapies and strategies to improve sexual function and satisfaction. Highly motivated patients should be counseled about alprostadil suppositories, vacuum erection devices and intracavernosal injection therapy when appropriate. Surgery with implantable penile devices should be reserved for patients with irreversible damage to their penile vasculature and microanatomy. Finally, as more drugs are recognized as potential risk factors for ED, doctors should broaden consideration of all potential organic and nonorganic causes in their differential diagnosis of ED.

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Chapter 8

Oral Therapy for Erectile Dysfunction

Erin R. McNamara and Craig F. Donatucci

Abstract As defined by the NIH, erectile dysfunction (ED) is the repeated inability to get an erection firm enough for sexual intercourse (NIH consensus conference. Impotence. NIH consensus development panel on impotence. *Journal of the American Medical Association*, 270, 83–90, 1993). The International Consultation on Sexual Medicine defined ED as the consistent or recurrent inability to attain and/or maintain penile erection sufficient for sexual performance (Jardin, *Recommendations of the 1st International Consultation on Erectile Dysfunction*. Plymouth, UK: Health Publications Ltd, 2000). These definitions exclude other causes of sexual dysfunction including decreased libido and premature ejaculation. According to most recent studies, 15–30 million men report sexual dysfunction. Impotence has been studied for hundreds of years, but not until the past few decades have we been able to understand and treat so effectively. Even in the early 1900s it was known that vascular, neurologic, and hormonal milieu played a part in erections as physicians performed dorsal vein ligations and testicular transplants. Aphrodisiacs were the oral therapy of the day and included Chinese herbs and other common plant and food items that

supposedly affected both desire and potency. However, the complex physiologic, neurologic, and psychological interaction is just starting to be appreciated.

Keywords Neurological components • Vascular components • Phosphodiesterase 5 inhibitors • Nitric oxide in erection physiology • Sildenafil • Vardenafil • Tadalafil

Introduction

Definition

As defined by the NIH, erectile dysfunction (ED) is the repeated inability to get an erection firm enough for sexual intercourse [1]. The International Consultation on Sexual Medicine defined ED as the consistent or recurrent inability to attain and/or maintain penile erection sufficient for sexual performance [2]. These definitions exclude other causes of sexual dysfunction including decreased libido and premature ejaculation. According to most recent studies, 15–30 million men report sexual dysfunction. There has also been an increase in self-reported ED according to the National Ambulatory Medical Care Survey, as men are seeking out simple treatments such as oral phosphodiesterase inhibitors (PDE5) [3].

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Historical Perspective

Impotence has been studied for hundreds of years, but not until the past few decades have we been able to understand and treat so effectively. Even in the early 1900s it was known that vascular, neurologic, and hormonal milieu played a part in erections as physicians performed dorsal vein ligations and testicular transplants. Aphrodisiacs were the oral therapy of the day and included Chinese herbs and other common plant and food items that supposedly affected both desire and potency. However, the complex physiologic, neurologic, and psychological interaction is only just starting to be appreciated.

With the dawn of pharmacologic treatment in the 1980s and advancement in ultrasound techniques, physicians were able to create erections and monitor blood flow into and out of the penis and have a way of measuring efficacy of treatment. Intracavernosal therapy was the primary and most efficacious treatment at that time until the discovery of nitric oxide (NO) and its role in erection physiology. Pharmacological treatment has changed as we understand more about the etiology of ED. It has been eleven years since the FDA approved sildenafil (Viagra®), an oral phosphodiesterase inhibitor, and there is a new algorithm of treatment, which is centered on patients' goals and motivations and evidence-based principles [4]. Over 70% of ED can now be treated with oral medications. Oral pharmacotherapy is the first-line treatment without question for almost all types of ED according to the AUA/EUA guidelines and the WHO-sponsored International Consultation on treatment for ED [5–7].

First Line Therapy

With the availability and efficacy of oral medications, primary care physicians are now evaluating and counseling men with ED and beginning treatment. In 2002, the majority of Viagra® prescriptions were written by primary care physicians (69%) as compared to urologists (13%) [3]. With this transition, it is important to be

thoughtful in our treatment of ED. First, it is important to know all the different treatment options and not just write a prescription for the patient. Secondly, with more recent evidence, it has been shown that ED may be a precursor to coronary artery disease and is associated with other chronic illnesses such as diabetes mellitus, hyperlipidemia, obesity, hypertension, and depression [8]. When treating ED, it is important to see the patient as a whole and consider medication side effects, interactions, and efficacy in certain populations. As the population ages and men continue to seek out treatment for ED, it is necessary for healthcare providers to be equipped with the proper knowledge about available therapy for ED in order to provide the most appropriate goal-directed therapy.

This chapter will focus on the current first line oral pharmacotherapy for treatment of ED while also looking at the trends toward future oral therapy. Other treatment options will be described in other chapters.

Mechanism of Erection

Neurologic

In order to understand the success of the current oral therapy for ED, we first have to look at a brief overview of erectile physiology. Erections are initiated, maintained, and terminated due to a complex interaction between the neural and vascular components. Both central and peripheral factors are responsible for successful erections.

Vascular

The main event that seems to have the most influence on the maintenance of erections is the release of NO both from the autonomic nerve endings and the endothelial cells in the corpora cavernosum. The release of NO causes vasodilation of the smooth muscle cells (SMCs) and allows for tumescence to occur. NO facilitates

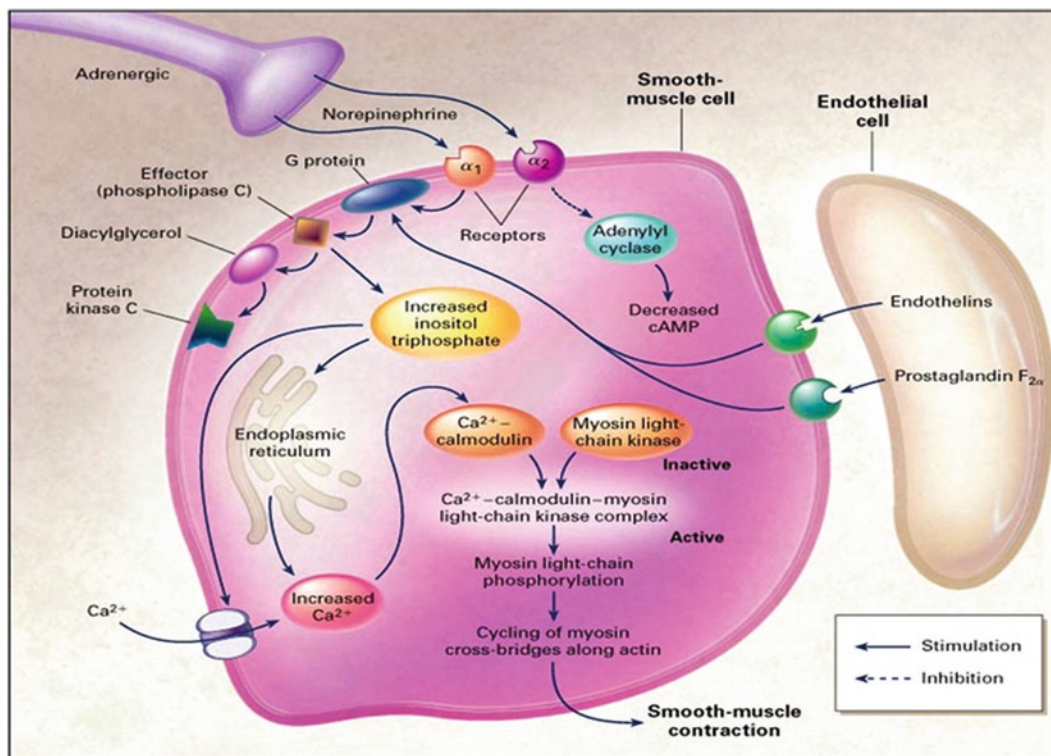


Fig. 8.1 Mechanism of smooth muscle relaxation and role of PDE5 and nitric oxide [5]

vasodilation and relaxation by activating guanylate cyclase. This enzyme converts guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP), which is directly responsible for smooth muscle relaxation by its effect on intracellular calcium levels. Hyperpolarization occurs at the cell membrane, there is a decrease in cytoplasmic calcium, and the SMC relaxes (Fig. 8.1). Levels of cGMP in the SMCs of the penis are regulated by the enzyme phosphodiesterase type 5 (PDE-5) [9–11]. Detumescence occurs with sympathetic nerve firing. Adrenergic nerves release norepinephrine (NE) that binds to α_1 or α_2 receptors on the SMC. This neurotransmitter is responsible for the activation of a G-protein and an influx of calcium into the SMC. As PDE-5 continues to breakdown cGMP to guanosine monophosphate (GMP), the SMCs and the endothelial cells contract; this is the chronic state of the flaccid penis (Fig. 8.2).

Oral Phosphodiesterase Inhibitors

- PDE-5
- Pharmacokinetics and pharmacodynamics
- Side effects
- Safety
- Comparison

Phosphodiesterase, as mentioned in the previous section, is paramount to the breakdown of cGMP in the SMC. This enzyme is found in several different tissues throughout the body and has been categorized into 11 families. The family that is found in corpora cavernosum tissue as well as smooth muscle and vascular smooth muscle is PDE-5. As the role of PDE-5 was elucidated in the 1980s, drugs were targeted to inhibit this enzyme and increase the NO in SMCs. A result of this was an unexpected increase in NO in penile tissue and improvement in erectile function.

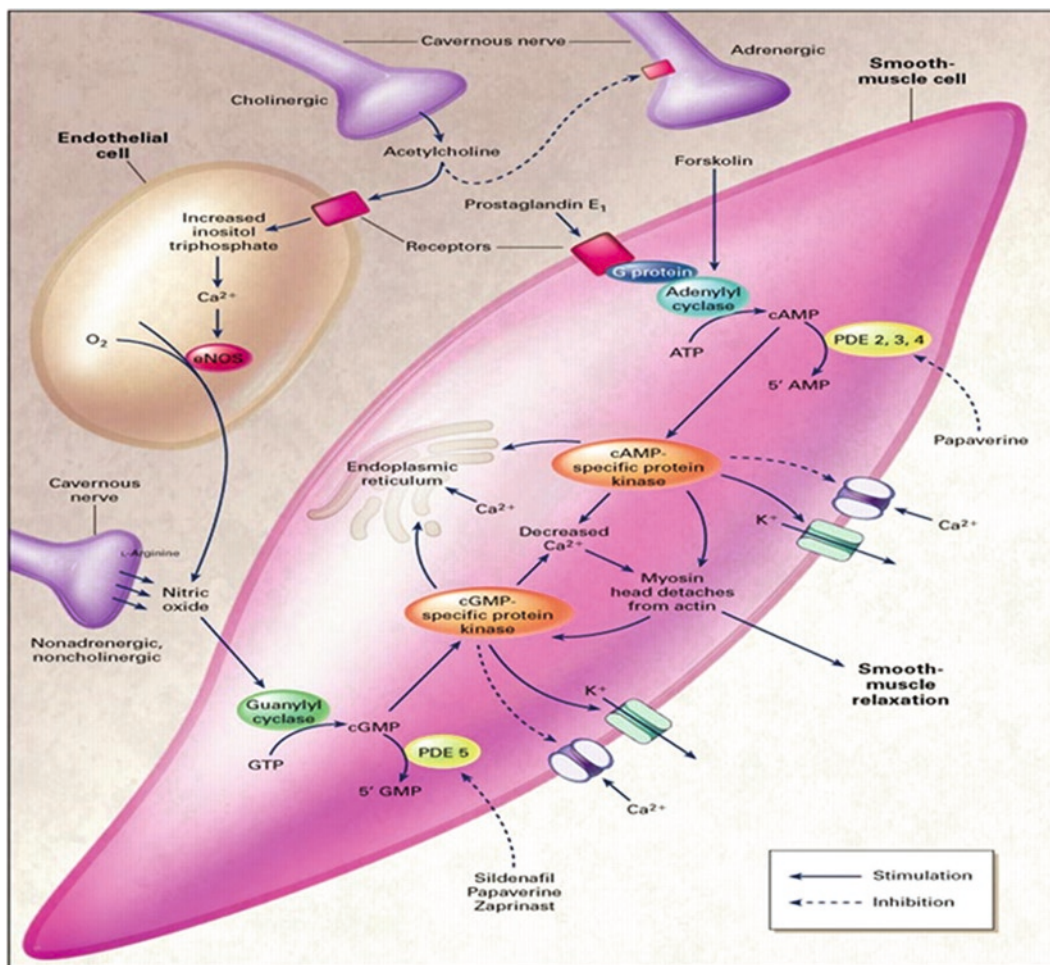


Fig. 8.2 Mechanism of smooth muscle contraction [5]

PDE-5 inhibitors were first marketed in 1998 with the dawn of sildenafil (Viagra®). This was followed closely in 2003 with vardenafil (Levitra®) and tadalafil (Cialis®). As the market for these drugs has increased, it has been important to identify the safety, efficacy, and limitations of these drugs. When choosing a PDE-5 inhibitor for a patient, it is important to know the onset of action, efficacy, and duration. Studies usually will define the maximal plasma concentration (C_{max}), time to reach this plasma concentration (T_{max}), and the plasma half-life ($t_{1/2}$). How well these laboratory findings correlate to clinical findings is sometimes difficult to determine and the measuring tool most commonly used to evaluate efficacy is the

International Index of Erectile Function (IIEF) domain score.

Viagra®

The most studied of these drugs is sildenafil (Viagra®). In several placebo controlled, randomized trials, this drug has been shown to improve erectile function. The pivotal study for sildenafil was published in 1998, which showed a clinically and statistically significant improvement in IIEF domain scores for men suffering from ED for greater than 5 years [12]. The onset of action of sildenafil is approximately 20 min

with a reported $t_{1/2}$ of 3–5 h and duration of action as long as 12 h [13]. The important thing about sildenafil is that it should not be taken with a high-fat meal because this will decrease the absorption of the medication [10, 14].

Levitra®

The FDA approved vardenafil (Levitra®) in 2003 after a study of 805 men with ED showed a clinically and statistically significant improvement in IIEF scores when compared to placebo. In this study, different doses were evaluated and men were categorized into mild, moderate, and severe ED. Approximately 40% of the moderate and severe ED men had improvement with the highest dose and over 79% of the mild ED men had improvement [15, 16]. Vardenafil is quickly absorbed with a $T_{\max}$ of 45 min and a reported $t_{1/2}$ of 4–5 h. Onset of action has been recorded as early as 10 min [17]. Just as in sildenafil, it is recommended that high-fat meals are avoided [18].

Cialis®

Tadalafil (Cialis®) was approved at the same time as vardenafil and acquired the nickname “the weekend pill” because of the longer half-life than the other two drugs in its class. The $T_{\max}$ of tadalafil is closer to 2 h and the $t_{1/2}$ is 17.5 h with a clinical efficacy reported of 12–36 h [19]. Several studies showed the efficacy of tadalafil and the most important study involved 1,112 patients with mean duration of ED > 1 year. In this group, over 80% of the men had improved erections up to 36 h after administration of the drug [20]. One other thing that differs from sildenafil and vardenafil is the absorption of tadalafil does not seem to be affected by high-fat meals so there are no dietary restrictions [21].

The side effect profile for these drugs is very similar and is a result of the incomplete selectivity of PDE-5 and the other sites that can be affected by inhibiting PDE-5. PDE-6 and PDE-11 are the

two most common families also affected by the drugs and contribute to the visual disturbances and myalgias, respectively. These side effects include headache, flushing, dyspepsia, and rhinitis. It has been shown with the continued use of vardenafil that these side effects are reduced significantly after the first few weeks [22]. There is less than a 5% drop out rate secondary to side effects [23].

There are two things to warn your patients about with the use of PDE-5 inhibitors. The first is that these drugs cannot be taken with nitrates. When sildenafil has been used, it is recommended to wait at least 24 h and when tadalafil has been used, 48 h is recommended. The results can be severe hypotension and all patients need to be aware of this contraindication. The second thing is patients need to be counseled to seek medical attention if they have any visual changes. Some visual changes can be mild and transient; however, there is a condition known as nonarteritic anterior ischemic optic neuropathy (NAION) that has been linked to the use of PDE-5 inhibitors. This is independent of any effect on PDE-6 found in the eye. It is an ischemic event to the optic nerve and is most likely seen in men with risk factors for diabetes, hypercholesterolemia, hypertension, and cardiovascular disease. This link was first made after a few cases were reported in a series of men using sildenafil [24]. A review of all the available clinical trials with more than 13,000 men analyzed has shown no causation. Current recommendations are not to change prescription habits, but to advise patients to seek medical attention if they experience visual changes while taking a PDE-5 inhibitor [25].

Initially there were concerns about the cardiovascular safety of these drugs. It is known that sildenafil can act as a mild vasodilator and there are warnings about orthostatic hypotension with concomitant use of α -blockers. The use of PDE-5 inhibitors is not contraindicated in men who are also on α -blockers; they just need to be stabilized on this blood pressure medication prior to initiation of therapy. There were also concerns that use of PDE-5 inhibitors would increase cardiovascular events. The safety of

these drugs has been confirmed in several controlled trials with no increase in myocardial ischemic events or overall mortality compared to the general population [26–28]. While there has been no increase of cardiovascular events associated with the use of these drugs, it is important to do a thorough cardiovascular history and exam prior to prescribing PDE-5 inhibitors as the risk factors are shared for ED and cardiovascular disease.

Cardiovascular Assessment

- Princeton Consensus Panel 2005 [29]

There is now increasing evidence and knowledge about endothelial dysfunction and NO in both ED and cardiovascular disease, and it has become essential to identify and diagnose patients with ED and assess their cardiovascular status. It is also an important part in counseling patients prior to initiating therapy, as there are some risk factors that make sexual intercourse not advisable. In 2000, the Princeton Consensus Panel came up with a model to stratify patients into low-risk, intermediate-risk, and high-risk and then made decisions about treatment accordingly [30]. The consensus study from the Second Princeton Consensus Conference in 2005 corroborates and clarifies the algorithm and emphasizes the importance of risk factor evaluation and management for all patients with ED. Below are the cardiovascular risk factors and risk categories along with an algorithm for treatment (Fig. 8.3):

Cardiovascular risk factors
Age
Male gender
Hypertension
Diabetes mellitus
Cigarette smoking
Dyslipidemia
Sedentary lifestyle
Family history of premature coronary artery disease

Low risk
Asymptomatic, <3 cardiovascular risk factors
Controlled hypertension
Mild, stable angina pectoris
Postrevascularization
Past myocardial infarction >6–8 weeks
Mild valvular disease
Left ventricular dysfunction class I
Intermediate risk
Asymptomatic, ≥3 risk factors (excluding gender)
Moderate, stable angina pectoris
History of MI (>2 weeks, <6 weeks)
Left ventricular dysfunction or congestive heart failure (NYHA class II)
Patients in NYHA class II congestive heart failure or with asymptomatic left
Noncardiac sequelae of atherosclerotic disease
High risk
Unstable or refractory angina pectoris
Uncontrolled hypertension
Congestive heart failure (NYHA class III or IV)
Recent MI (<2 weeks)
High-risk arrhythmia
Obstructive hypertrophic cardiomyopathy
Moderate to severe valve disease, particularly aortic stenosis

The take-home message is that if a patient is in the intermediate or high-risk group, they should be evaluated by a cardiologist prior to treatment for ED and initiation of sexual activity. This is a key component when considering oral pharmacotherapy treatment for ED.

Comparison of PDE-5 Inhibitors

With the available information about the different PDE-5 inhibitors, is there any way to know what will be the best option for the patient? Carson and Lue looked at all the different drugs and trials and concluded there is no feasible way to compare sildenafil, vardenafil, and tadalafil with the current data [31]. These drugs have all been shown to be effective in the treatment of ED and are well tolerated. Even in the more difficult to treat patients (diabetic ED, or

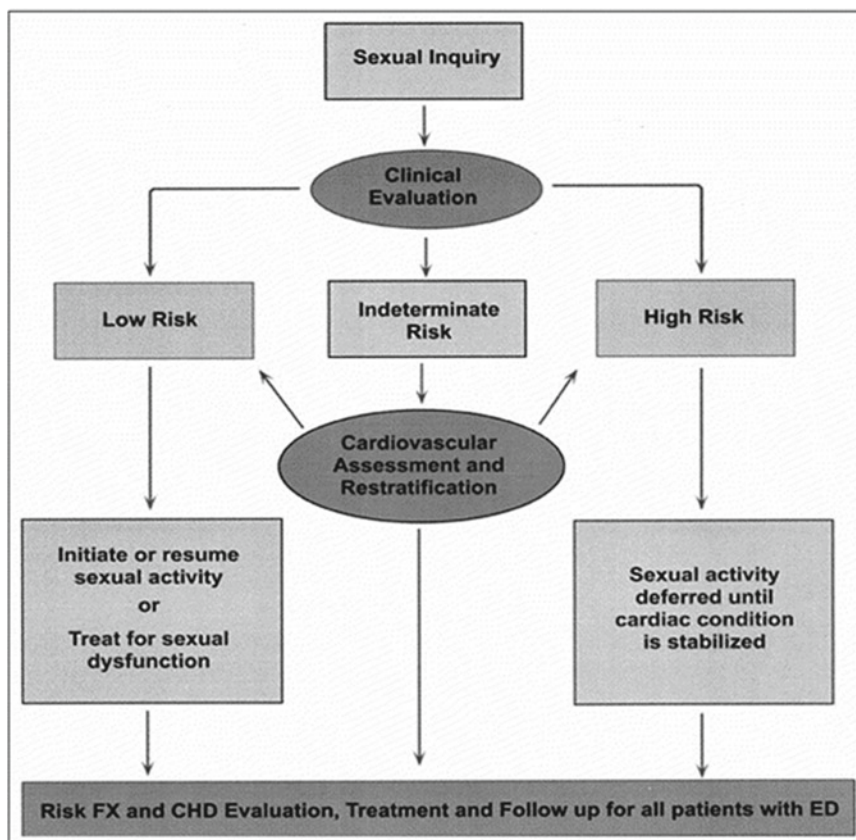


Fig. 8.3 Algorithm for treatment in men with ED and cardiovascular risk factors

post-prostatectomy) they have the ability to improve erectile function. The Sildenafil Diabetes Study Group showed that over 50% of men with ED and diabetes mellitus had improved erections as compared to placebo [32]. Several studies have shown the benefit of PDE-5 inhibitors post prostatectomy, while the best results are in men who have had nerve-sparing surgery [31, 33–36].

After prescribing a drug for ED, the patient must be followed up and patient preference and partner satisfaction should be evaluated. If the patient is discouraged about lack of effectiveness, there has been data to show that with continued use, the probability of success increases. McCullough et al. showed there is increased success after the first 9–10 attempts with sildenafil [37]. There have also been trials to show improvement in erectile function with vardenafil in

sildenafil non-responders [38, 39]. It is advisable to try a different oral therapy if the first one fails.

Even though over 60% of men will respond, there are still reasons men will not be compliant with effective therapy. Klotz et al. looked at 234 patients with successful response to sildenafil and determined that only 161 (69%) refilled their prescription. Of the 73 patients that did not refill the prescription, the most common reason was lack of opportunity or desire for sexual intercourse (45%). Lack of partner interest (23%) was the second most common reason with high cost of medication (12%) and adverse effects (5%) as less prevalent reasons [23]. This information highlights the importance of communication with the patient to meet their goals in treatment for ED.

Below is a chart that briefly highlights the differences between the available PDE-5 inhibitors. (Table 8.1).

Table 8.1 Comparison of PDE-5 inhibitors [40]

Drug	Onset of action	$t_{1/2}$	Dose	Adverse effects	Contraindications
Sildenafil (Viagra®)	$T_{\max}$ 30–120 m Duration 4 h High-fat meal decreases absorption ETOH may affect efficacy	2–5 h	25–100 mg Starting dose 50 mg	Headache, flushing, dyspepsia, nasal congestion, and altered vision	Nitrates Hypotension CV risk factors Retinitis pigmentosa Change dose with some antiretrovirals Should be on stable dose of α -blockers
Vardenafil (Levitra®)	$T_{\max}$ 30–120 m Duration 4–5 h High-fat meal decreases absorption ETOH may affect efficacy	4.5 h	5–10 mg	Headache, flushing, rhinitis, and dyspepsia	Same as sildenafil May have minor prolongation of QT interval Concomitant use of class I anti-arrhythmic
Tadalafil (Cialis®)	$T_{\max}$ 30–60 m Duration 12–36 h Plasma conc. not affected by food or ETOH	17.5 h	10 mg, 20 mg 2.5 or 5 mg for daily dose	Headache, dyspepsia, backpain, nasal congestion, and myalgia	Same as sildenafil

Other Oral Therapy

- Central acting
- Peripheral acting
- Others/herbal supplements
- New PDE5 inhibitors

In addition to the local neurologic influences, including the autonomic and somatic nervous systems, there is the role of the central nervous system that aids in erections. The visual, olfactory, tactile, and limbic regions of the cortex are stimulated and send signals to the hypothalamus. Here in the medial preoptic area (MPOA) and paraventricular nucleus (PVN) of the hypothalamus, dopamine receptors are abundant and contribute to erectile physiology [41–43]. These nuclei then communicate directly with the autonomic spinal nerves. For several years, scientists have been searching for a central acting drug that is specific for sexual desire and erectile function.

The only agent that is approved for use in Europe, but not in the US, is sublingual

apomorphine. This is a dopamine agonist that acts in the PVN. The peak plasma concentration is reached at 40–60 min and the $t_{1/2}$ is 3 h. Several studies have been done to look at apomorphine versus placebo and other oral agents. Dula et al. showed that apomorphine was better than placebo in attaining firm erections and increasing intercourse rate [44]. However, in men who are diabetic or who have undergone radical prostatectomy, there has been no evidence to show that apomorphine is effective [34, 45]. There are also side effects, including dizziness, nausea, and vomiting that limit patient use. When compared to sildenafil, most patients preferred sildenafil and had better satisfaction scores [46]. Although safe, apomorphine has not been shown to be very effective.

Yohimbine is another centrally acting agent that also works at the peripheral α adrenoreceptors as an antagonist [47]. Yohimbine is a substance from the *Corynanthe yohimbe* tree, which has been touted as an aphrodisiac for

Table 8.2 New PDE-5 inhibitors [67]

Drug	Onset of action	$t_{1/2}$	Additional info
Avanafil [61]	T_{max} 35 min	≤ 1.5 h	May be taken within 12 h of nitrate [62]
Udenafil (Zydena®) [63, 64]	T_{max} 1–1.5 h	11–13 h	Several placebo controlled studies show efficacy
SLx2101 [65]	T_{max} 1–2.8 h	8–14 h	Has metabolite, which remains active for a longer period of time
Mirodenafil (SK3530) [66]	T_{max} 1.25 h	2.5 h	50, 100 mg dose

several years. It is postulated that yohimbine is proerectile because it acts as an antagonist at the α_2 receptors of the smooth muscle and that it may promote release of NO. Clinically there is little evidence to support yohimbine as an effective treatment for ED [48]. It may have some role in psychogenic ED as shown by one small trial [49]. The 2005 AUA guidelines on ED do not recommend the use of yohimbine [6].

Phentolamine is a peripherally acting drug that acts at both the α_1 and α_2 receptors in the SMC. An oral formulation (Vasomax®) was tested in an open label study and shown to be effective for ED [50]. The FDA has not approved oral phentolamine for ED as of this time.

With the discovery of NO and the role it plays in erection, scientists have started to look at all the compounds that play a role in synthesis and degradation of NO. L-arginine is the precursor of NO and has been tested as a supplement to increase erectile function. In vivo data showed that L-arginine caused relaxation of the human corpora cavernosum [51]. There was also a study that looked at the combination of orally administered yohimbine and L-arginine, looking at the safety while administered with nitroglycerine [52]. There are no randomized trials to look at the effect on ED. This is one step in NO synthesis that may be modified and targeted as therapy.

Other local factors that have been shown to aid in vasoconstriction in the corpora cavernosum and may limit the ability to achieve and maintain erections are endothelin-1 and angiotensin II. It has been shown there is a local renin-angiotensin system within the corpora cavernosum and that angiotensin II blockers may facilitate erections in animal studies [53–58].

Hypotheses exist for several other supplements including but not limited to zinc, folic acid, vitamin E, and Korean red ginseng. However, there are no controlled trials and data is very limited [59, 60]. This is clearly an area of research, as ED becomes more prevalent with our aging population.

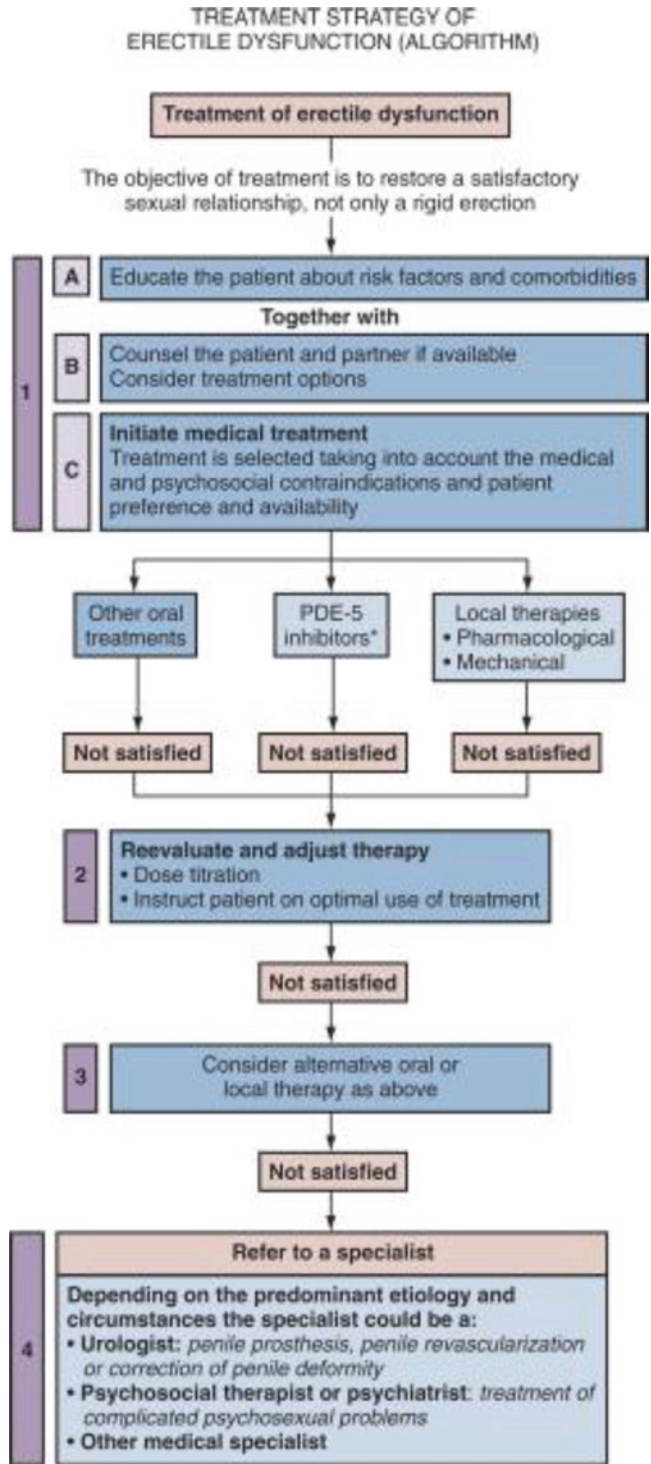
Since 2003 and the FDA approval of vardenafil (Levitra®) and tadalafil (Cialis®), there have been several newer PDE-5 inhibitors tested. The goal would obviously be to decrease side effects while increasing efficacy. To this date, most of the newer PDE-5 inhibitors have the same profile as the older PDE-5 inhibitors even if they show more promise in vitro. Ideally, there would be a large randomized double blinded placebo controlled trial comparing any of these newer agents with sildenafil to compare efficacy and side effect profile. As seen in Table 8.2 there are a few items that make these unique. Avanafil is one agent that has a much shorter onset of action and half-life, which may be useful in patients that are at risk for nitrate use. Another agent, SLx2101 has an active metabolite that is active for 48 h and may appeal to men who prefer tadalafil because of the frequency of use. None of these drugs have been approved in the US at this time.

Combination Therapy

- Testosterone therapy
- PDE5 inhibitors & PGE1

While PDE-5 inhibitors alone are effective in the majority of ED cases, it makes sense that combining this therapy with other pharmacologic therapy would have increased benefit.

Fig. 8.4 Treatment algorithm from second International Consultation on Sexual Medicine (ICSM) [74]



*PDE-5 inhibitors are the preferred treatment option in the large majority of patients

Hormonal therapy is not an accepted monotherapy for ED. However, it is worth mentioning that some hypogonadal men who complain of ED may benefit from both testosterone therapy and a PDE-5 inhibitor. Rosenthal and Shabsigh demonstrated this in randomized, placebo-controlled studies. They showed that hypogonadal men, who did not respond to sildenafil alone, had improvement in their erectile function when started on testosterone therapy [68–71].

PDE-5 inhibitors have also been used and hypothesized to improve erectile function when used in combination with other treatments (i.e. MUSE™ [72] and intracavernosal treatments). This use of PDE5 inhibitors has not been approved by the FDA and any combination is “off label” [73].

Future of Oral Therapy

Scientists and physicians continue to move forward looking for newer and better treatments for ED. The reality is that since the birth of oral pharmacotherapy for ED in 1998, we effectively treat the majority of men. There is still research to be done to target therapies for men who do not respond to our first line treatment and there is still the need for more efficacious and less deleterious treatment. The future of ED treatment might lie in genetic technology and stem cell research, but the standard of care has been raised in the last ten years and patients will not accept anything less.

Conclusion

Oral therapy is the first-line treatment for ED. It has been shown to be effective and safe with minimal side effects. The widespread use of PDE-5 inhibitors makes it important to understand the proper use and potential side effects of these drugs. This chapter also briefly discussed other oral therapies that have not had the same

robust data to support their use. Proper evaluation and treatment of ED includes a patient-centered approach that provides all the appropriate options and a physician who is willing to work with the patient to meet his goals. An algorithm for treatment is described in Fig. 8.4.

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Chapter 9

Self-Injection, Transurethral and Topical Therapy in Erectile Dysfunction

Herbert J. Wiser and Tobias S. Köhler

Abstract Currently there are three main agents for intracavernosal injection (ICI) therapy and one agent for intraurethral therapy approved by the FDA for the treatment of erectile dysfunction (ED). These effective agents were the focus of intense interest in the mid1990s, but were quickly relegated to second line therapy after the appearance of sildenafil. Indeed, while sildenafil prescriptions nearly doubled to 14 million from 1998 to 2001, prescriptions for alprostadil injections dropped by one third to 159,000 and MUSE™ prescriptions fell by two thirds to 132,000 (Wysowski & Swann, *Journal of Urology*, 169, 1040–1042, 2003). It must be noted, however, that the phosphodiesterase-5 inhibitors (PDE5Is) are ineffective in about 22–35% of men (McMahon, Samali, & Johnson, *Journal of Urology*, 164, 1192–1196, 2000). Furthermore, of the men treated with oral agents, a significant proportion will ultimately fail (even after PDE5I dose escalation) secondary to progression of their disease. Additionally, there are a significant number of men with contraindications to PDE5Is. The result is a large number of men who are unable to utilize oral treatments for erectile dysfunction. Fortunately, second line therapies in the form of vacuum erection devices (discussed in detail in a separate chapter), ICI

and MUSE™ are highly effective treatments that may be used when PDE5Is are contraindicated.

Keywords Phosphodiesterase-5 inhibitors • Sildenafil • Alprostadil • Prostaglandin E₁ • Papaverine • Phentolamine

Introduction

Currently there are three main agents for intracavernosal injection (ICI) therapy and one agent for intraurethral therapy approved by the FDA for the treatment of erectile dysfunction (ED). These effective agents were the focus of intense interest in the mid1990s, but were quickly relegated to second line therapy after the appearance of sildenafil. Indeed, while sildenafil prescriptions nearly doubled to 14 million from 1998 to 2001, prescriptions for alprostadil injections dropped by one third to 159,000 and MUSE™ prescriptions fell by two thirds to 132,000 [1]. It must be noted, however, that the phosphodiesterase-5 inhibitors (PDE5Is) are ineffective in about 22–35% of men [2]. Furthermore, of the men treated with oral agents, a significant proportion will ultimately fail (even after PDE5I dose escalation) secondary to progression of their disease. Additionally, there are a significant number of men with contraindications to PDE5Is. The result is a large number of men who are unable to utilize oral treatments for erectile dysfunction. Fortunately, second line therapies in the form of vacuum erection devices (discussed in detail in a separate

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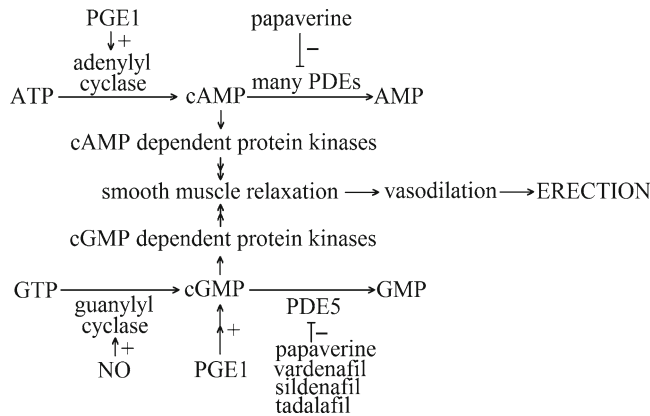


Fig. 9.1 Mechanism of action in producing erections for alprostadil (PGE₁), papaverine and the PDE-5 inhibitors

chapter), ICI and MUSETM are highly effective treatments that may be used when PDE5Is are contraindicated. Interestingly, there is also a significant subset of men who prefer intracavernous injection to PDE5I therapy, even when both are effective. Hatzichristou et al. [3] tested the efficacy of sildenafil in 155 men who were using intracavernous injections and obtaining successful results. Seventy-five percent (116) of those men achieved erections sufficient for intercourse. Of those 116 men in whom both treatments were successful, 33% (38 men) chose to continue intracavernous injection therapy instead of switching to oral medications. In short, despite being overshadowed by the mass marketing and convenience of administration of PDE5Is, knowledge and utilization of ICI and MUSETM remain critical in the approach to treatment of erectile dysfunction.

PGE₁ (Alprostadil)

Alprostadil acts via multiple pathways to cause cavernosal vascular smooth muscle relaxation and thus erection. The best characterized of these pathways is via increase in cAMP, which results in increased activity of cAMP dependent kinases, thus decreased cytoplasmic Ca²⁺, and relaxation of smooth muscle [4]. Other less well characterized pathways including cAMP mediated increases in cGMP and the indirect blockade of adrenergic

and angiotensin II signaling by PGE₁ [5, 6], are also likely to play a role. The mechanism is illustrated in Fig. 9.1.

Prostaglandin E₁ is now the preferred injectable agent and only transurethral erectile agent. Trade names for the injectable form are CaverjectTM (Pfizer Inc.) and Edex/ViridalTM (Schwarz Pharma). Generic injectable alprostadil is also available and typically is more cost effective, but does not include sophisticated delivery systems as described below. MUSETM (Medicated Urethral System for Erection, Vivus Inc.) is currently the only transurethral erectile agent approved by the FDA. Typical doses are 10–20 µg for injectable alprostadil and 250–1,000 µg for MUSETM alprostadil.

Response rates to alprostadil alone are high. In his 1996 metaanalysis [7], Porst reported a 70% rate of erection sufficient for intercourse with alprostadil injection alone in greater than 10,000 patients (see Table 9.1). This included 4,500 patients from his own series and more than 5,000 from a literature review. A later publication by Porst [8] reported on 162 patients using alprostadil ICI, 58 of which were followed for 4 years for a total of 16,886 injections. Success rates were greater than 90% in each year of the study (see Table 9.2).

Perhaps more important than generalized efficacy is efficacy in PDE5I non-responders. Shabsigh et al. [9] reported on 67 patients with no response to PDE5Is. Of these, 59 (88%) reported achieving erections suitable for intercourse using ICI.

Table 9.1 Response rates to PGE₁, papaverine, and papaverine + phentolamine [7]

Drug	Total # patients	Dosage	Responders
<i>PGE₁</i>			
Literature review	10,353	5–40 µg	7,519/10,353 (72.6%)
Porst series	4,577	5–20 µg	3,206/4,577 (70%)
<i>Papaverine</i>			
Literature review	2,161	30–110 mg	987/1,611 (61%)
Porst series	950	12.5–50 mg	370/950 (39%)
<i>Papaverine + phentolamine</i>			
Literature review	3,016	15 mg + 1.25 mg 60 mg + 2 mg	2,065/3,016 (68.5%)
Porst series	249	15 mg + 1 mg 50 mg + 2 mg	151/249 (60.6%)

Table 9.2 Success rates for alprostadil ICI over 4 years [8]

Year	#Patients	# Injections	Successful coitus (%)
1	162	6,935	6,293 (90.7)
2	81	3,937	3,691 (93.8)
3	68	3,233	3,050 (94.3)
4	58	2,781	2,679 (96.3)

Nagai et al. [10] reported a similar study which tested the efficacy of intracavernous alprostadil on 64 patients who failed PDE5I therapy. Ninety-one percent of these patients achieved erections suitable for intercourse with ICI alprostadil therapy.

Interestingly, the converse is also sometimes true and approximately a third of patients who do not respond to intracavernous therapy respond to PDE5Is. McMahon et al. [11] challenged 93 men who previously failed ICI with ED with oral sildenafil, 50 mg, escalating to 100 mg if the low dose was unsuccessful and found that 34% achieved erections suitable for intercourse. Thirty of these 32 required the 100 mg dose of sildenafil.

Administration

Caverject™ comes in two forms, a vial containing powdered alprostadil and a prefilled dialable syringe (Caverject™ Impulse). The first type comes in doses of 5 µg, 10 µg, and 20 µg and requires premixing with a diluent, which is either bacteriostatic water or simply sterile water. The injection site is selected as per Fig. 9.2. The penis is grasped by the glans and stretched against one

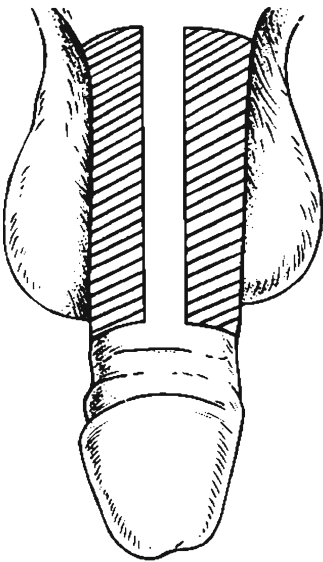


Fig. 9.2 Penile injection site. Shaded areas represent ideal injection sites for ICI [12]

thigh. The site is cleaned with an alcohol swab and the solution is injected into the corpus cavernosum as per Fig. 9.3. Care is taken to avoid the neurovascular structures on the dorsum of the penis and the corpus spongiosum on the ventral side of the penis. Pressure should be applied to the injection site for 5 min to prevent hematoma formation. The patient is instructed to alternate sites [12].

Caverject™ Impulse is available in two strengths 10 µg and 20 µg. Administration is similar except that both the diluent and the drug are present in the same syringe, and mixing is accomplished by turning the plunger rod. The patient’s dose is then dialed in on the syringe and the drug is injected in the

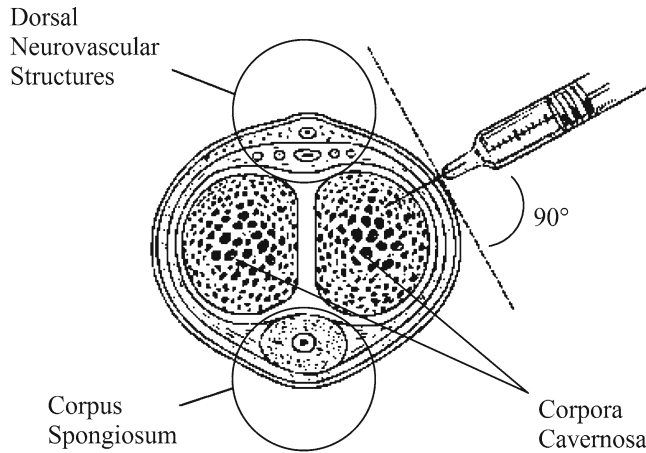


Fig. 9.3 Avoid injection into important dorsal and ventral penile structures [12]

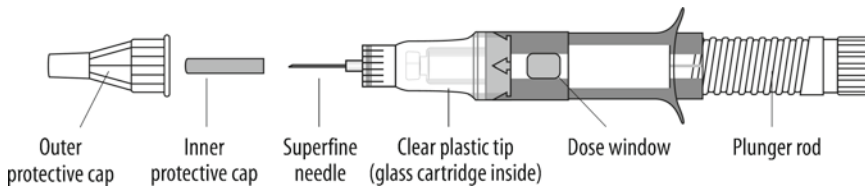


Fig. 9.4 Caverject™ impulse syringe [56]

same fashion as the original drug. The package insert diagram of the syringe is shown in Fig. 9.4.

Edex™ is a system somewhat similar to Caverject™ Impulse. It consists of a reusable injection device with single use and dual chambered medication cartridges. The system is shown in Fig. 9.5.

The cartridge is inserted into the injection device and the plunger is depressed to add the diluent to the medication. The medication is then swirled into the diluent and injected into the penis as per the above directions for Caverject™.

Generic alprostadil is available in powdered vials which require mixing with diluent and are administered as per the directions for Caverject™. Premixed generic alprostadil can also be obtained from specialized pharmacies. Recommended needle size is ½ in., 27–30 gauge.

Side Effects

Penile pain is the most significant side effect of alprostadil. In his 1996 literature review [7], Porst describes the experience of 2,745 patients over ten publications (see Table 9.3). He notes that the rate of penile pain with ICI alprostadil is 7.2%. Higher rates of pain are noted by the European Alprostadil Study Group [13]. They noted that 44% of their 848 patients experienced penile pain, but this was described as mild in over half of those patients and only 3% discontinued because of pain. Smaller studies note intermediate outcomes [14]. Priapism and fibrosis occurred at low rates of 0.36% and 0.8% [7]. The European Alprostadil Study Group [13] notes 0.9% and 4% rates for those same phenomena.

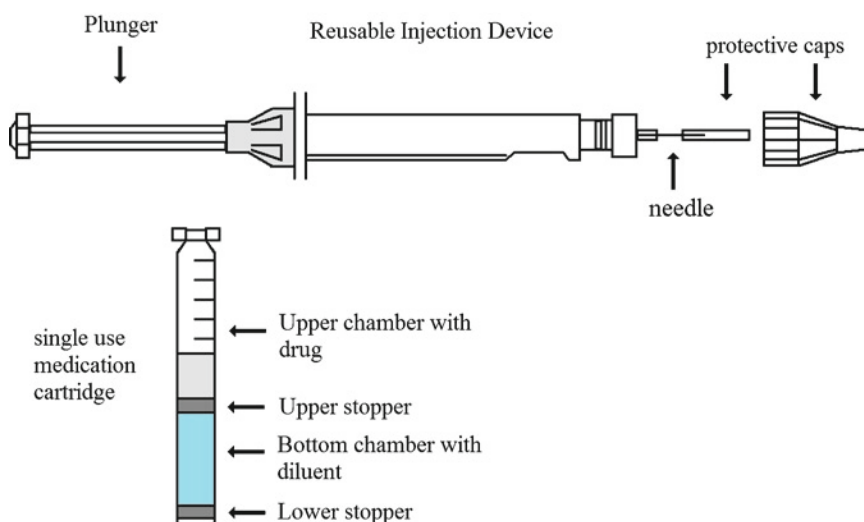


Fig. 9.5 Edex™ cartridge and injection device diagrams [57]

Table 9.3 Complications of ICI therapy: alprostadil, papaverine, and bimix [7]

Drug	Total # patients	Priapism >6 h	Nodules, indurations, fibrosis	Pain	Hematoma
Alprostadil	2,745	0.36%	0.8%	7.2%	6.6%
Bimix	2,263	7.8%	12.4%	11.6%	25.6%
Papaverine	1,527	7.1%	5.7%	4.0%	11.4%

Alprostadil Summary Points

- Alprostadil ICI is highly efficacious (>70%) in producing erections.
- In patients who fail PDE5 inhibitors, efficacy is ~90%.
- This is the most commonly used ICI agent. It is FDA approved and is available at most pharmacies.
- The most significant side effect of pain occurs at a rate of ~7% of patients. Higher rates of up to 40% are sometimes reported, but this is likely due to the inclusion of minor pain. It is popularly thought to have the highest rates of penile pain of all the ICI agents; however, this is not borne out in the literature.
- Rates of serious side effects of priapism and fibrosis are low.

Papaverine

Papaverine acts as a non-specific phosphodiesterase inhibitor to block both the breakdown of cAMP and cGMP, the accumulation of both of which leads to decreased intracellular calcium and thus smooth muscle relaxation [15]. The mechanism of action is illustrated in Fig. 9.1.

Papaverine was the first agent discovered to be effective as intracavernous pharmacotherapy for erectile dysfunction [16]. It is highly effective, but has fallen out of favor as monotherapy because of its high rates of fibrosis. Rates of success are between 60–93% [17–21], though some of these studies use very high doses of papaverine. Up to 120 mg of papaverine was used in Brindley's series of 73 patients. Porst's literature review [7] (Table 9.1) revealed 987 responders of 1,611 subjects (61%) for dosages ranging from 30 to 110 mg. His personal series of 950 patients showed a more modest response rate of 39% (390 responders) at more commonly used doses ranging from 12.5 to 50 mg.

Administration

Papaverine is obtained only as a generic medication in the United States. In Europe, it is approved and marketed as Androscat. It comes in 2 and 10 mL vials of papaverine 30 mg/mL solution. Typical doses range from 30 to 60 mg. It is and injected in the same fashion as Caverject™.

Side Effects

Virag et al. [22] reported one of the largest series of patients using papaverine ICI for erectile dysfunction. In this series, 163,042 papaverine injections were administered to 1,748 patients. The main side effects noted were priapism and fibrosis. Priapism occurred in 106 (6%) of patients after 235 (0.14%) of the injections. Fibrosis or nodule formation occurred in 187 (11%) of patients.

A literature review by Porst [7] which did not include the above study by Virag et al. revealed slightly different rates. Priapism was noted in 92 (7%) of 1,300 patients. Fibrosis, induration, and nodules occurred in 5.7% (60 of 1,056 patients) in the literature review. Other important side effects were injection site pain, which occurred in 4% (18/452 patients), and hematoma, which occurred in 11% (98/858 patients). Elevated liver enzymes, commonly seen with oral papaverine use [23], was seen in 1.6% (5/314) of patients using intracavernosal papaverine.

Papaverine Summary Points

- Papaverine is efficacious (39–61%); however, it's high rate of serious side effects, priapism, and fibrosis, at the high doses often needed for solitary use make its use unattractive.
- Both efficacy and side effects are likely dose dependent.

Phentolamine

Alpha-blockers inhibit smooth muscle contraction in the corpora by, as the class name implies, inhibiting alpha-adrenergic receptors. The main alpha-blockers used for erectile dysfunction are phentolamine and moxisylyte. Moxisylyte was available in Europe as Icavex, but was withdrawn in 2005. Currently, only phentolamine is widely used for erectile dysfunction.

Phentolamine has poor efficacy as a solo drug for erectile dysfunction. This stems from the fact that phentolamine induces tumescence relatively poorly, but instead it is more effective in countering the body's intrinsic cascade to induce detumescence by blocking the effects on norepinephrine. In a small study on eight impotent patients and two normal controls, Blum et al. [24] noted that the control patients achieved full erections, but that the impotent patients achieved only tumescence, not full erections.

Side Effects

Since phentolamine is almost universally used in conjunction with papaverine and alprostadil, data on its side effects as a solo therapy for erectile dysfunction is not adequately reported.

Intracavernous Injection Combinations

Combination therapy for intracavernous injections was conceived to improve efficacy as a result of the synergistic effects of the drugs, and later, to reduce side effects as a result of using lower dosages of each agent.

One difficulty encountered with the use of combination agents is the need for the pharmacy to compound these agents since there are no combination intracavernous injection drugs currently approved by the FDA. In Europe, bimix is approved in several countries. Besides the obvious logistical difficulties

in obtaining the medications, it also then becomes necessary for the patient to use combinations containing alprostadil with some degree of expediency. This is due to the degradation of alprostadil in solution which occurs at a rate of approximately 30% over the course of 2 months [25].

Bimix (Papaverine, Phentolamine)

The combination of papaverine/phentolamine is attractive since it is highly effective. No FDA approved combination exists. In Europe, a papaverine/phentolamine combination is marketed as Androskat. It is distributed as a 2 mL ampule of papaverine 15 mg/mL and phentolamine 0.5 mg/mL.

The combination of papaverine and phentolamine is seen as an alternative to alprostadil monotherapy when significant pain results from alprostadil injection. Unfortunately, bimix also results in significant pain in a large percentage of patients using it, though the populations experiencing pain from the two regimens do not necessarily overlap.

Efficacy of bimix in Porst's literature review [7] is shown in Table 9.1. It should be noted that bimix and alprostadil have nearly equivocal efficacies at 68.5% and 73% respectively. The approximate dose equivalency of 10 μ g of alprostadil has similar efficacy to 30 mg papaverine + 1 mg phentolamine.

Trimix (PGE₁, Papaverine, Phentolamine)

No standardized mixture is approved by the FDA or any European regulatory agencies and so these must be compounded by the pharmacy based on physician instructions. Concentrations of each component vary widely in the literature, but ratios of 12–30 mg papaverine: 10–20 μ g alprostadil: 1 mg phentolamine are fairly standard. Albaugh [26] recommends a mixture of 30 mg papaverine + 10 μ g alprostadil + 1 mg phentolamine per 1 mL with a starting dose of 0.1–0.5 mL.

Bechara et al. [27] reported a crossover study of alprostadil versus trimix in a group of 32 men who had failed high dose bimix therapy. In this study, 50% responded to trimix compared to only 22% responding to alprostadil. Rates of pain for alprostadil were significantly higher than for trimix (41% vs. 12.5%).

Seyam et al. [28] studied multiple combinations of trimix ingredients versus alprostadil in 180 men with erectile dysfunction. They found that all tested mixtures were highly effective and produce erections that are of equal frequency and quality to those produced by alprostadil. Sixty-eight percent of men using alprostadil and 67% of men using trimix achieved a rigid erection. However, duration of erections is longer than alprostadil and a larger number of episodes of priapism (5% vs. 0.6%) were produced. Interestingly, rates of pain were similar between the combined trimix group and the alprostadil group (14.5% vs. 17.9%, respectively).

Combining trimix with sildenafil increases efficacy even in patients who are recalcitrant to many other pharmaceutical therapies. McMahon et al. [11] found that of 62 patients who failed high dose sildenafil, high dose alprostadil, and high dose trimix separately, 29 (47.5%) achieved erections sufficient for intercourse by combining trimix with oral sildenafil. Trimix concentration used in this study was 24 mg papaverine + 20 μ g alprostadil + 1.6 mg phentolamine per 1 mL with a mean dose of 0.6 mL and a dose range from 0.15 mL to 1 mL.

Limited data exists about the potential for trimix to cause fibrosis. One study [29] reported 2 (3.8%) episodes of clinically evident fibrosis of 53 patients using trimix. Few studies report data on fibrosis. While it is important to know that fibrosis can occur on trimix, stated rates of occurrence are misleading as there is no standard ratio, dose, or recommended frequency of trimix administration, and fibrosis is likely a phenomenon related to dose of phentolamine.

Dose equivalence data comparing alprostadil to trimix was published by Kulaksizoglu et al. [30]. Table 9.4 demonstrates their findings.

Table 9.4 Dose equivalence of alprostadil and a trimix mixture [30]

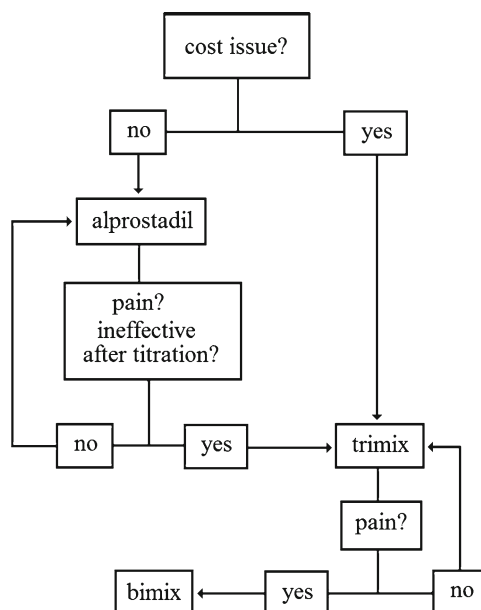
Alprostadil powder (μg)	Papaverine (mg)/phentolamine (mg)/alprostadil (μg)
4	1.47/0.05/0.49
8	3.2/0.1/1.1
12	4.6/0.15/1.55
16	6.8/0.22/2.27
20	7.6/0.25/2.5

Quadmix (PGE₁, Papaverine, Phentolamine, Atropine)

Minimal data exists about this mixture. Sogari et al. [31] randomized 230 men to office tests of trimix versus quadmix and found no significant difference between the two. Both resulted in full erection in 52 of the 114 in their respective groups.

ICI Combination Summary Points

- These are not FDA approved and thus must be compounded in the pharmacy, limiting their availability and use.
- Bimix (papaverine/phentolamine) was a popular combination. It is highly efficacious, but, like solo papaverine, is now infrequently used due to the high incidence of priapism and fibrosis. Currently, it is used when even small amounts of alprostadil result in penile pain necessitating its removal from the injection combination.
- Trimix (papaverine/phentolamine/alprostadil) is commonly used if alprostadil monotherapy produces excessive pain. The lower effective doses of each component limit the side effects while maintaining efficacy; it is at least as efficacious as alprostadil.
- Efficacy and side effect rates of trimix are highly variable and related to the concentration, doses, and frequency of its components.

**Fig. 9.6** Selecting an intracavernous injection agent [26]

Selection of Injectable Agents

Though all aforementioned agents are available, the small but real risk of significant permanent side effects of papaverine generally precludes its use, alone or with phentolamine, as an initial agent. This leaves only alprostadil and trimix as initial agents, both of which are appropriate choices. Generally alprostadil is chosen as a first line therapy given its low risk of priapism and fibrosis. Trimix may be used as an initial agent if alprostadil is cost prohibitive and a compounding pharmacy is available. Recommended starting doses for alprostadil and trimix are dependent on age and history of previous radical prostatectomy [26]. An algorithm to help select an intracavernous agent is shown in Fig. 9.6.

The package insert for Caverject™ recommends a 2.5 μg starting dose, with an optional second dose of 2.5 μg if the first dose is unsuccessful. Thereafter, titration may proceed by 5–10 μg steps. These increases after the first two doses should be at least 24 h apart. Albaugh notes that initial doses of 5 and 10 μg are common in the literature and suggests starting with 5 μg if the patient is less than 65 or has had a radical prostatectomy in the past 2 years.

Table 9.5 Representative prices of different ICI prices from one pharmacy [32]

Formula	Volume (mL)	Papaverine (mg/mL)	Phentolamine (mg/mL)	Alprostadil (µg/mL)	Price range (\$)
Trimix #1	10	16.7	0.56	5.6	55–70
Trimix #2	10	30	1	10	70–85
Trimix #3	8.25	21.8	1.21	15	60–80
Trimix #4	14.4	20.8	1.4	14	120–150
Trimix #5	12.5	24	0.8	20	80–110
Alprostadil #1	12.5	–	–	20	55–70
Alprostadil #2	12.5	–	–	40	55–75
Bimix	12.5	30	2	–	70–80

If the man is younger than 55 and has had a prostatectomy in the past 2 years, the dose should be reduced to 2.5 µg. If the man is greater than 65 and has not had a radical prostatectomy in the past 2 years, the initial dose may be increased to 10 µg.

Given the wide range of trimix mixtures, there are no standard recommendations on starting doses, as such, tailoring of mixtures and starting doses is the norm. As a starting point, the recommendations from Albaugh are as follows. A mixture of alprostadil 10 µg, phentolamine 1 mg, and papaverine 30 mg per mL is used. Starting doses are 0.1–0.2 mL for patients less than 60 years old who are less than 2 years post-prostatectomy. A higher dose of 0.3 mL is used in all other patients.

If pain or cost is a significant issue with alprostadil use (relevant in non-generic formulations), switching to trimix is recommended. If pain remains an issue with trimix, a subsequent change to bimix is recommended. Table 9.5 lists prices for generic alprostadil, bimix and trimix from one pharmacy [32].

Notes on the Clinic Visit

Intracavernous injections and MUSE™ should not be prescribed without first undergoing instruction and dose titration in the clinic. It may take several visits to find the correct drug and titrate the dose. It is also necessary to obtain consent before starting injections, especially considering the non-FDA approved nature of many of the ICI regimens. The patient should also be thoroughly educated about priapism and instructed on the

way to respond to a prolonged erection. Namely, the patient should first attempt ejaculation and if this is unsuccessful, oral terbutaline or pseudoephedrine can be taken in an attempt to initiate detumescence. If a painful, non-bendable erection persists after these have been tried, then a visit to the ER is warranted.

Contraindications to ICI

Intracavernous injections should not be used in men with conditions which predispose them to priapism. These notably include men with sickle-cell disease, multiple myeloma, and leukemia. They should also not be used in conditions which cause penile angulation such as Peyronie's or cavernosal fibrosis [12]. Also, they should not be used for patients in whom sexual activity is inadvisable.

Anticoagulation is not a contraindication to ICI. In a series of 605 injections in 33 men using warfarin for anticoagulation, Limoge et al. [33] recorded only three ecchymoses. This rate of 9% of patients is comparable to the 14% (434/3,143) of patients on PGE₁, papaverine, or bimix who developed hematoma in Porst's literature review [7]. Despite this, it is advisable that the physician stress the need, in anticoagulated patients, to place pressure on the injection site for five full, uninterrupted minutes of pressure to prevent hematoma.

Management of Side Effects

Patients must be made aware of the risk of priapism that occurs with ICI, particularly papaverine

ICI, use and educated about the proper course of action to take should they experience a prolonged erection. Sympathomimetic drugs, namely pseudoephedrine and terbutaline, are commonly prescribed or recommended to patients as a way of aiding detumescence in cases of prolonged erection and priapism. Some evidence exists to support their use. Lowe and Jarow [34] tested the use of terbutaline, pseudoephedrine, and placebo (sodium bicarbonate) in 75 men with prolonged erections due to alprostadil ICI. Both terbutaline and pseudoephedrine performed better than placebo, with detumescence resulting in 36%, 28%, and 12% respectively. Only the difference between terbutaline and placebo achieved statistical significance. Notable in this study, oral terbutaline or pseudoephedrine only worked in a third of patients. The other two thirds required irrigation and/or phenylephrine injections. None required surgical intervention. A study by Priyadarshi [35] showing detumescence in 42% of patients with ICI induced priapism compared with 15% detumescence with placebo in 68 men confirms the efficacy of terbutaline. Consequently, prescription for two tablets of terbutaline 5 mg is a common practice. The patient is instructed to take one, and if detumescence has not occurred, to take the second after 15 min.

Cavernosal fibrosis is another serious side effect of intracavernosal injections. It occurs most commonly with injectables containing papaverine. Rates are less than one percent with alprostadil,

approximately 6% with papaverine, and around 12% with bimix. Rates with trimix were 4% in a small study. These are likely dependant on dose and frequency of use. There is no treatment to reverse penile fibrosis, though it sometimes regresses on its own. Tsao and Nehra [36] recommend temporary discontinuation of ICI for 3–4 months to allow resolution. Persistence of fibrosis should prompt a change to more invasive methods of improving erectile function, i.e. placing a penile prosthesis.

Pain is a significant side effect, especially in a drug whose sole purpose is improvement in quality of life. Pain, coupled with the psychological aspects of injection of the penis can be seen as a fatal flaw of intracavernous injection. Reported rates of pain with injection are 7% for alprostadil, 4% with papaverine, 12% with bimix [7], and 12–15% with trimix [27, 28]. Significantly, it has been observed that pain decreases substantially during the course of treatment [13], so it is likely that the psychological component plays a large role. Albaugh and Ferrans [37] reported a study on pain with intracavernosal injection. They separated the pain into needle pain and medication pain, both measured on a scale of 0–10 with 10 being the worst imaginable pain. Findings are represented in Figs. 9.7 and 9.8.

Two other important results of this study were that only 4 of 65 patients reported that they would discontinue ICI as a result of pain, and pain was significantly higher in post-prostatectomy

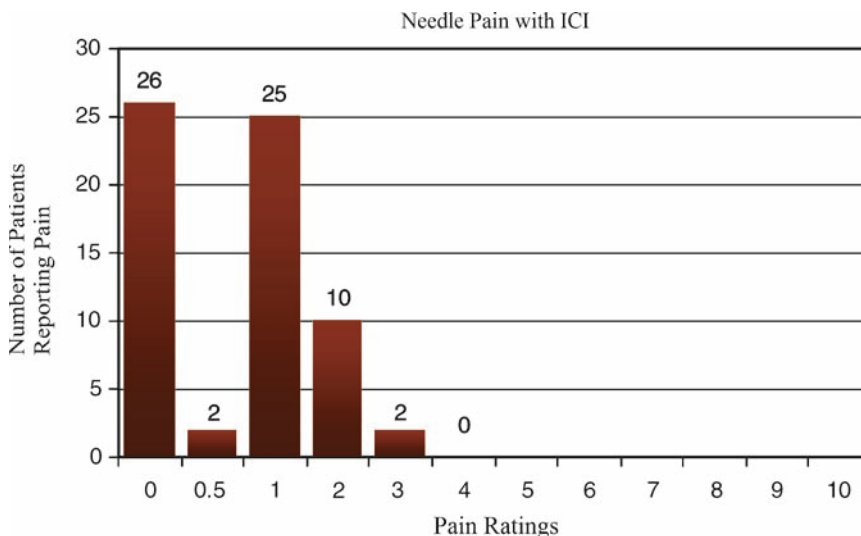


Fig. 9.7 Needle induced pain in ICI [37]

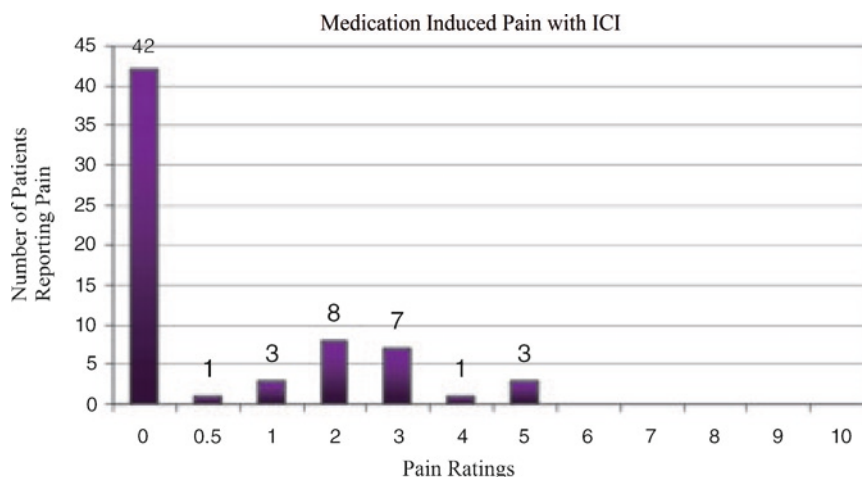


Fig. 9.8 Medication induced pain in ICI [37]

patients (52% vs. 24%). As stated previously, of patients in whom both PDE5Is and ICI are effective, one third will choose ICI [3]. Given this and the findings of Albaugh and Ferrans, patients seeking highly efficacious ED treatment can be counseled to try ICI with the assurance that most men have very minimal to no pain.

Contraindications and Side Effects Summary Points

- Contraindications to ICI: sickle-cell disease, multiple myeloma and leukemia, Peyronie's, cavernosal fibrosis, and patients in whom sexual activity is not advisable.
- Anticoagulation is not a contraindication to intracavernosal injections.
- Patients on ICI need to be educated about priapism. A prescription for two tablets of terbutaline 5 mg or instructions on pseudoephedrine use may be helpful in inducing detumescence, thus reducing ER visits for prolonged erections and priapism.
- Fibrosis is a serious side effect tied to papaverine use that warrants at least temporary discontinuation of treatment.
- Pain is reported as a side effect in many studies. However, it is insignificant in a large majority of cases and should not deter trial of ICI.

Muse™

Efficacy

MUSE™ (Medicated Urethral System for Erection, Vivus Inc.) is an alternative way to deliver alprostadil to the corporal bodies. MUSE™ involves the insertion of the delivery catheter into the meatus and depositing an alprostadil pellet in the urethra. One of the largest studies to describe the efficacy of MUSE™ was published by Padma-Nathan et al. [38]. Notable in this study, 995/1,511 patients had in-office responses to MUSE™. Of those patients with in-clinic response to MUSE™, only 299 of the 461 patients assigned to the MUSE™ arm of the trial achieved intercourse at home. Thus, the true success rate of MUSE™ in this large study was only 42–44%. Furthermore, of the patients who did achieve intercourse at home, only 73% of doses (2,634/3,593) were successful in achieving intercourse, orgasm, or a 10 min erection sufficient for intercourse. MUSE™ is also efficacious in men who have undergone radical prostatectomy. Costabile et al. [39] reported a 40% rate of at home success for MUSE™ in a group of 384 men greater than 3 months post-prostatectomy.

There are many direct comparison trials between MUSE™ alprostadil and ICI alprostadil, and these are summarized in Table 9.6. It is both intuitive and noteworthy that despite the

Table 9.6 Success rates of MUSE™ versus ICI (success rates listed as rigid erections/all erections sufficient for intercourse)

Trial	# pts	MUSE™ success rate	ICI success rate
Porst [40]	103	10/43%	48/70%
Werthman and Rajfer [59]	100	7/37%	49/89%
Shabsigh et al. [14]	68	NA/62% (with penile ring)	NA/93%

higher success rate of ICI, some studies [40] show that some patients prefer MUSE™. Additionally, it has been suggested as a possible rescue medication after ICI failure [41].

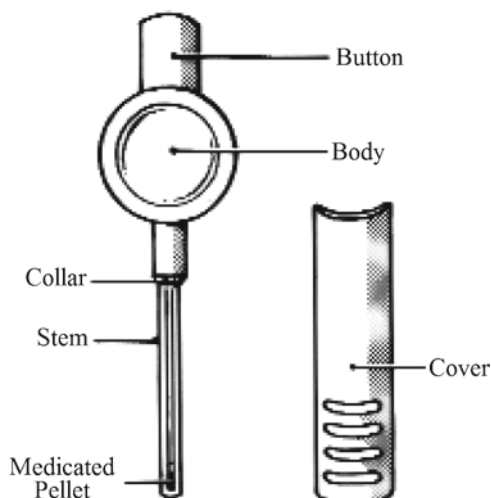
Administration

MUSE™ is available in doses of 100 µg, 250 µg, 500 µg, and 1,000 µg. The applicator is shown in Fig. 9.9.

Instructions for application include urinating before use. Residual urine in the urethra aids in dissolution and dispersal of the medicine along the urethra. The penis is then pulled straight and held pointing up. The 3.5 cm applicator stem is placed approximately 3 cm into the urethra and the button is depressed. The applicator is moved slightly to separate the pellet from the applicator tip and the applicator is removed. The penis is kept upright and rolled between the hands to aid in dissolution and dispersal of medication. The patient is then advised to walk or stand and not to lay flat for approximately 10 min to aid in blood flow.

Side Effects

MUSE™ alprostadil had similar rates of pain to ICI alprostadil, but priapism and fibrosis were rare. Side effect rates are noted in Table 9.7. Other side effects unique to MUSE™ compared to ICI were dizziness, hypotension, and sweating. These occurred at a frequency of 1–6%. Syncope occurred at a rate of <1% and urethral bleeding also occurred at a rate of 1–5%.

**Fig. 9.9** MUSE™ applicator [58]**Table 9.7** Side effects of MUSE™

Trial	# pts	Pain	Priapism	Fibrosis
Hellstrom [60]	68	9–18%	–	–
Porst [40]	103	31%	–	–
Werthman and Rajfer [59]	100	24%	1%	–
Shabsigh et al. [14]	68	25%	–	–
Padma-Nathan et al. [38]	486	33%	0%	0%

One strategy for optimizing erectile function in PDE5 inhibitor failures while still avoiding ICI is to combine MUSE™ with PDE5 inhibitors. The theoretical basis of this is strong as sildenafil acts to improve and sustain erections, but does not help in initiation, whereas alprostadil jump-starts erection initiation in addition to

MUSE™ Summary Points

- MUSE™ is less effective than ICI alprostadil (~40% vs. ~70%), but patients may prefer the intraurethral route as compared to the injection route.
- Rates of pain, priapism, and fibrosis with MUSE™ are comparable to those of ICI alprostadil. Penile hematoma does not occur with MUSE™, but urethral bleeding does occur in ~5%.

aiding in maintenance of erections. Raina et al. [42] published a small study of 23 post-prostatectomy patients unsatisfied with sildenafil. Patient satisfaction was measured using a questionnaire. An improvement from 38% satisfaction with sildenafil alone to 76% satisfaction with combined MUSE™/sildenafil was demonstrated.

Topicals

Efficacy

Compared with both oral and injection therapies, topical routes are quite attractive. Theoretically, systemic effects are minimized compared to the oral route, and it is certainly less invasive, and thus would undoubtedly be more popular than injection or intraurethral therapies.

To date, however, no sufficiently effective product exists. Topical alprostadil was combined with agents to improve skin penetration (SEPA and NexACT). Vitaros, the combination of alprostadil and NexACT, formerly called Alprox-TD, was recently denied approval by the FDA due to potential carcinogenicity [43]. In trials of alprostadil with SEPA, doses of 2,500 µg alprostadil were used with a resulting 39% of patients achieving erection sufficient for penetration versus 7% of the placebo group [44]. Unfortunately, baseline characteristics were not provided in this study. Ultimately, alprostadil/SEPA trials were discontinued because of their apparent lack of efficacy at safe doses.

A large trial of topical alprostadil without a skin penetration enhancer was also published by Padma-Nathan and Yeager [45] which showed a statistically significant, but very slight improvement in sexual function with topical alprostadil. This study used 100, 200, and 300 µg doses of alprostadil and achieved successful penetration rates of 57.5%, up from a baseline of 50% at the highest dose. A criticism of this study is that its high initial function rates do not adequately represent population seeking treatment for erectile dysfunction.

Topical Agent Summary

No agents are currently FDA approved for topical use, and none are currently being widely used off label.

Topical minoxidil, nitroglycerin, and papaverine were also tested variably alone and with skin penetration enhancers, but with little success.

Treatment of Erectile Dysfunction After Radical Prostatectomy

Penson et al. [46] analyzed the data from the large Prostate Cancer Outcomes Study which included 1,213 men who underwent prostatectomy for prostate cancer. They reported on urinary and sexual outcomes at up to 5 years postoperatively. Compared to baseline rates of 81% with erections firm enough for penetration, rates at 6, 12, 24 and 60 months were 9, 17, 22, and 28% respectively. Notably, the data was collected on men diagnosed from 1994 to 1995 and the 60 month survey was distributed in 2000. Thus, all patients theoretically were exposed to intracavernous injection in the early postoperative period, but sildenafil was not available until around 3 years postoperatively. Consequently, this provides a relatively good estimation of the natural history of erectile dysfunction post-prostatectomy, though the improvement in erectile function seen between years 2–5 could have been significantly affected by the introduction of PDE5 inhibitors. Indeed, 43% of the study patients had used sildenafil at least one time and of these 520 patients, 32% reported achieving an erection suitable for intercourse. Of the technologies available around the beginning of the study, intracavernous injection was tried by 17%, vacuum erection devices were tried by 25%, “other” therapies including MUSE™ were used

in 7%, and penile prostheses were implanted in 4% of the men.

Treatment of erectile dysfunction in post-prostatectomy men is unique compared with ED caused by other factors; in that rehabilitation (ED recovery) from treatment induced nerve and vascular injury are plausible. Thus, treatment of post-prostatectomy ED must keep two goals in mind: immediate erectile function facilitated by medication use and ultimate return to pre-prostatectomy erection status without use of adjunctive medications.

Penile injections do not require neuronal integrity to function. Injections have been shown to have the highest functional erection success rates following RRP with multiple studies showing $\geq 90\%$ efficacy at 6 months post-op [47, 48]. Like penile injections, MUSE™ works independent of nerve status. This medication has been shown to be effective in men with ED after RRP, producing an erection thought to be sufficient for intercourse in the clinic in 70% of subjects, and leading to successful intercourse at home in 40% of subjects compared to 7% in placebo [39]. Similar results were found in a study where 55% of subjects had successful intercourse and 48% effectively used MUSE™ long term (2 years) after RRP [49].

The potential to regain some erectile function with time (typically maximized at 18–24 months) after radical prostatectomy is well established in the literature. The potential of pharmacotherapy to aid in return to pre-op, baseline erectile function status with return of spontaneous, medication unassisted erections adequate for penetration is not only theoretically intuitive, but also has been reported in numerous small studies. The theoretical support is drawn from the results of denervating the cavernosum of rats and observation of the ensuing hypoxia and fibrosis [50, 51] coupled with the knowledge that erections increase the oxygenation of the cavernosum. Phosphodiesterase inhibitors are likely the most commonly used rehabilitative pharmaceutical though they have lower theoretical rehabilitative potential than

ICI or MUSE™ as they require a threshold level of neural integrity to be effective. McCullough et al. [52] published a study using 50 and 100 mg nightly doses of sildenafil followed by an 8 week washout period. This study showed that men on daily sildenafil treatment had much higher rates of erectile function than those taking placebo, namely 24% for 50 mg sildenafil and 33% for 100 mg sildenafil versus 5% for placebo.

Rates of return to spontaneous erection with ICI and MUSE™ should theoretically be higher because they are more effective at producing erections during the neuropraxic period post prostatectomy. Montorsi et al. [53] published one of the first papers on erectile rehabilitation comparing 3 months of t.i.w. ICI alprostadil to patients

Post-prostatectomy Penile Rehabilitation Summary Points

- Unlike PDE inhibitors, efficacy in achieving erections adequate for penetration in the post prostatectomy setting is well established for ICI ($\geq 90\%$) and MUSE™ (40–55%).
- Intracavernous injections and MUSE™ have both been studied for rehabilitation potential in post-prostatectomy patients, and show promise. In small studies, 40–60% of patients who were potent prior to prostatectomy regained unassisted erectile function, this is compared to only 10–20% who did not use MUSE™ or ICI (see Table 9.8).
- No randomized controlled trials have been done to test the efficacy of MUSE™ or ICI against PDE5 inhibitors for penile rehabilitation, but it is likely that both are superior to PDE5 inhibitors. Escalation of PDE5 inhibitors to either MUSE™ or ICI therapy, or combination therapy of these drugs will likely be utilized in future penile rehab programs (Table 9.9).

Table 9.8 Penile rehabilitation: rates of return of spontaneous erectile function with different pharmacotherapy regimens

		Time of assessment (Months post prostatectomy)	Rate of return of spontaneous EF	
Therapy/study	Study size		Treatment group	Non-treatment group
<i>PDE5I</i>				
McCullough et al. [52]	54 (17 pts @ 50 mg, 18 pts @ 100 mg, 19 pts placebo)	11	24%, 33%	5%
<i>ICI</i>				
Montorsi et al. [53]	27 (12 ICI, 15 no tx)	6	67%	20%
Mulhall et al. [54]	132 (58 ICI protocol, 74 non protocol)	18	52%	19%
<i>MUSE</i> TM				
Raina et al. [55]	91 (56 MUSE TM , 35 prn)	9	40%	11%

receiving no treatment. Patients were assessed at a 6 month follow up, i.e. after a 2 month period without t.i.w. alprostadil. Eight (67%) were noted to have return of spontaneous erection which only required the use of ICI alprostadil one in 4.2 times for successful intercourse. The other four patients in the ICI group reported needing to use ICI greater than 50% of the time to achieve successful intercourse. Only 20% of the placebo group reported spontaneous erections that were sufficient for intercourse. This study, although often cited, likely suffers from methodological flaws as no other studies have replicated these impressive results. A larger study by Mulhall et al. [54] examined a group of men with functional preoperative erections prior to prostatectomy and who were non-responders to sildenafil in the early post-operative period. At 18 months postop, men who followed a regimen of t.i.w. ICI were compared to those who did not follow the protocol. Of the 58 men in the protocol group, 52% had a return of spontaneous erections compared to 19% of the 74 men in the non-protocol group. Although encouraging, this study suffers from a high degree of self selection bias, as the patients who were not having success and ultimately stopped treatment, but

adhered to follow-up were simply included in the non-protocol group.

The efficacy of MUSE™ in penile rehabilitation has also been tested. Raina et al. [55] reported on 97 men post-prostatectomy, 56 of whom used t.i.w. MUSE™ for 6 months and 35 of whom used only p.r.n. erectile aids. Those who used MUSE™ attained a fourfold higher rate of spontaneous erections than those who did not (40% vs. 11%).

Conclusion

Intracavernosal injection therapy and MUSE™ remain excellent treatment options for men suffering from erectile dysfunction. Both have demonstrated effectiveness in numerous settings, and are especially relevant in men for whom PDE5I therapy is contraindicated, not tolerated, or ineffective. ICI and MUSE™ maintain effectiveness in the post-prostatectomy period, and likely will play a central role in aggressive penile rehabilitation programs.

Table 9.9 Chapter summary table

Drug	Mechanism	Efficacy	Side effects	Comments
ICI alprostadil	Increases cAMP and cGMP	>70%	Pain ~7% Priapism <1% Fibrosis <1%	High efficacy, good first line for ICI, reputation as causing highest rates of pain not borne out in head to head trials
ICI papaverine	Non-specific PDE inhibitor	39–61%	Pain 4% Priapism 7% Fibrosis 6%	Rarely used as solo therapy, efficacy and fibrosis both dose dependant
ICI phentolamine	Alpha-blocker	NA	NA	Rarely used as solo therapy
Bimix (papaverine + phentolamine)	PDE inhibitor + alpha-blocker	68.5%	Pain 12% Priapism 8%	High efficacy, poor side effect profile
Trimix (papaverine + phentolamine + alprostadil)	Direct and indirect increase in cAMP/cGMP + PDE inhibitor + alpha-blocker	>70%, up to 90%	Fibrosis 12% Pain 12–15% Priapism 5% Fibrosis 4%	High efficacy, low side effects, low cost
Quadmix (papaverine + phentolamine + alprostadil + atropine)	Release of endothelium derived relaxing factor (Direct and indirect increase in cAMP/ cGMP + PDE inhibitor + alpha-blocker)	As per trimix	Variable, dependant on mixture/dose Similar to trimix	No apparent additional efficacy over trimix
MUSE™	Increases cAMP and cGMP	~40%	Pain ~25–30% Urethral bleeding 5%	Intermediate range efficacy, usually more acceptable to patients than ICI
Topicals (main investigational drug was alprostadil)	Dependant on drug	Very poor in safe doses	Genital “warmth” to severe genital pain, dose dependant	None are currently on the market, no accepted off-label use

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Chapter 10

Quantification of Erectile Dysfunction After Prostate Cancer Treatment

Jeff Albaugh, Robert O. Wayment, and Tobias S. Köhler

Abstract Determining if a man has erectile dysfunction (ED) seems like an innocuous task. However, this seemingly straightforward determination is fraught with peril, especially when applied to the reporting of erectile function after prostate cancer treatment. Is the wide range in ED outcomes following prostate cancer treatment really due to inherent biologic variability, or are there biases or other factors at work confounding the data? The goal of this chapter is to detail the specific difficulties for the quantification of ED in the context of challenges inherent to all scientific research: optimization of a study's internal and external validity. Only through the understanding of the factors that influence the quantification of ED can consistent, standardized outcomes be obtained to advance the field of study.

Keywords Cancer of the prostate • Biostatics • Comorbidities for ED • ED measurement • Neuropraxia • Androgen ablation therapy

Introduction

Determining if a man has erectile dysfunction (ED) seems like an innocuous task. However, this seemingly straightforward determination is

fraught with peril, especially when applied to the reporting of erectile function after prostate cancer treatment. This point is well illustrated by the drastic variance of ED rates following prostate cancer treatment found in the scientific literature of 9–100%. Indeed, experts have recently stated that the data on erectile function outcomes after prostate cancer treatment are often poorly interpretable, inconsistent, and yield widely disparate results [1]. Is the wide range in ED outcomes following prostate cancer treatment really due to inherent biologic variability, or are there biases or other factors at work confounding the data? The goal of this chapter is to detail the specific difficulties for the quantification of ED in the context of challenges inherent to all scientific research: optimization of a study's internal and external validity. Only through the understanding of the factors that influence the quantification of ED can consistent, standardized outcomes be obtained to advance the field of study.

ED Quantification, Biological Variability, and Study Validity

Sexual dysfunction exists as one of the most significant detractors to the quality of life measures in patients treated for localized cancer of the prostate (CAP). A study in 2003 found that even as long as 92 months after radical retropubic prostatectomy (RRP), more than 75% of the treated men were sad or tearful about ED and over 70% felt that the quality of life was adversely

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affected [2]. ED is an unfortunate consequence that accompanies CAP treatment.

After an extensive abstraction process, an AUA prostate cancer guideline update panel task force attempted to establish ED prevalence rates after RRP, XRT, and brachytherapy, with non-specific results from 31 articles. The article noted that subcategorization of results according to specific variables was not feasible due to imprecise or absent descriptions of these variables in the original articles. In an attempt to develop a basic source for patients and physicians to look up the likelihood of the developing ED after the various prostate cancer treatments stratified by risk factors that were listed, we summarize the 31 articles previously abstracted in addition to articles commenting on cryotherapy, androgen ablation, and prostate cancer treatment comparison studies. In selecting these articles, we placed importance on studies with high power, or those that elaborated on important patient factors (age, medical comorbidities, and preoperative erectile status) and those that used consistent ED definitions and validated ED information collection tools. Our experience was similar to that of the AUA task force, finding unacceptably large variance in the data and the quality of study methodology. Table 10.1 summarizes our findings, and may be of some use to individuals who happen to have matching criteria for their particular treatment choice. Indeed, the final version of Table 10.1 predicated the focus of the remainder of the chapter, how to perform high-quality trials for ED quantification.

Review of literature reveals that 9–100% of men have erectile dysfunction following prostate cancer treatment. Substratification of the different prostate cancer treatment approaches leads to a similarly disturbing wide range of ED prevalence: 24–87% after RRP; 13–70% after radiation therapy (brachytherapy [BT] or external beam radiation [XRT]); 53–95% after cryotherapy (CT); and 45–92% in patients undergoing hormonal androgen ablation (AA) (Table 10.1). Do these wide ED prevalence rates represent truth from biological variability, or are different factors at play? Although there is likely some biologic variability in the preservation of erectile

factors after prostate cancer treatment insult (genetics, nutrition, age, wound healing, etc.), flawed study methodology of ED quantification studies likely lies at the heart of the matter.

If there were no differences between humans, scientific research would be extremely easy. Any one subject could be exposed to an intervention, and that one subject's intervention outcome could be extrapolated to the general population. Of course this is not the case, and we are faced with numerous challenges on how to infer study findings from our sample to our target population. Hence, the foundation for the development of biostatistics stems from the challenges of extrapolating useful real world data from a sample which is inherently biologically variable [3].

The transfer of “truth” from a study sample to the general population requires that the study has optimized both internal and external validity. The categorization of study criteria into internal and external validity provides a conceptual framework to organize data. They are by no means mutually exclusive, and factors among them often overlap. Internal validity refers to the degree to which results are true for the patients being studied. In general, factors related to internal validity are study protocol and the statistics utilized. Common detractors to internal validity for ED quantification include varied definitions of ED, inconsistent use of ED measurement tools that have been validated, time-frame of when to measure ED, patient report versus researcher acquisition of ED data, the use and reporting of phosphodiesterase inhibitors, study completion rates, and the role of chance. External validity refers to the degree to which study results can be generalized to the population outside the study. Factors related to external validity include eligibility and exclusion criteria. Some of the most likely sources to decrease external validity in ED quantification include patient interest and partner availability; patient age; baseline sexual function; physician factors; the ability to spare nerves with CAP treatment; and comorbidities for ED.

The importance of study design and execution cannot be overstated. Others have advocated the use of a qualified biostatistician in study design and the analysis for trials in ED for

Table 10.1 Prevalence of erectile dysfunction following treatment for localized prostate cancer

Author and topic	Subjects and setting	Prevalence of erectile dysfunction	Conclusions
<i>Radical retropubic prostatectomy</i>			
Quinlan et al. [49] Radical prostatectomy	600 patients underwent radical prostatectomy (503 men potent preoperatively included in data analysis); university-based urology practice; Baltimore, MD	Prevalence of potency: 68%. 76% potency for preservation of both neurovascular bundles; 63% for 1 preserved bundle and 1 partially preserved bundle; 56% for wide excision of 1 bundle; 0% for bilateral excision	Return of sexual function postoperatively is related quantitatively to the degree of preservation of autonomic innervation. In the future, when it is necessary to excise the neurovascular bundle on 1 side, autonomic restoration should be considered through nerve regeneration, for instance, by partial excision or cavernous nerve grafts. Age was also a factor, as in men under 50 with adequate postoperative potency, there was no influence if 1 bundle was excised
Catalona et al. [51] Radical prostatectomy	784 men (mean age 64.02 years) treated by nerve sparing radical retropubic prostatectomy; university-based urology practice; Saint Louis, MO	295 men assessed for sexual function. Prevalence of postoperative potency: 63% in bilateral nerve sparing group, 41% in unilateral group	Erection recovery correlated with patient age and tumor stage in patients treated with bilateral nerve sparing. No significant correlations were found in unilateral nerve sparing, which also had lower potency rates
Jonler et al. [52] Radical prostatectomy	93 men (mean age at surgery 64 years, mean age at follow-up 66 years) underwent radical prostatectomy; university-based urology practice; questionnaire; Madison, WI	Prevalence: 9% of patients able to have full erections postoperatively, 38% partial erections. 51% reported sexual function posturgery was a substantial problem. 17% reported trying ED treatment	Adverse sequelae following surgery were high, including ED. However, a majority of patients were happy with treatment selection
Noldus et al. [22] Radical prostatectomy	511 patients aged 42–75 (mean 63.4 years) underwent radical retropubic prostatectomies; university-based urology practice; Germany	Prevalence: All patients with nonnerve sparing surgery had the loss of potency. 26.7% of patients with unilateral nerve sparing had full erection detected by Doppler sonography	Commonest late complication in this series was ED. Authors believe that they can offer unilateral nerve sparing to 20% of patients. The surgery, as it improves, may lead to a higher potency rate. Patients with intact pudendal nerves may be ideal candidates for intracavernous injections or vacuum devices
Vegh. [53] Radical prostatectomy	82 patients (average age 62, none over 70) underwent radical prostatectomy; military hospital urology practice; Hungary	Prevalence of ED: 85%	Radical prostatectomy was performed by two methods – bladder-neck pull-down to the pelvic floor ($n=40$), and urethral trunk sewing to the bladder neck ($n=42$). The number of cases of ED was similar (36 and 35, respectively). Mention was made of nerve sparing

(continued)

Table 10.1 (continued)

Author and topic	Subjects and setting	Prevalence of erectile dysfunction	Conclusions
Catalona et al. [23] Radical prostatectomy	1,870 men aged 38–79 (mean 63) underwent radical retropubic prostatectomy (93% at least partial-nerve sparing); single surgeon at university-based urology practice; Saint Louis, MS	858 patients analyzed for ED. Prevalence: 68% (of 798) in bilateral nerve sparing group had recovery erections; 47% (of 60) in unilateral group	Results in sexual preservation comparable to other studies. Recovery of erections linked closest to younger ages and bilateral nerve sparing surgery
Stanford et al. [24] Radical prostatectomy	1,291 men treated with radical prostatectomy; population-based cancer registries; six regions of the USA.	Prevalence: 59.9% erections not firm enough for intercourse, 44.2% unable to have any erections at all	Radical prostatectomy is associated with significant ED, which varied with age and race. 67.5% of patients used sexual aids following surgery
Noldus et al. [54] Radical prostatectomy	366 patients aged 42–74 years (mean 62.5) underwent nerve-sparing radical prostatectomy; university-based urology practice; questionnaire; Germany	76% of patients returned questionnaires. Prevalence: 69% reported rigidity in unilateral nerve sparing, 93% in bilateral. Unassisted erections satisfactory for intercourse in 13–16% of unilateral nerve sparing, 50–60% in bilateral	Erection recovery depends on the extent of preservation of neurovascular bundles. A high rate of men reported erections insufficient for unassisted intercourse, but these patients may benefit from assisting drugs
Salomon et al. [55] Radical prostatectomy	Radical prostatectomy 205 patients treated with radical prostatectomy; authors proposed score to jointly evaluate cancer control and functional results; France, Germany	Prevalence: 32.7% of patients potent one year after radical prostatectomy	Authors developed a score to help evaluate both cancer control and functional results following surgery. Potency maintained in some patients, but not all patients with good cancer control are potent
Penson et al. [56] Radical prostatectomy	1,213 patients after radical prostatectomy followed for the quality of life for 5 years. Large population-based cohort from six Surveillance, Epidemiology, and End Results (SEER) cancer registries. Prostate cancer outcomes study (PCOS) USA	Only 28% of men reported erections firm enough for intercourse at 5 years. Functional outcomes were stratified by nerve sparing status and age. Men with bilateral nerve sparing were more likely to have erections sufficient for intercourse at 5 years compared to unilateral or no nerve sparing; 40% vs. 23% & 23%. Men who had bilateral nerve sparing were sub stratified by age with 61% of men age 39–54 years were able to achieve erections sufficient for intercourse compared to 49% of men 55–59 years, 44% of men 60–64 years and 18% of men older than 65	71% of men were unable to achieve erections sufficient for intercourse 5 years following radical prostatectomy. Few patients experienced and increase in function between years 2 & 5, however, function remained stable in the majority of men over this time frame. These results should be applicable to the general population and may aide in counseling patients preoperatively
<i>Laparoscopic prostatectomy</i>			
Guillonneau et al. [57] Laparoscopic prostatectomy	120 patients aged 50–72 years (mean 64) treated with laparoscopic prostatectomy; 40 patients questioned about sexual function; Paris, France	Prevalence: 45% of 20 patients sexually active preoperatively reported spontaneous erections at under 3 months follow-up (1 patient reported rigidity sufficient for intercourse)	Laparoscopic radical prostatectomy is associated with ED at short-term follow-up; systematic preservation of neurovascular pedicles may allow more patients to resume satisfactory sex lives

Salomon et al. [29] Laparoscopic prostatectomy	235 patients aged 46.9–77.1 (mean age 63.8) treated with laparoscopic radical prostatectomy; university-based urology practices; self-administered questionnaire; New York, France	Prevalence: For 77 patients, potency increased from 16.8% to 49.3% in the first year after surgery. With 0, 1, and 2 neurovascular bundle preservations, potency increased from 7.4%, 15.4%, and 23.5% one month post-surgery to 38.4%, 53.8%, and 58.8% Prevalence: 21 % reported erections at 1 month after surgery; 31% at 3 months; 29.1% at 6 months; 53.8% at 1 year	Preservation of neurovascular bundles, young patient age, and surgeon experience are the main factors associated with best erectile function results. Bilateral nerve preservation also produces better results. Overall results compare favorably to previous similar studies The rate of erections at 1 year is similar to that for open surgery. Patients did better with bilateral than unilateral nerve preservation. Overall encouraging results following laparoscopic prostatectomy
Katz et al. [58] Laparoscopic prostatectomy	232 men treated with laparoscopic radical prostatectomy (61.6% potent pre-operatively); pre- and post-operative questionnaires; France		
<i>External beam radiation therapy</i>			
Shipley et al. [26] Radiation therapy	2,611 patients underwent irradiation; literature review; Boston, MA, Philadelphia, PA, Houston, TX	Prevalence: Potency maintenance ranged from 30 to 61% Prevalence of ED: 27%	The broad range of ED frequency most likely reflects heterogeneity in age groups as well as difficulties with definition of ED. Radiation induced impotence is most likely due to endarteritis of internal pudendal and penile arteries Occurrence of ED noted to be dependent on patient age, baseline level of sexual activity, and tumor stage. In the future it would be beneficial for physicians of different disciplines to jointly develop protocols to determine optimal management for patients to maximize efficacy and minimize morbidity
Perez et al. [27] Radiation therapy	963 men treated with radiation therapy; university-based radiation oncology practice; Saint Louis, MO		
Hart et al. [59] Conformal sequential neutron photon irradiation	76 patients aged 45–80 (mean 65.7) underwent conformal sequential neutron photon irradiation (with or without neoadjuvant hormonal therapy); university-based radiation oncology practice; Detroit, MI	Prevalence: 67% of 52 initially potent patients retained potency following treatment	A significant number of patients receiving neutrons as part of EBRT maintained erectile function. Patients with functional pretreatment erections were more likely to maintain function than those with nonfunctional erections. No significant potency changes seen with age or neoadjuvant therapy
Reddy et al. [60] 3D-conformal neutron and proton irradiation	75 patients underwent 3D conformal neutron and proton irradiation; self-assessment questionnaire; Detroit, MI	Prevalence: 87% of patients able to obtain partial or full erections before treatment maintained erectile function post-therapy. However, only 25% of all patients had unchanged sexual function. 11 patients underwent therapy for ED	The majority of patients were able to obtain erections following radiation therapy, but many of these patients reported less satisfactory function. Rates of impotence were similar between photon and neutron treatment

(continued)

Table 10.1 (continued)

Author and topic	Subjects and setting	Prevalence of erectile dysfunction	Conclusions
Hanks et al. [61] 3D-CRT	223 patients aged 50–84 (mean 69) treated by 3D-CRT; cancer hospital-based urology practice; Philadelphia, PA.	3-year potency only assessed for 23 patients aged <65 years. Prevalence: 61 % potency at 3 years	The rate of GI and GU morbidity in this series of low-stage cancers is low. 3-year prevalence of potency preservation is favorable, but only was assessed in limited, small group of patients
Wilder et al. [62] 3D-CRT	198 men treated with 3D-conformal radiotherapy (3D-CRT); 51 patients with pre-treatment PSA of 10 ng/mL or less, Gleason score of 6 or less, and a 1997 AJCC stage T1bN0M0 to T2bN0M0 were assessed; university-based radiation oncology practice; Davis, CA	Of 35 initially potent patients, 0%, 17%, and 37% were impotent 1, 2, and 3 years following 3D-CRT, respectively	Preliminary data suggest ED risk with 3D-CRT similar to conventional radiotherapy. Multivariate analysis showed age, dose, TURP history had no effect on potency. 3 of 7 patients using sildenafil after becoming ED achieved adequate erections, suggesting the mechanism of ED following 3D-CRT is arteriogenic
Yeoh et al. [63] Radiation therapy	120 men treated with radiotherapy aged 44.3–82.8 (63.6); university-based radiation oncology practice; Australia	Sexual function questionnaire only fully completed by 25 patients. 9 (25%) impotent at baseline, increased to 13 (52%) 1 month after therapy, and sustained at 1 and 2 years	Sexual questionnaire incomplete for most patients, but the approximate 30% increase in ED following therapy is consistent with most other similar studies
Michalski et al. [64] 3D-CRT	424 patients registered for 3D-CRT (393 analyzable for toxicity); university-based radiation oncology practice; Saint Louis, MO	Prevalence: No specific data on ED. Grade 2+ GU toxicities 10% for dose level I (68.4 Gy), 13% for dose level II (73.8 Gy)	The occurrence of low-grade toxicity was higher with increasing doses of radiation. However, the occurrence of grade 3 toxicity did not rise with increasing radiation dose. No grade 4 or 5 toxicity was recorded. Further clinical trials should use quality of life measures to assess tradeoffs between severity and rates of toxicity
<i>Interstitial radiation therapy</i>			
Wallner et al. [65] I-125 implantation	62 patients aged 58–80 (mean 67 years) treated with CT-based transperineal I-125 implantation; university-based radiation oncology practice; New York, NY	Prevalence: Of 38 patients sexually potent prior to implantation, 81% remained potent at 3 years	Short-term potency preservation compares favorably with nerve-sparing prostatectomy
Wallner et al. [66] I-125 implantation	92 patients treated with CT-based transperineal I-125 implantation; university-based radiation oncology practice; New York, NY	Prevalence: Of 56 patients sexually potent preimplantation, 86% remained potent at 3 years. All patients under 60 remained potent post-implantation	Sexual preservation compares favorably with short-term results following prostatectomy. Morbidity may decrease with increased experience

Zelefsky et al. [30] I-125 implantation	248 men aged 45–80 (mean age 65) with localized cancer underwent CT-planned permanent I-125 implantation with transperineal technique; university-based radiation oncology practice; New York, NY	Prevalence = 29% following therapy, 2- and 5-year likelihood of post-treatment ED in patients who were potent initially was 21% and 43%, respectively	Prevalence following transperineal implantation is substantial. Authors suspect that impotence rates after this technique are underestimated in literature, but that decreased ED rates may be achieved with decreased doses around neurovascular bundle
Talcott et al. [33] Brachytherapy	105 patients (median age 70 at treatment, 75 at survey) treated by brachytherapy alone or plus EBRT; cross-sectional survey; Boston, MA	Prevalence: 50% had no erections 4 weeks prior to survey, 73% had no erections firm enough for penetration without manual assistance. 51% of those having baseline erections reported no erections at all in survey	ED was found in most patients following therapy. However, because the study design precluded documenting baseline symptoms and subsequent clinical interventions, the contribution of factors other than brachytherapy is unclear
<i>Androgen deprivation therapy</i>			
Potosky et al. [67] Androgen deprivation (medical/surgical)	431 men with all stages of prostate cancer treated with ADT; surgical $n = 132$ (orchiectomy) & medical $n = 299$ (LHRH agonist); patient completed surveys and SEER database; six different regions, USA	Pretreatment impotence rates of 56.7% and 51.9%. Rates increased to 85.1% and 83.9% with treatment. 73% of men who had erections before treatment reported no erections following treatment. No significant difference between treatment groups	Sexual function is a significant impairment after androgen deprivation and are similar between surgical versus medical therapy
Potosky et al. [68] Androgen deprivation or watchful waiting	661 men with new diagnosis prostate cancer treated with ADT ($n = 245$) or no therapy ($n = 416$) for 1 year; SEER database and patient completed surveys; six different regions, USA	Rate of new onset impotence in ADT was 80% compared to 30% for no therapy. ADT group reported more discomfort and decrease in vitality	Men quality of life parameters are decreased in ADT, especially erectile function and libido. Patients were more pleased with the decision to undergo ADT despite the morbidity
Hoffman et al. [31] Androgen deprivation; SEER database	2365 men with localized prostate cancer in six registries for the SEER database. Patient satisfaction with their chosen modality treatment was measured as part of prostate cancer outcomes study at 2 years following treatment. Mailed patient surveys; six centers, USA	179 men had undergone ADT as the primary treatment for localized prostate cancer. Erectile dysfunction was reported by 93.9% of men; 85.8% had no erections at all and another 8.1% reported “some or a lot” when describing erectile dysfunction	The majority of patients were satisfied with their treatment decision (among all groups). Among men with normal function at baseline, 40% of men who completely lost erectile function reported that poor function was only a small problem. Erectile dysfunction is a major side effect for most men undergoing ADT

(continued)

Table 10.1 (continued)

Author and topic	Subjects and setting	Prevalence of erectile dysfunction	Conclusions
<i>Cryoablation therapy</i>			
Bahn et al. [69] Cryoablation	590 men underwent primary cryoablation for localized prostate cancer. Men were followed for the efficacy of treatment and long-term side effects. Mean follow-up of 5.43 years was available; Rochester, MI	Of 373 men who were potent before surgery, 94.9% were impotent; 5.1% recovered potency at an average time of 16.4 months	Cryoablation shows efficacy as a treatment for localized prostate cancer with long-term follow-up. Cryoablation however, is a significant side effect of treatment in most men
Han et al. [70] Cryoablation	104 men at multiple centers treated with primary cryoablation for organ confined prostate cancer. Patients had minimum of 12 months follow-up; multiple centers	87% of previously potent men were impotent following surgery. Few men had penile paresthesia that resolved	Impotency is a significant problem in the majority of men treated with cryoablation of the prostate
Ellis et al. [34] Cryoablation with penile rehabilitation	416 men treated with primary whole gland cryoablation for localized prostate cancer. 127 (39.1%) were potent preoperatively and were followed for the return of potency at 6-month intervals up to 5 years. Patients were encouraged to use a vacuum erection device daily from 6 weeks on and oral PDEI every other day from 6 months on until the return of potency. Potency was defined as an erection sufficient for intercourse with or without oral PDEI; Arlington, TX	Followed prospectively, men potent preoperatively who used the outlined penile rehabilitation plan could regain potency at a rate of 19.1%, 48.5%, and 51.3% at 1, 2, and 4 years, respectively. Potency is defined as the ability to achieve an erection sufficient for intercourse with or without oral PDEIs. The percent of men using oral PDEIs is not reported	Aggressive penile rehabilitation may allow approximately half of men treated with primary whole gland cryoablation to achieve erections sufficient for intercourse 4 years following surgery. These men may or may not be using oral PDEIs even after therapy. Return of sexual function improves with time from surgery
Asterling and Greene [71] Cryoablation	57 men were followed prospectively for erectile dysfunction following primary cryoablation. Potency was defined as the ability to achieve erection sufficient for intercourse without medical assistance; Sunderland, UK	96% of men were impotent immediately following surgery. Of the 23 patients were fully potent before surgery, 39% were potent at 24 months. This dropped to 30% with further follow-up	Men who are potent before surgery have a 30% chance of regaining long-term potency. Erectile aids should be made available to others to improve this percentage
Jones et al. [72] Cryoablation; COLD registry	1,198 men treated with primary cryoablation by 27 different physicians. Average follow-up was 24 months. Information entered into the Cryo online data registry (COLD); multiple centers	Of 354 men potent at the time of surgery 25.2% were able to have erections sufficient for intercourse but only 8.8% were able without medical or device assistance	Largest data set with pretreatment and posttreatment information on patients undergoing primary cryoablation treatment for prostate cancer. Erectile dysfunction remains as a significant problem for greater than 90% of men who were fully potent prior to surgery

Comparison studies

Helgason et al. [32] Prostate cancer treatment: ADT, radical prostatectomy, XRT, and old age	Men age 50–80 years. 431 men 1.5–2 years following diagnosis of clinically localized prostate cancer and 435 age matched controls; Radiumhemmet scale; Stockholm, Sweden	Factors affecting physiologic impotence: prostate cancer, myocardial infarction, diuretics, hydrogen blockers and warfarin type anticoagulants. Subgroup analysis of prostate cancer patients found impotence in 91% ADT, 86% RRP, 57% XRT, and 53% in general	Adjusted for age, ADT and RRP were significantly higher risk for developing impotence compared to XRT
Siegel et al. [73] Radical prostatectomy, EBRT, and watchful waiting comparison	802 (aged 44–88 years, mean 66) of 2,956 patients treated with radical prostatectomy, external beam radiation therapy (EBRT), and watchful waiting; prospective centralized database at single Army institution; Washington, D.C.	Posttreatment potency rates: 10% for radical prostatectomy, 15% for EBRT, 38% for watchful waiting. Potency was significantly higher in watchful waiting group, but no significant difference was noted posttreatment between prostatectomy and EBRT groups. Race and clinical stage were significant ED predictors, age was not	Over 80% of patients actively treated for prostate cancer had ED (including both patients who were and were not potent before therapy). While race and clinical stage were predictors of potency loss, ED still occurred following treatment, suggesting that the development of ED depends on whether or not patients receive active therapy
Sharkey et al. [74] Brachytherapy and radical prostatectomy comparison	1,305 men treated by brachytherapy ($n = 1,074$, mean age 63.6) and radical retropubic prostatectomy ($n = 231$, mean age 63.6); community-based private practice urology group; New Port Richey, FL	1,077 patients (869 brachytherapy and 208 prostatectomy) had data sufficient for analysis. Prevalence of ED: 10–15% for brachytherapy (depending on preoperative potency, when information available), and 45% for prostatectomy	Study compares brachytherapy to prostatectomy. Based on information collected over a decade, brachytherapy offers a comparable cure rate, with a lower rate of complications
Schwartz et al. [75] Radical prostatectomy or radiation therapy comparison	398 men treated with radical prostatectomy or radiation therapy (304 with localized disease); telephone interview; Detroit, MI	Pretreatment prevalence of ED: 40% in both groups. Posttreatment prevalence of difficult erections: 86.9% in radical prostatectomy group, 75.7% in radiation therapy group. However, when comparing ED in men with no difficulties pretreatment, men undergoing prostatectomy were four times more likely to experience ED	Both treatment groups showed a significant increase in men reporting difficult erections. When comparing outcomes in only men with no symptoms at baseline, erectile problems were significantly more common in the radical prostatectomy group
Hoffman et al. [31] Watchful waiting, androgen deprivation, radiation therapy, radical prostatectomy comparison	2,365 men with clinically localized prostate cancer treated with various modalities; record review and patient-completed surveys; USA	Prevalence of complete ED: watchful waiting 32.5%, androgen deprivation 85.8%, radiation 42.7%, radical prostatectomy 58.4%	A significant number (59.2%) of patients were satisfied with their choice of treatment and would make the same decision again. Among other factors, the preservation of erectile function was associated with satisfaction. Even among patients with ED, however, the sense of being cancer-free tended to minimize regrets

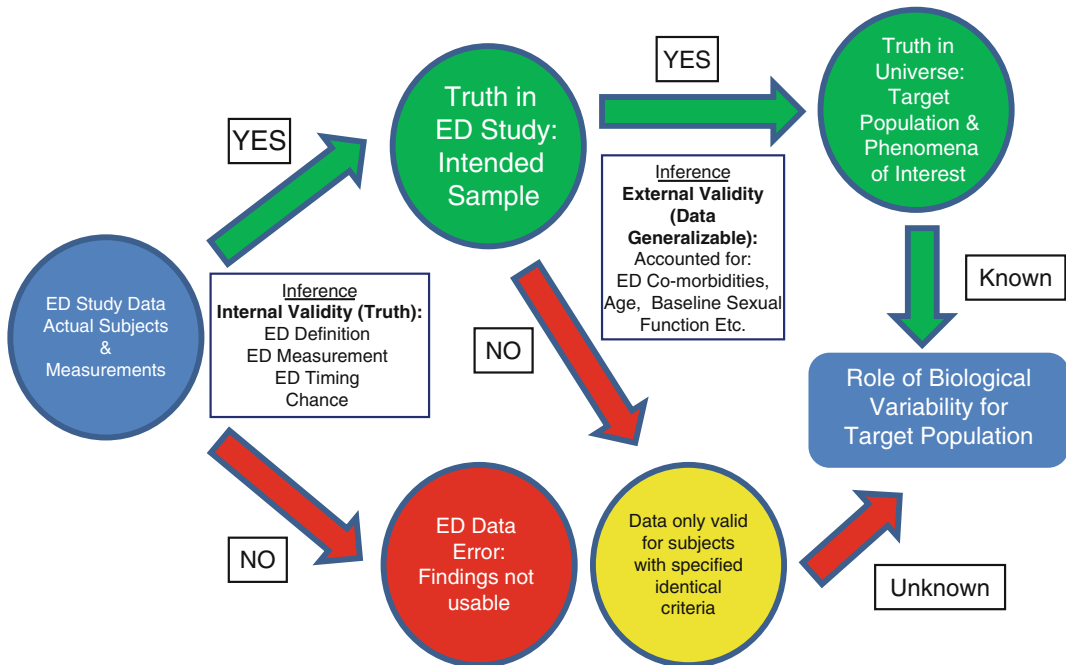


Fig. 10.1 Interplay of ED quantification: Data, Validity, & Biologic Variability

specific issues of sample power, statistical modeling and design, covariate subgroup analyses, and effect size calculation [4]. It is crucial to remember, however, that no amount of statistical methodology or power can compensate for biased data (garbage in = garbage out), or where necessary information was failed to be recorded (Fig. 10.1). Graphically depicts the interplay of ED quantification data, biologic variability, and study validity.

Internal Validity in ED Quantification

Obtaining reliable and valid data in general is a difficult undertaking. Information and data collected optimally is both precise (repeatable) and accurate (degree to which a variable represents what it is supposed to represent). Common methodologies to increase precision for studies include the standardization of measurement with an operation manual, training and certification of the observer, refinement of instruments, automation of instruments, and repetition of measurements with

value averaging [5]. These techniques ultimately attempt to minimize the role of chance or random error. Similar techniques are used to maximize accuracy, where bias by the subject, observer, or instrument creates systematic errors in the data. Additional techniques utilized in addition to those previously mentioned to maximize precision, include making unobtrusive measurements, instrument calibration, and blinding. The most common pitfalls to internal validity include the definition of ED, ED measurement, time frame for measurement, patient versus MD recording of data, attrition bias, and the role of chance.

ED Definition

An important factor that can influence ED study outcomes is the seemingly innocuous definition selected for erectile function. Two identical studies, one with EF defined as the ability to achieve and maintain penile erection sufficient for satisfactory sexual performance, the other as partial erections occasionally sufficient for penetrative intercourse

could yield very different results. A cohort study of 260 men revealed 5% reported erections firm enough for intercourse, but 61% reported sexual function as good or very good [6]. Differences could be further exacerbated if the use of erectile aides such as PDE5I is allowed and documented in one study but not in the other.

The National Institute of Health (NIH) identified the definition of erectile dysfunction as the “inability to attain and/or maintain a penile erection sufficient for satisfactory sexual performance” [7] and this definition was subsequently accepted by the World Health Organization and the International Consultation on Urologic Disease [8]. The NIH definition provides an excellent overall definition for researchers and clinicians to utilize as a starting point in explicating a precise operational definition of erectile dysfunction according to the particulars of the situation being explored.

Many studies in the literature do not explicate a specific definition of erectile dysfunction and those that did vary greatly in the literature. Examples of imprecision in terminology in the ED literature include terms like “sexual concerns,” statements describing “tumescence,” “impotence,” “loss of potency,” “cannot get erections,” and “difficulty with erections.” Defining erectile dysfunction in terms of the inability to penetrate and/or have intercourse with the erection may better describe the level of functional rigidity for men who are engaged in a sexual relationship involving intercourse. Despite being more precise, definitions with strict functional rigidity criteria may not apply to sexual relationships in which penetrative intercourse is considered less important (such as some homosexual relationships). Today’s erectile function definitions must specify whether PDE5I or other erectile aides are allowed or excluded.

ED Measurement

Perhaps the single most important factor in ED outcomes study is the ED measurement tool utilized. Quantitative comparison of ED outcomes is severely

undermined by the number of established and newly developing (sometimes self-invented) ED measurement tools available to researchers of which not all are specifically defined to address ED. An optimal measurement tool is one that has literature-documented validity and reliability. The use of nonvalidated instruments has been repeatedly shown to overestimate EF [9]. Table 10.2 describes various methods of ED measurement found in the literature and comments on reliability and validity.

The Sexual Health Inventory for Men (SHIM) is a five item subscale within the International Index of Erectile Function (IIEF) (its domains include erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall sexual satisfaction) pertaining to ED and was developed to determine the severity and presence of erectile dysfunction [10]. The five items focus on erections (4 items) and intercourse satisfaction (1 item) and are measured on a 5-point Likert scale ranging from very low to very high. Beside its excellent sensitivity, specificity, reliability, and validity, the SHIM can differentiate among the levels of severity of erectile dysfunction using specified cutoffs (surprisingly underutilized in the literature and sometimes researchers specify their own cutoffs): no ED (≥ 22), mild (17–21), moderate (8–16), and severe ED (≤ 7). One shortcoming of the SHIM is that it asks about a time period of “over the last 6 months.” Alternatively, the IIEF-6 and the entire IIEF, in general, use a time period of over the last 4 weeks. This time period is more appropriate when assessing erectile function more often (every 3 months) which is common when assessing ED in the immediate post treatment period. The IIEF-6 and SHIM thus have only minor differences, both yielding robust, reliable data with a high predictive correlation [11]. Table 10.3 shows the IIEF and describes the specific questions which entail the SHIM and IIEF-6. IIEF-6 cutoffs are: no ED (≥ 26), minimal ED (18–25), moderate ED (11–17), and severe ED (≤ 10). When assessing change in ED status after CAP treatment, outcomes can be reported as shifting between ED severities, not as a dichotomous (yes/no) ED variable. A common dichotomous question for ED studies is the ability to achieve

Table 10.2 Common tools used to evaluate erectile dysfunction

Instrument	Development	Validity	Reliability	Cutoffs for ED
IIIEF/SHIM [11, 76, 77] IIIEF 15 items with five subscales-erectile dysfunction [6], orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction	Utilized a comprehensive literature review and existing questionnaires, such as the BMSFI from above. Interviewed male patients with erectile dysfunction and their partners 4 dimensions: erectile dysfunction, orgasmic function, desire and satisfaction Pilot testing with a principal components analysis which revealed a robust factor structure with five dimensions resulting (five factors with eigenvalues >1.0):	Construct validity (convergent validity): The erectile function domain correlated with the independent blinded clinical interview with a correlation of 0.75, $p < 0.001$ Discriminant validity was performed through a comparison of the group of men with erectile dysfunction and a control group, and there was a significant difference in terms of the erectile dysfunction domain ($p < 0.001$)	Cronbach's alpha for the erectile function subscale is 0.92–0.96 (in three separate studies) Stability in terms of test-retest reliability is 0.84 for the erectile function domain and 0.82 for the entire instrument	Yes. A score of 21 is a cutoff for diagnosing erectile dysfunction and there are also cutoffs used for the severity of erectile dysfunction
EORTC prostate cancer quality of life questionnaire [78] $N = 1,138$ 36 items, four focused on sexual dysfunction Four point scale from not at all to very much Does your condition limit your interest in sex? Are you limited in your ability to have or maintain erection? Does condition prevent you from ejaculating? Does condition interfere w/ enjoyment of sex?	Utilized experts and information from previous studies to identify problem areas for these patients to come up with items for 3 hypothesized dimensions Factor analysis was performed utilizing principal components analysis revealing three factors with eigenvalues >1.0- confirmed the three dimensions of sexuality (four items loaded on the sexuality factor with results ranging from 0.82 to 0.89), urinary symptoms and bowel symptoms	Multitrait analysis was performed with convergent validity ranging from 0.79 to 0.85 and discriminant validity correlations at 0.08–0.28	Cronbach's alpha for sexuality scale was 0.92 No report on stability was provided	No

International Continence Society Sex Questionnaire (four items) Also similar questions used as part of the ICS-male questionnaire Designed specifically for men with lower urinary tract symptoms (LUTS) associated with BPH [79, 80]	Developed utilizing evaluation from urologists and then patient evaluations of the tool	Content validity – 1,256 patients completed the ICSmale questionnaire (94% unaided without any questions), Missing data was very rare (1–3% on any given item) Construct validity – The ICSsex question about reduced rigidity of erections was significantly worse according to age as would be expected with a linear trend ($p<0.001$), the researchers also report confirmation of an expected difference in reduced all areas of sexual symptoms in the clinic patients as compared to the community patients in regards to the rigidity of erections ($M=59.5$ versus $M=53.3$, $p=0.02$), reduced ejaculation ($M=62.3$ versus $M=47$, $p<0.001$), pain on ejaculation ($M=16.6$ versus $M=4.8$, $p<0.001$), and sex life spoiled by LUTS ($M=45.9$ versus $M=7.7$, $p<0.001$)	None reported for the ICSsex	No
Brief Male Sexual Function Inventory (BMSFI) [81] During the last 30 days... 5 point scale ratings on each question 11 items Three items on erectile dysfunction	Literature review conducted leading to selection of sexual function questions and alternative versions of the questions were developed. Pilot testing done with 50 questions representing four domains (libido, erectile function, ejaculation, and overall satisfaction). Utilized patients to evaluate questions for clarity and eliminated some questions	Content-utilized literature and patients to come up with initial questions the erectile function domain questions had Convergent validity was reported by a correlation of 0.87 between men reporting never having firm enough erections for sex and men reporting no morning full erections Discriminant validity was determined by comparing men seeking treatment for erectile dysfunction and the age-adjusted scores on the erection domain of a control group of men ($p=0.0001$)	Cronbach's alpha for the erectile dysfunction domain was 0.95 Stability according to test-retest had a correlation of 0.85	No

(continued)

Table 10.2 (continued)

Instrument	Development	Validity	Reliability	Cutoffs for ED
UCLA Prostate Cancer Index (PCI) [82] 20 items total with 6 subscales representing 3 domains (urinary function), sexual function (8 items), bowel function, urinary bother, sexual bother (one item), and bowel bother EPIC – Expanded Prostate Cancer Index Composite content from UCLA-PCI (50 items, 13 in the sexual domain) [83]	Developed with input of four focus groups composed of prostate cancer survivors and spouses and a review of the literature. Drafted a questionnaire. Used exploratory factor analysis and multitrait scaling analysis to determine the best items (any items with a item scale correlation of <0.35 was discarded and duplicate items were discarded)	Convergent validity with high correlations between all subscales (ability to have an erection correlated with sexual item scale at 0.87, quality of erections correlated with the sexual item scale at 0.82) as well as with the CARES-SF sexual function scale with ($r=0.43$, $p<0.001$) Discriminant validity was provided with significant differences between men with prostate cancer and a control group ($p<0.0001$) and a negative correlation between sexual function and age ($r=-0.24$, $p<0.0001$) EPIC – No validation specifically for the	Cronbach's alpha on the sexual function subscale is 0.93 Stability in terms of test-retest correlations of 0.92 for sexual function and 0.70 for sexual bother EPIC – Cronbach's alpha=0.93 Stability in terms of test-retest=0.91	No
Common toxicity criteria version 2.0 [84] 3 items for men on sexual dysfunction Libido rated 0 (normal)–2 (severe loss of interest) Male infertility rated as either normal, oligospermia (low sperm count), azospermia (no sperm count) Sexual reproductive function rated as 0 (none)–4 (disabling)	An expanded version of the original CTC to merge systemic, radiation, and surgical criteria into one comprehensive and standardized system. They utilized experts from around the world from the Radiation Treatment Oncology Group and the World Health Organization and this was piloted on a group of 68 patients. Developed through focus group discussion with patients and review of oncology experts	No specific validity reported for the sexual/reproductive function category	No specific validity reported for the sexual/reproductive function category	No
Cleveland clinic erectile function/Cleveland clinic prostate [85] 13 questions, 3 on erections before radiation, after radiation, after Viagra	A nonvalidated, practical questionnaire developed for clinical practice in the offices at Cleveland Clinic. Open ended questions mostly about erections and efficacy of treatment with sildenafil used with IIEF always to provide qualitative information with quantitative data from IIEF	None	None	No

Table 10.3 International Index of Erectile Function (IIEF) (*Questions 1–15; Reported for the past 4 weeks*). International Index of Erectile Function-6 (IIEF-6) (*Questions 1–5 & 15; Reported for the past 4 weeks*). Sexual Health Inventory for Men (SHIM) (*Questions 2, 4, 5, 7 & 15; reported for the past 6 months*)

- Q1: How often were you able to get an erection during sexual activity?
0. No sexual activity
 1. Almost never or never
 2. A few times (less than half the time)
 3. Sometimes (about half the time)
 4. Most times (more than half the time)
 5. Almost always or always
- Q2: When you had erections with sexual stimulation, how often were your erections hard enough for penetration?
0. No sexual activity
 1. Almost never or never
 2. A few times (less than half the time)
 3. Sometimes (about half the time)
 4. Most times (more than half the time)
 5. Almost always or always
- Q3: When you attempted intercourse, how often were you able to penetrate (enter) your partner?
0. Did not attempt intercourse
 1. Almost never or never
 2. A few times (less than half the time)
 3. Sometimes (about half the time)
 4. Most times (more than half the time)
 5. Almost always or always
- Q4: During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
0. Did not attempt intercourse
 1. Almost never or never
 2. A few times (less than half the time)
 3. Sometimes (about half the time)
 4. Most times (more than half the time)
 5. Almost always or always
- Q5: During sexual intercourse, how difficult was it to maintain your erection to the completion of intercourse?
0. Did not attempt intercourse
 1. Extremely difficult
 2. Very difficult
 3. Difficult
 4. Slightly difficult
 5. Not difficult
- Q6: How many times have you attempted sexual intercourse?
0. No attempts
 1. One to two attempts
 2. Three to four attempts

3. Five to six attempts
 4. Seven to ten attempts
 5. Eleven or more attempts
- Q7: When you attempted sexual intercourse, how often was it satisfactory for you?
0. Did not attempt intercourse
 1. Almost never or never
 2. A few times (less than half the time)
 3. Sometimes (about half the time)
 4. Most times (more than half the time)
 5. Almost always or always
- Q8: How much have you enjoyed sexual intercourse?
0. No intercourse
 1. No enjoyment at all
 2. Not very enjoyable
 3. Fairly enjoyable
 4. Highly enjoyable
 5. Very highly enjoyable
- Q9: When you had sexual stimulation or intercourse, how often did you ejaculate?
0. No sexual stimulation or intercourse
 1. Almost never or never
 2. A few times (less than half the time)
 3. Sometimes (about half the time)
 4. Most times (more than half the time)
 5. Almost always or always
- Q10: When you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax?
1. Almost never or never
 2. A few times (less than half the time)
 3. Sometimes (about half the time)
 4. Most times (more than half the time)
 5. Almost always or always
- Q11: How often have you felt sexual desire?
1. Almost never or never
 2. A few times (less than half the time)
 3. Sometimes (about half the time)
 4. Most times (more than half the time)
 5. Almost always or always
- Q12: How would you rate your level of sexual desire?
1. Very low or none at all
 2. Low
 3. Moderate
 4. High
 5. Very high
- Q13: How satisfied have you been with your overall sex life?
1. Very dissatisfied
 2. Moderately dissatisfied
 3. Equally satisfied and dissatisfied
 4. Moderately satisfied
 5. Very satisfied

(continued)

Table 10.3 (continued)

Q14: How satisfied have you been with your sexual relationship with your partner?
1. Very dissatisfied
2. Moderately dissatisfied
3. Equally satisfied and dissatisfied
4. Moderately satisfied
5. Very satisfied
Q15: How do you rate your confidence that you could get and keep an erection?
1. Very low
2. Low
3. Moderate
4. High
5. Very high

penetrative intercourse. There is intrinsic appeal in single item ED assessment tools for convenience, and may be collected in addition to IIEF-related information, but these have proven inferior in quantifying ED [12]. The SHIM has been utilized in over 50 research studies examining prevalence, treatment efficacy, as inclusion criteria, and/or correlation studies since it was initially validated in 1999 [13]. Not surprisingly, many authors, as well as the American Brachytherapy Society and the American Urological Association recommend the use of the validated and reliable SHIM or IIEF-5 for the evaluation of erectile dysfunction [14–20].

Time Frame Utilized

The time frame for evaluating erectile dysfunction depends on what the clinician or investigator is trying to determine. It is important to establish baseline erectile function before any interventions take place for prostate cancer or for the subsequent erectile dysfunction that may occur after the treatment. Indeed, even being informed of the diagnosis of prostate cancer prior to the treatment has been shown to induce ED [9]. If outcome comparisons are to be made between different prostate cancer treatments, such as radiation therapy versus prostatectomy, it is essential to compare them at the appropriate timeframes. Understanding of the proposed mechanism for ED from the varied prostate cancer treatments is

important for ED quantification, as they have unique characteristics related to the pathophysiology and timing of presentation.

Proposed mechanisms of ED following radical prostatectomy include those of neurogenic or vascular origin [21, 22] with neurogenic factors likely being most significant. Arguments favoring a neurogenic cause are relation with the number of spared neurovascular bundles, as well as the occurrence of ED despite the absence of general vascular disease [21]. Furthermore, immediately following surgery, virtually all men experience ED, including the loss of nocturnal erections; an etiology considered to be the result of intraoperative neuropraxia [23, 24]. The recovery of erectile function in those who experience a return can require as long as 18–24 months, consistent with a slowly resolving neuropraxia [23]. The source of vascular injury from RRP, likely stems from damage to the accessory pudendal arteries when they are anatomically present [25].

In contrast to RRP, the onset of ED after radiation is not immediate, but is a time dependent process. Whereas the mechanism of ED with surgical therapy favors a neurogenic etiology, multiple studies suggest that an insidious vascular mechanism is more likely with XRT secondary to endarteritis of the internal pudendal and penile arteries [26–28]. In one study with BT, the median onset to ED was 5.4 months [29]. In another study, using 3D-Conformal Radiation Therapy, the rate of ED at 1 year was 0%, but rose to 17% and 37% at 2 and 3 years, respectively, again suggesting a potential delayed ED effect with XRT [26]. The response of some patients to sildenafil is also suggestive of an arteriogenic mechanism; however, a neurogenic component may also impact ED [26]. Accordingly, it is proposed that decreased radiation doses around the neurovascular bundle may achieve lower ED rates [30].

Investigators state that the etiology of ED for cryotherapy is freeze damage to the neurovascular bundles, especially in the areas of the apex and periprostic tissues, and that the depression of sexual function can be viewed as a marker for complete treatment of the posterolateral aspect of the prostate [31]. Other researchers hypothesize that since the nerves are not cut during the

procedure, they maintain potential to recover function. One study described results where 13% of patients fully recovered EF, and another 34% were able to have intercourse with erectile aids at 3 years after CT [32].

Androgen ablation (AA) therapy is most important in the settings of recurrent or metastatic disease; however, it has a role in the primary treatment of localized CAP [33]. Unlike other treatments for prostate cancer, decrease in libido is nearly universal for men on AA. Testosterone plays a large role in the maintenance of libido and sexual function. Lack of testosterone limits these and may also have a direct effect on cavernosal nerves involved in producing erections [34].

In general, the acquisition of ED information preoperatively followed by every 3 months for the first year, every 6 months the second year, then yearly thereafter allows for robust, comparable data between studies. Also, the time period in question from standardized questionnaires must be considered – using the SHIM questionnaire which assumes a time period “over the past 6 months” is inappropriate when assessing erectile status 3 months after RRP.

Pt Versus MD Reported

The patient is the ultimate judge of the quality and performance associated with his erections and how sufficient the erection is for sexual performance. Physician report ultimately relies on the interpretation of the patients’ report and introduces an unnecessary source of bias that usually overestimates EF. A large population-based study showed significant differences existed between the patient and physician report of sexual dysfunction, which supports the need for patient self-report of erectile dysfunction [35].

Attrition Bias

Patient completion rates of studies should be optimized. Attrition bias can describe the phenomenon where patients doing poorly drop out

of the study, and perhaps their result is not reported. Scrupulous reporting of study drop outs and their reason for discontinuation of the study is essential. Intention to treat analysis forces researchers to take these subjects into account. Thus, when a large discrepancy between the number of patients entered into a study (or potentially treated) and the number of patients being reported upon exists, bias resulting in more favorable outcomes typically occurs.

Chance

Also of importance for internal validity is the role of chance in drawing conclusions. Myriad techniques to establish whether findings could have been replicated by chance exist. Modern reporting of these results includes the use of estimation of effect sizes, presented as point estimates with confidence intervals, with de-emphasis of p -values [36]. Lest we be duped by “the glitter of the t table [which] diverts attention from the inadequacies of the fare” [37], we must remember that statistics only accounts for the role of chance, nothing more. Considering p -values in the context of repetition of trials is sometimes helpful, that is to say a p -value of $p=0.05$ means that if the same study were replicated 100 times, 5 times by chance alone would similar results be obtained in the absence of any true association between the study variables. The number of patients in study is directly proportional to the study power, with a higher n leading to a decrease in the role of chance to produce spurious results.

External Validity in ED Quantification

External validity refers to the degree to which study results can be inferred to the general population. When studies do not specifically account for relevant eligibility and exclusion criteria, the findings cannot reliably be extrapolated to the general population. For example, as stated earlier,

review of the literature reveals pooled estimates (where many of the important factors listed are absent) of 24–87% ED for men following nerve-sparing radical retropubic prostatectomy. Counseling a patient of this fact prior to his RRP is not very helpful. Alternatively, researchers can begin to stratify their populations by factors that are known to influence sought outcomes. Giving a patient post RRP ED rates for his specific age, ED comorbidities, and baseline erectile function yields a much narrower prevalence range and clinically useful discussion.

Cognisance and collection of information on the factors that are already known to affect the outcome variable is crucial. Recognition of these factors can help researchers systematically eliminate the phenomenon of selection bias. “Hidden” factors (or those not accounted for by the researcher) that can affect the outcome variable not solely based on biological variability are known as confounders. Ultimately, confounding and selection bias can be dealt with through proper study design and statistical methodologies – provided the necessary information is collected during the study.

Several factors have been born out in the literature to affect external validity for the quantification of erectile dysfunction after prostate cancer treatment. These include ED comorbidities, patient interest and partner availability, age, baseline sexual function, surgeon factors, and the ability to preserve nerves during prostatectomy.

ED Comorbidities

Medical comorbidities that often contribute to ED can easily confound erectile function outcomes data. Risks for developing ED are discussed at length in different sections of this book. Suffice it to say that the documentation of ED risk factors, such as diabetes, hypertension, heart disease, dyslipidemia, smoking status, depression, lower urinary tract symptoms, endocrine status, neurologic diseases, hepatic and renal insufficiency, and medications (in particular antiandrogen therapy), use both before and after intervention is essential and must be adjusted for in outcomes research.

Patient Interest and Partner Availability

When assessing ED outcomes after prostate cancer therapy, patients not interested in or not having a partner for sexual activity pooled together with those who are interested and have a sexual partner negatively affects outcomes. When patients select a “did not attempt intercourse,” a standardized questionnaire cannot distinguish between a patient who simply was not interested and one who was discouraged from previous failed attempts. This is particularly true in men participating in penile rehabilitation, where possible improvement in spontaneous erectile function is likely long-term, not immediate. A recent survey study of 724 subjects that between 1995 and 1999 had undergone RRP, brachytherapy, conformal external beam radiotherapy, or no therapy (healthy control group) for localized prostate cancer revealed 50% of the men were “sexually indifferent” [38]. Sexual indifference was defined as an answer as “no” or “small problem” when asked “Overall, how big a problem has your sexual function or lack of sexual function been for you during the past 4 weeks?” A discrepancy was found in the number of men who were bothered by poor erections and used medications or devices to improve erections after RRP 77%, brachytherapy 52%, and 39% XRT. The study also found that the use of one erection aid was an independent predictor for higher quality of life. A separate study of 1,977 men who had undergone either RRP or XRT in 1994 and 1995 revealed that only 51% of men in the study had ever used ED treatment [39]. Subject age, regular sexual partner, and baseline sexual activity predicted the utilization of ED treatment.

Age

As with prostate cancer, it is important to remember that ED is also an age-related process. Men in their 50s have twice the RR for ED compared to men in their 40s. As men continue to age, they

tend to have more advanced symptoms; 52% of men aged 40–70 years experience some degree of ED and two-third of these men have moderate to severe symptoms [40]. Review of the literature demonstrates that the majority of men experience ED as they age and since prostate cancer affects a population already at risk for erectile dysfunction, it can be expected that treatment and subsequent recovery period exacerbates this risk. Studies have repeatedly demonstrated patient age before cancer treatment as an indicator for successful erectile function recovery. For example, a study of 314 men who underwent RRP over a 4-year period at a single institution stratified potency status by age. Compared to men age <60, men ages 60–65 with full erections preoperatively were only 56% (CI 37–84%) as likely to regain erections sufficient for intercourse, men age >65 were 47% (CI 23–96) as likely to recover potency [41]. The study also looked at preoperative erectile function, and found men who declared their erectile function as “partial erections occasionally satisfactory for intercourse” were 47% (CI 23–96) as likely to recover potency when compared to men with “full erections.”

Baseline Sexual Function

Perhaps the most important point in pre-ED intervention quantification is the collection of baseline sexual function information. This data can then be used for direct comparison of erectile function before and after intervention yet the literature contains a surprising number of studies in which this data is not presented. Erectile dysfunction has been shown to occur following operations not expected to cause it such as orthopedic joint replacement surgery or circumcision [42–44]. These studies highlight the possibility that surgical procedures, in general, may result in sexual dysfunction. Alternatively, those with baseline ED or other sexual disorders may not have had a chronologic event with which to associate the onset of their disease, thus spuriously indicting their operation as a potential cause. These scenarios provide a conceptual rationale

for a patient’s possible overestimation of sexual function before surgery, a form of recall bias. As a result, any net decrease in potency when comparing patient’s perceptions of erectile function before and after surgery is exaggerated.

ED can be expected in up to 50% of all men before their prostate cancer diagnosis [45]. Those remaining men with erectile function need to be informed that prostate cancer treatment never improves their erectile function. After successful cancer treatment, the goal remains to return patients to their preintervention erectile function status. Some have estimated this likelihood of return to pre-op erectile status (without erectile aids) at $\leq 10\%$ for men who have undergone bilateral nerve sparing prostatectomy [46]. Pretreatment erectile function has been repeatedly demonstrated to affect ED outcomes in the literature. In a study in which 1,246 men filled out standardized questionnaires at an average of 4.3 years posttreatment in the form of RRP of definitive radiotherapy for localized prostate carcinoma, men were almost four times as likely (CI 2.6–5.57 $p < 0.0001$) to have a functional erection at time of follow up if they were classified as having good erections before the treatment was initiated [47]. This study also illustrated the importance of age for erectile function after the treatment. When 1,100 men in the study were stratified by age, the likelihood of having a score of ≥ 22 on the IIEF erectile domain was 35% for ages 42–62, 23% ages 63–67, 19% ages 68–71, 16% ages 72–75, and 10% ages 76–88.

Surgeon Factors

Surgeon procedure volume and expertise are often cited as important factors for successful surgical outcomes. ED outcomes in regards to individual surgical volumes have been mixed. In a study of 1,778 prostatectomy patients operated upon by 14 different surgeons, patient age, the surgeon performing the RRP, and neurovascular bundle status, but not surgical volume were found to be significant predictors of erectile function adequate for penetrative relations recovery [48].

Number of Nerves Spared

Advances in prostatectomy surgical technique, the use of loupe magnification, and the understanding of cavernosal nerve anatomy have improved sexual function outcomes. Number of nerves spared has been a consistent predictor of erectile function postprostatectomy. Surgical margins required for cancer control has obvious implications on the ability to spare nerves. One of the original reports in 1991 stated that age, clinical and pathological stage, and the preservation of neurovascular bundles were significant factors in return of preoperative potency in 503 patients undergoing prostatectomy [49]. A recent review article summarizing ED patients after nerve sparing RRP of ≥ 50 patients, ≥ 1 year f/u, prospective interview or patient questionnaire outcomes, and erectile function defined as the ability to achieve unassisted intercourse with vaginal penetration showed erectile function as 31–86% for bilateral nerve sparing procedures, 13–56% for unilateral nerve sparing, and 0–17% in nonnerve sparing prostatectomies. Further stratification by age showed erectile function as 61–100% postprocedure for age < 50 (for both unilateral and bilateral

nerve sparing), 47–58% and 44–90% for unilateral and bilateral nerve sparing, respectively, for ages 50–70 and 0–51% for any nerve sparing procedure age > 70 [50].

Conclusion

The current literature on ED prevalence after CAP treatment is inconsistent, often poorly interpretable, and yield unacceptably disparate results. Data from Table 10.1 are offered to help give the reader general information and quotable references from what we feel are high-quality publications relating to CAP treatment. The wide range of ED prevalence rates indicates suboptimal study design and data acquisition, as biological variability alone is not likely to account for such drastically wide ED prevalence rates after CAP treatment. Study methodologies pertaining to internal and external validity of the data account for some of the ED data variability. Table 10.4 summarizes these study factors and provides recommendations for appropriate study

Table 10.4 ED quantification recommendation summary

External validity factors

- Patient interest and partner availability: Ensure available patient partner status and assess for level of sexual interest
- Age: Record and adjust for in outcomes analysis
- Baseline sexual function: Assess as below prior to prostate cancer intervention and prior to cancer diagnosis if possible
- Surgeon factor: Adjust for surgeon in study when combining multiple surgeon data
- Nerves spared: Record and adjust for in outcomes analysis
- ED comorbidities: Record and adjust for diabetes, hypertension, heart disease, cholesterol levels, smoking status, depression, endocrine status, and medications before and after treatment

Internal validity factors

- ED definition: Utilize precise definition, preferably the NIH consensus definition
- ED measurement tool: At a minimum, utilize IIEF-6 questionnaire and stratify results using validated criteria for cutoffs, full IIEF survey completion facilitates more complete outcomes data, single item questionnaires can be asked in addition, but should not be used as sole data source
- Erectile aides: Document frequency and quantity of use, also inquire about unassisted “spontaneous” erections sufficient for satisfactory sexual performance, can have patients answer IIEF-6 twice in same setting (with and without erectile aides)
- Timing of measurement: Prior to intervention (and if possible prior to diagnosis), every 3 months for at least 1st year, every 6 months in year 2, yearly thereafter (For radiation patients, more frequent assessment in later years is recommended)
- Patient report: Patient to fill out questionnaires in private
- Attrition bias: Maximize study completion rates and fully describe dropouts
- Chance: Increase power by maximizing the number of patients in study
- General: Utilize biostatistician in study design and the analysis for issues of sample power, statistical modeling and design, covariate subgroup analyses, and effect size calculation

methodology to help maximize the quality of ED quantification outcomes. Only through optimal ED quantification study can consistent, standardized outcomes be obtained to properly counsel patients and advance the field of study.

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Chapter 11

Vacuum Constriction Device: A New Paradigm for Treatment of Erectile Dysfunction

Anthony N. Hoang, Claudio Romero, and John C. Hairston

Abstract In 1996, the American Urological Association began to recommend the vacuum constriction device (VCD) as an alternative to the treatment of erectile dysfunction (ED) (Montague et al. *Journal of Urology* 156, 2007–2111, 1996). Since then, millions of Americans have benefitted from the device. It remains well-accepted and popular among patients due to its efficacy, noninvasiveness, ease of administration, and affordability. Nearly all patients, including those with hematological disorders, experience some degree of erection with the device. The process of applying negative pressure to passively fill the corpus cavernosum via arterial and venous sources remains the basis of mechanism since its conception in 1874. With the advent of oral pharmacotherapy for the treatment of ED, its usage and availability have decreased tremendously. However, its application is being expanded into new realms. Penile rehabilitation following prostatectomy is a perfect example. Despite increasing success of surgical and medical therapy for ED, the demand for a noninvasive, effective, safe, drug-free, and cost-effective treatment persists. This chapter presents the development of VCD, its mechanism of action, indications, safety profile, efficacy, and future directions.

Keywords Prostatectomy • Penile rehabilitation • Corpora cavernosa • Tumescence • Penile length preservation

Introduction

In 1996, the American Urological Association began to recommend the vacuum constriction device (VCD) as an alternative to the treatment of erectile dysfunction (ED) [1]. Since then, millions of Americans have benefitted from the device. It remains well-accepted and popular among patients due to its efficacy, noninvasiveness, ease of administration, and affordability. Nearly all patients, including those with hematological disorders, experience some degree of erection with the device. The process of applying negative pressure to passively fill the corpus cavernosum via arterial and venous sources remains the basis of mechanism since its conception in 1874. With the advent of oral pharmacotherapy for the treatment of ED, its usage and availability have decreased tremendously. However, its application is being expanded into new realms. Penile rehabilitation following prostatectomy is a perfect example. Despite increasing the success of surgical and medical therapy for ED, the demand for a noninvasive, effective, safe, drug-free, and cost-effective treatment persists. This chapter presents the development of VCD, its mechanism of action, indications, safety profile, efficacy, and future directions.

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History

John King, a nineteenth-century physician, is credited with conceptualizing a “small, exhausting pump” applying negative pressure to the penis for the treatment of ED. He advocated that a “glass exhauster should be applied to the part, once a day” [2, 3]. Unfortunately, his device failed to maintain the erection once the glass exhauster was taken off the penis. It was not until 1917 when Otto Lederer patented the first VCD that used a compression ring to maintain the erection [3, 4]. However, it failed to win over medical peers’ approval. In 1974, an American entrepreneur, Geddings Osbon, invented and developed the first commercially available device, which became FDA approved in 1982 [3, 5]. Though it was reported that Osbon used this device on himself for more than 20 years without failure, the device was initially met with skepticism among the medical community. Instrumental to its widespread popularity was Hadig, who published one of the earliest studies supporting its efficacy and safety profile [6]. As more evidence emerged, acceptance by the urologic community culminated in the device being recommended by the American Urological Association as one of three treatment alternatives for organic ED [1].

Mechanism of Action

More than 90% of men experience a functional erection with the VCD [7]. Several companies have developed and marketed both hand-operated and battery-operated VCDs (Figs. 11.1 and 11.2). These include Timm Medical Technologies (Eden Prairie, MN), Mission Pharmacal (San Antonio, TX), Encore (Louisville, KY), Mentor (Santa Barbara, CA), and Post-T-Vac (Dodge City, KS).

Even though these devices have been commercially available since the 1980s, the mechanics remain the same. They comprise three components: vacuum cylinder, battery or manually operated vacuum pump, and constriction rings of varying sizes. Usage involves placing the correct constriction ring on the open end of the cylinder, then applying copious amount of lubricant to the penis to create a seal once the vacuum cylinder is placed over. The manual or battery operated pump is activated to create negative pressure inside the cylinder, effectively drawing blood into the penis to create an artificial erection. Once the desired state is achieved, the constriction ring is moved onto the base of the penis to maintain the erect state; trial and error is used to determine the ring size that is most comfortable and effective. The cylinder is



Fig. 11.1 Hand-operated and battery-operated models. Courtesy of Timm Medical Technologies



Fig. 11.2 Hand-operated and battery-operated models. Courtesy of Timm Medical Technologies

then removed and the patient is ready for sexual intercourse. To avoid ischemic injury to the cavernosal tissue, the constriction ring should not be left on for more than 30 min [8].

Unlike the normal physiology of penile erection in which a complex interplay between neural inputs, vascular patency, and hormonal secretion is required, tumescence from VCD results from passive flow of mixed venous and arterial blood [9]. Broderick et al. demonstrated by color Doppler ultrasound that the negative pressure transiently draws arterial blood into the sinusoidal spaces of the cavernosal tissues, increasing its diameter nearly twofold [8]. The change in diameter owes itself to both intracorporal and extracorporal distention. The constriction ring placed at the base of the penis prevents the venous outflow. Color Doppler ultrasound performed after the placement of constriction ring, however, revealed no arterial inflow into the penis. This led to the recommendation that the constriction ring should not be left on for >30 min to prevent ischemic injury to the penis.

A recent review of literature revealed more than 63 reported cases of penile strangulation or incarceration from circular constriction objects placed on the penis [10]. These objects ranged from metal rings to plastic bottles, condom rings, rubber bands, threads, and even hair.

The rationale behind using these improvised constriction rings was almost universally for erotic or autoerotic purposes; in some cases, however, patients were afflicted with mental illnesses. The degree of penile injury not only correlated to the type of objects used but more importantly, to the duration of ischemia. Nonmetallic objects had a tendency to cause more injury, possibly due to their elasticity. Silberstein et al. reported that patients who presented after 72 h were more likely to sustain high-grade penile injuries [10]. These patients were considered urologic emergencies and immediate intervention was warranted. In most cases, conservative management after the removal of constriction device was adequate. Nevertheless, in some instances, the evaluation of urethra either cystoscopically or radiographically was warranted to rule out urethral injury. In rare cases, surgical debridement or partial penectomy was indicated.

Indications and Contraindications

Almost anyone with ED is qualified for VCD therapy. Its indication ranges from ED to postprostatectomy penile rehabilitation and even

penile length preservation. Its application is constantly being expanded to new horizons in keeping up with the technological evolution.

Erectile Dysfunction

There are hardly any contraindications for the use of VCD therapy in patients with ED. Before the 5-phosphodiesterase inhibitors (5-PDEi) era, VCD was among the first-line therapies for ED regardless of etiology [6]. In patients who cannot tolerate 5-PDEi side effects, or in whom these medications are contraindicated, VCD becomes an optimal treatment option. It has also been recommended for elderly patients who have sporadic sexual intimacy, as younger patients may have perception of an unnatural erection [11]. On the other hand, Chen et al. demonstrated that VCD remained a preferred treatment option in a certain subset of patients who achieved satisfactory erections with both VCD and oral 5-PDEi [12]. However, those patients who had used both oral 5-PDEi and VCD simultaneously reported higher sexual satisfaction and penile rigidity [13].

Penile Rehabilitation

Penile rehabilitation refers to the therapeutic measures focused on the prevention of damage to cavernous tissue after radical prostatectomy (RP) by providing adequate oxygenation to the cavernous tissues. The main purpose is to prevent structural alterations within the corpus cavernosal smooth muscle, maximizing the chance to recover functional erections in a man who has undergone RP and is hoping to regain his preoperative level of erectile function. Penile rehabilitation objectives include the protection and/or regeneration of the following elements from the corpora cavernosa: cavernous nerves, corporal smooth muscle, and corporal endothelium. This should be started as early as two weeks post-op, as venous leak, suggestive of corporal smooth muscle fibrosis, may develop [14]. VCD has an important role in penile rehabilitation by producing an artificial erection

and inducing blood flow to the penis, thereby “oxygenating” the corpora cavernosa [15]. It is recommended that VCD therapy is started as early as possible after RP, either alone or in combination with oral medications [16, 17].

Penile Length Preservation

Penile shortening after RP is a common phenomenon. In fact, more than 60% of those patients experience penile shortening with varying degrees, ranging from 0.5 to 5 cm [18, 19]. Several investigators have looked into using VCD after RP to preserve penile length and girth. Dalkin et al. reported only a 3% rate of stretched penile length reduction of 1 cm or more in compliant patients. In his study, both pre- and postoperative stretched flaccid penis length were measured. After the Foley catheter was removed, these patients were asked to use VCD on a regular basis. Among those who were at least 50% compliant, 35/36 (97%) maintained their preoperative stretched penile length [20]. Other authors had come up with equally convincing evidence as well [17]. As more data emerges, it is becoming normal to use VCD therapy postprostatectomy to maintain penile length, as well as to regain preoperative erectile function.

Contraindications

There are a few contraindications to VCD therapy. These include bleeding disorders, anatomical deformation of the penis, and unexplained priapism. Those patients on anticoagulation are more prone to develop bruising or hematoma formation, whereas patients with blood dyscrasias are at increased risk of developing priapism. Relative contraindications include cultural issues that consider it taboo to obtain an artificial erection with the aid of external devices, and patients with cervical or high-thoracic spinal cord injuries, neurological, or degenerative joint diseases with poor manual dexterity, unless their sexual partners are willing to be involved in the process.

Evidence

Prostate cancer is the leading cancer in men. According to the National Cancer Institute, there are more than 189,000 new cases of prostate cancer diagnosed each year (Fig. 11.3) [21]. Despite the fact that the incidence and mortality rate from prostate cancer are declining, more and more patients are taking an active role in their health. Parallel to the rate of treatment is

the incidence of ED. It is estimated that the incidence of ED after RP ranges between 40 and 85% (Fig. 11.4) [22, 23]. Even after the introduction of nerve sparing technique, the potency rates vary, depending on individual surgeon's experience and technique, as well as patient's age, comorbidities, and preoperative sexual function. This new trend has led to the novel application of VCD therapy, including penile rehabilitation following RP.

Fig. 11.3 Prostate cancer incidence and distribution of treatment options

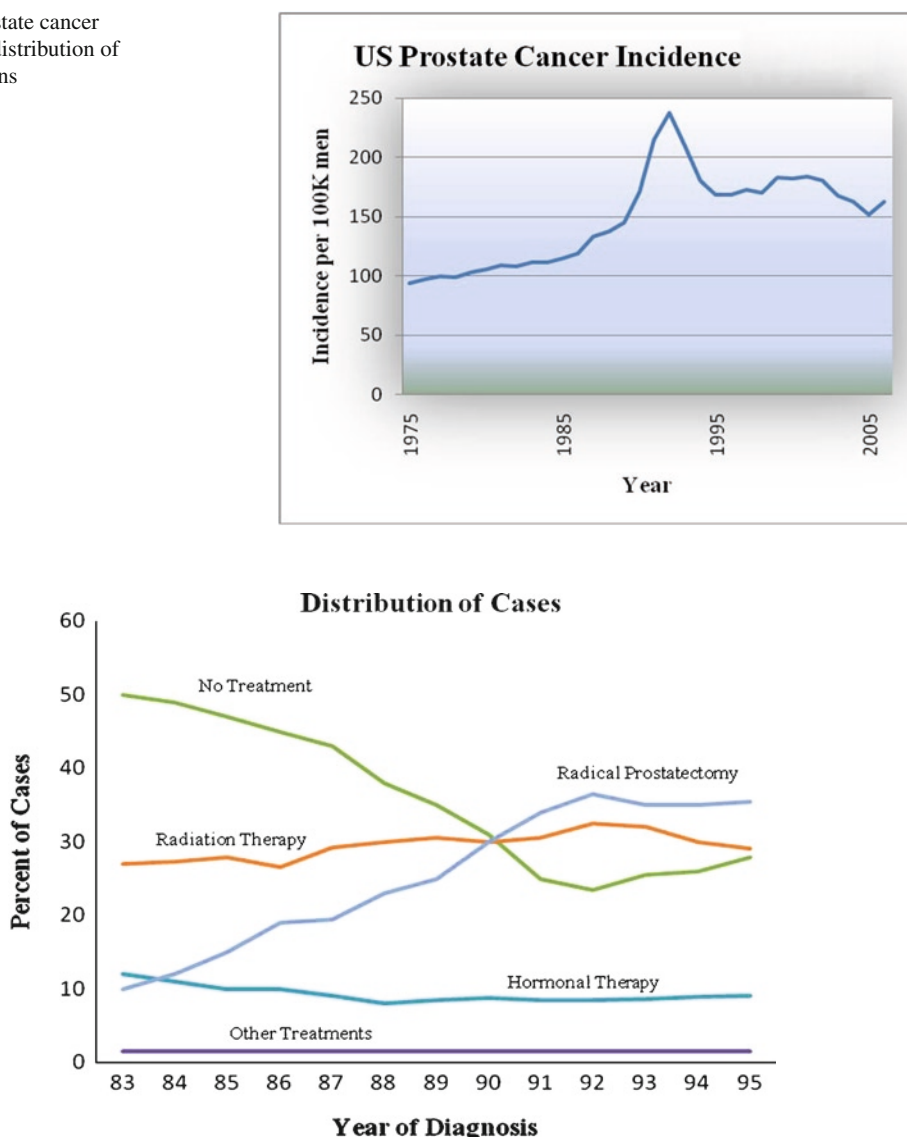


Fig. 11.4 Prostate cancer incidence and distribution of treatment options

Data From Nih Seer Program

Until Nadig published his results on its efficacy, VCD was relatively unknown to the urological community. In his original study, more than 90% of patients (32/35) achieved firm erections sufficient for vaginal penetration [6]. This was followed by a long-term study published in 1993 that reported excellent, durable results of patient's satisfaction and quality of erections greater than 90% [24]. Since then, many studies have demonstrated that VCD therapy is an effective noninvasive treatment alternative for ED (Table 11.1). However, many of these studies were done in the mid-1990s when the role of VCD was still being defined.

Following the Nadig study, Segenreich et al. published similar results in which 150 enrollees were followed on an average of 25 months [25]. Out of 150 enrollees, more than 75% achieved adequate erections; however, only 72 patients purchased the device. Satisfaction rate among these patients was more than 90%. Baltaci also achieved comparable results in which 67 enrollees were followed over a 12-month period [26]. Of the 61 participants, 49 purchased the device and used it regularly. Among these participants, the efficacy and satisfaction rates were 67% and 84%, respectively. Nevertheless, roughly one third of the participants were unable to achieve or maintain erection with the device.

One important point ascertained clearly in this study was that those with proven arteriogenic impotence also benefited from using the device. In addition, Kolettis et al. demonstrated that VCD was a safe, acceptable alternative treatment for corporeal veno-occlusive dysfunction as well [27].

While some displayed compelling satisfaction and success rates, others revealed less than convincing results (Table 11.1). Vrijhof et al. reported that only 50% of his enrollees were able to achieve adequate erections for intercourse; meanwhile, Sidi et al., reported only 68% satisfaction rate with the therapy [28, 29]. Dutta et al., on the other hand, revealed an attrition rate of 65% and satisfaction rate of only 35% [30]. In this study, participants were divided into three groups: mild, moderate, and severe ED. Many of those who discontinued using the device came from the mild and severe groups; however, even in the moderate group, the attrition rate was 55%. Top three reasons for discontinuation were ineffectiveness, pain, and cumbersomeness.

With the role of VCD firmly established, the focus was being shifted toward expanding its applications. Recently, this focus has been directed toward penile rehabilitation, postprostatectomy. Table 11.2 lists a summary of all the latest rehabilitation trials. Most trials utilized 5-PDEi to improve oxygen delivery to penile tissues seeking to preserve penile sexual health, as

Table 11.1 Efficacy of vacuum constriction devices

References	Study design	Enrollee (mean follow-up)	Results
Nadig et al. [6]	Prospective	35 (8–22 months)	>90% achieved adequate erections. 80% use regularly
Sidi et al. [29]	Prospective	100 (7.9 months)	68% satisfaction rate
Cookson et al. [24]	Retrospective	216 (29 months)	70% use regularly. Quality of erection plus satisfaction >90%
Segenreich et al. [25]	Prospective	150 (25 months)	75% achieved adequate erection. >90% satisfaction rate
Vrijhof et al. [28]	Prospective	67	50% achieved adequate erection
Baltaci et al. [26]	Retrospective	61 (12.8 months)	>80% satisfaction rate. 67% effectiveness rate
Bosshardt et al. [31]	Prospective	30 (6 months)	Quality of erection 80%
Kolettis et al. [27]	Prospective	50	56% satisfaction rate. An acceptable treatment mode for CVOD
Dutta et al. [30]	Prospective	129 (37 months)	High attrition rate (65%). 35% satisfaction rate

CVOD corporeal veno-occlusive dysfunction

Table 11.2 Summary table of penile rehabilitation trials

References	Treatment regimen	Study design	Enrollee	Results
Schwartz et al. [33]	QOD PDEi	Prospective	21	No loss of smooth muscle in 50 mg group, gain of smooth muscle in 100 mg group
Bannowsky et al. [34]	Daily PDEi	Prospective, randomized control	41	Treatment group has significantly higher IIEF and higher spontaneous erection rates
McCoullough et al. [35]	Daily PDEi	Prospective, randomized, placebo control	54	Treatment group had higher return of rigidity, higher rate of spontaneous erections
Raina et al. [16]	Daily VCD	Prospective, randomized control	109	Improved sexual satisfaction, higher rate of spontaneous erections
Kohler et al. [32]	Daily VCD (10 min), immediate vs. delayed	Prospective, randomized	28	Delayed use of VCD did not affect sexual satisfaction once use began. No statistical significance in penile shrinkage once VCD started
Montorsi et al. [36]	ICI 3 times weekly	Prospective, randomized control	30	Higher percentage of treatment group having spontaneous erections
Mulhall et al. [37]	ICI or PDEi to achieve erections 3 times weekly	Prospective, control	132	Treatment group had 2.7 times the rate of spontaneous erections, statistically higher IIEF scores
Nandipati et al. [38]	Daily PDEi and ICI 2–3 times weekly	Prospective	22	Assisted early sexual activity and satisfaction. Addition of PDEi allows lower dose of ICI

PDEi phosphodiesterase inhibitor, *ICI* intracorporeal injection, *IIEF* International index of erectile function, *VCD* vacuum constriction device
Source: Hinh and Wang: Overview of contemporary penile rehabilitation therapies. *Advances in Urology* 2008

well as to minimize any tissue injuries that otherwise occur during the postprostatectomy period. One limitation of 5-PDEi was its requirement of intact neural connections. The direct mechanism of VCD circumvented this limitation. Raina et al. randomized 109 post nerve-sparing prostatectomy patients to either early VCD daily usage (group 1, $N=70$) versus no erectogenic aid (group 2, $N=35$) [16]. Participants were followed by their Sexual Health Inventory for Men (SHIM) score. Secondary endpoints included compliance, changes in penile circumference or length, return of natural erectile function, and the ability for vaginal intercourse. At the end of 9 months follow-up, 80% (60/74) of group 1 were able to be sexually intimate using the device. Satisfaction rate was 55%. A total of 19 patients reported the return of natural erections with 17 having erections sufficient for vaginal penetrations. On the other hand, only 37% (13/37) of patients regained their natural erections in group 2. When evaluating for secondary endpoints, among those who used the device regularly, only 23% (14/60) reported a decrease in penile length and girth, whereas 22/35 (60%) patients in the control group complained of penile shrinkage. This result was confirmed by a study from Dalkin et al., in which 39 postprostatectomy men were given VCD therapy for 90 days postcatheter removal [20]. In their study, 97% of the compliant men maintained their pre-operative stretched penile length, with shrinkage being defined as ≥ 1 cm. The authors concluded that early usage of VCD facilitates early return of spontaneous erectile function, early resumption of sexual life resulting in spousal satisfaction, and the preservation of penile length and size.

Other authors investigated the timing of VCD therapy to maximize the benefits. Kohler et al. randomized 28 patients undergoing RP to early intervention (1 month post RP, group 1, $N=17$) and delayed intervention (6 months post RP, group 2, $N=11$) regarding VCD usage [32]. Group 1 was instructed to use VCD daily, starting 1 month post RP for two consecutive 5-min periods. Group 2 was instructed to use VCD; however, many times they wished, starting 6 months post RP. These men were followed by

International Index of Erectile Function (IIEF) scores. At 3 and 6 months follow-up, group 1 had a statistically higher IIEF score than group 2. Beyond 6 months when group 2 began to use VCD therapy, there was no statistically significant difference in IIEF scores between the two groups. When evaluating for penile shortening post RP, group 1 did not experience any significant penile length reduction, whereas group 2 experienced considerable reduction at 3-month (mean loss 1.87 cm) and 6-month follow-up (mean loss 1.82 cm). However, when group 2 began VCD therapy, the loss decreased to a mean of 1 cm. The authors concluded that early VCD therapy helped to improve early sexual function and preserve penile length.

Complications

The use of VCD is usually well tolerated. However, a diversity of side effects has been reported (Table 11.3). The most common side effects are related to the skin of the penis shaft, including subcutaneous hemorrhage, petechiae, ecchymosis, edema, abrasions, and bruising, with a more frequent presentation in patients on anticoagulation therapy [39–41]. Petechia can develop even at low vacuum settings (175 mmHg), while ecchymosis and penile hematoma develop at high pressures (greater than 250 mmHg). Patients may also complain of pain at the site where the rings sit, numbness or coldness of penile shaft, and ejaculatory dysfunction like delayed ejaculation or sensation of trapped ejaculate. Other complications not related to the penile shaft have been reported. These include leg spasms, testicular migration,

Table 11.3 Complications of vacuum constriction devices

Most common	Rare
Petechia or bruising	Penile skin necrosis
Ecchymosis	Penile gangrene
Penile hematoma	Fournier's syndrome
Penile numbness or coldness	Peyronie's disease
Ejaculatory dysfunction	

and urethral bleeding due to urethral varicosities. Major complications like Peyronie's disease, penile skin necrosis, penile gangrene, and Fournier's syndrome have been reported anecdotically [39–45].

The Future of VCD Therapy

VCD therapy is usually the next step in the treatment algorithm for ED after the failure of oral medical therapy. In many instances, it is commonly used in conjunction with 5-PDEi for better results. Penile rehabilitation is a new concept involving VCD therapy in postprostatectomy patients to regain preoperative sexual function as well as to prevent penile shrinkage. As more data is gathered, the movement is gaining support to establish VCD therapy as a normal part of post-prostatectomy penile rehabilitation. This movement parallels with the shift in focus from establishing the effectiveness of VCD therapy in expanding the novel applications beyond the realm of ED.

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Chapter 12

Hormonal Evaluation and Therapy in Erectile Dysfunction

Sergio A. Moreno and Abraham Morgentaler

Abstract Although endocrine causes of erectile dysfunction (ED) have been well recognized for decades, historically there has been little emphasis on endocrine evaluation or treatment for men with ED. Endocrine abnormalities as a cause or contributing factor for ED are important to recognize since these may be associated with significant additional medical problems, and also because correction of the endocrinopathy often leads to improvement or resolution of ED.

This chapter reviews the endocrine causes of ED, and provides a practical approach to the endocrine evaluation and treatment of men with ED. A major emphasis of this chapter is related to testosterone deficiency, which may contribute to ED at various levels, including the brain, peripheral nerves, vasculature, and penis. Testosterone deficiency is becoming increasingly recognized as an important health issue for aging men, with a high prevalence among the age groups at risk for development of ED. Testosterone therapy in these men may resolve ED completely, or may allow for greater responsiveness to more traditional therapies, such as the oral phosphodiesterase 5 inhibitors. A basic hormonal evaluation should be considered for all men presenting with sexual dysfunction.

Keywords Sexual dysfunction • Erectile dysfunction • Endocrine evaluation • Hormones • Hypogonadism • Testosterone • Prolactin • Estradiol • Thyroid hormone • Cortisol • Growth hormone • Testosterone deficiency

Introduction

Normal erectile function requires the integrity and interrelationship of vascular, neurological, and hormonal factors. Conditions that compromise any of these may result in erectile dysfunction (ED). In addition, psychological factors, systemic diseases, and medications may also contribute to ED [1].

Our current understanding of erectile physiology and pathophysiology was largely obtained through basic research performed in the decades of 1980s and 1990s with an emphasis on the vascular aspects of erection. The introduction of phosphodiesterase type 5 inhibitors (PDE5i) as the first effective oral therapies for ED in the late 1990s furthered the focus on vascular aspects of erection. Recognition of the endocrine role in regulating erectile function has been more recent, and remains a continuing area of active investigation, particularly the impact of testosterone deficiency (TD) on sexual function.

As awareness of the importance of TD has grown, there has similarly been increased recognition of the importance of hormonal evaluation for men with ED. This relatively new appreciation of the impact of hormonal abnormalities on ED was demonstrated by the recommendation at the Second International Consultation on Erectile

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and Sexual Dysfunction in Paris in 2003 that all men with ED be tested for TD. In addition, it was recommended that TD, also termed hypogonadism, should be treated before initiation of other ED treatments such as PDE5i's [2]. Similarly, The International Society for the Study of the Aging Male (ISSAM) recommended that the initial assessment of all men with erectile dysfunction and/or diminished libido should include determination of serum testosterone. ISSAM also noted that abnormal concentrations of hormones other than testosterone may also contribute to sexual dysfunction [3].

The term hormone is derived from a Greek verb *hormon*, which means "to excite," and was first used by William Bayliss and Ernest Starling in 1902 to describe the action of secretin [4]. More than 50 different hormones have been identified in humans, several of which have been shown to influence erectile function. The objectives of this chapter are as follows:

- To review the scientific evidence regarding the role of various hormones on normal erectile function, with special attention to testosterone
- To describe the mechanisms by which hormonal abnormalities may contribute to the pathophysiology of ED
- To provide a practical approach to the hormonal evaluation of men with ED
- To discuss the hormonal treatment of ED

Androgens and Erectile Dysfunction

General Concepts

Androgens are defined by their ability to specifically bind to the androgen receptor. A number of androgens are present in men. *Testosterone* (T) is the dominant circulating androgen. It is synthesized primarily by the Leydig cells in the testis, with a small portion (5%) produced by the adrenals. The adrenals also produce *dehydroepiandrosterone* (DHEA), and *androstenedione*.

In men, approximately 40–68% of T circulates in the bloodstream loosely bound to albumin,

approximately 30–60% is bound tightly to sex hormone-binding globulin (SHBG), and approximately 0.5–3% circulates unbound, termed free T [5–7]. Bioavailable T consists of the free and albumin-bound fractions, since it appears that the tight binding of T to SHBG renders it biologically unavailable.

Testosterone's effect may be direct, or mediated via local conversion to *dihydrotestosterone* (DHT) or *estradiol*. Testosterone is converted to DHT peripherally by the enzyme 5 α -reductase, and to estradiol by the enzyme aromatase. Adrenal androgens may be converted to testosterone and to DHT in target tissues.

Androgens in Physiology and Pathophysiology of Erectile Dysfunction

In animals models there is strong evidence that the penile erectile response is androgen-dependent [8–12]. Testosterone is directly involved in erectile physiology and pathophysiology, and may exert its effect on erection at various loci, including the central nervous system, peripheral nerves, penile vasculature, and structural components of the penis itself (Fig. 12.1).

Testosterone in the Brain

There is evidence that testosterone may mediate the libido and erectile response via a central nervous mechanism. Androgen receptor-linked brain sites are present in the hypothalamus, pituitary gland and medial preoptic area (MPOA). In the lizard, used as a model for the primitive brain, castration eliminates the male sexual response, and direct implantation of T into the preoptic area and hypothalamus restored the full range of sexual behaviors, including mounting and successful erection, although circulating levels of T were undetectable [13]. In the rat, direct electrical stimulation of MPOA induces an erection. Castration greatly attenuates this response, and testosterone substitution restores full erection [14, 15].

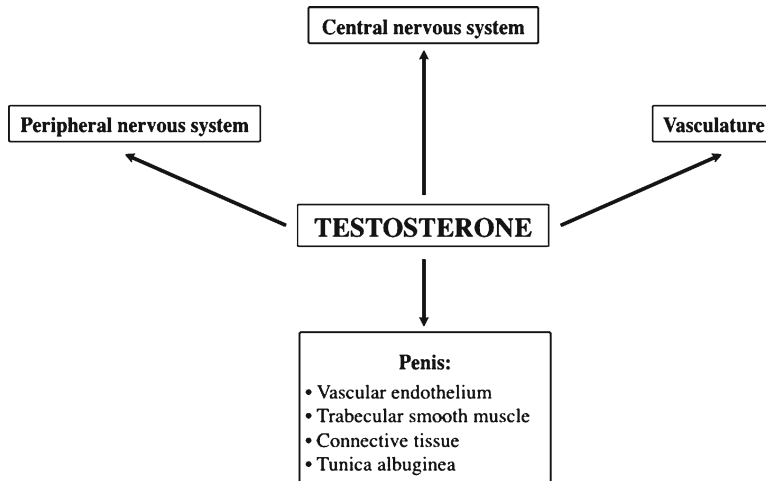


Fig. 12.1 Testosterone targets in erectile function

The brain effect of androgens on the sexual response in men is demonstrated also by functional brain imaging. Men with TD showed decreased activation in regions of the brain that are typically activated in healthy controls and in androgen-deficient men after testosterone replacement [16].

Curiously, erections associated with visual stimulation in men appear to be unaffected by TD, suggesting that these types of erections are largely androgen-independent [17].

Testosterone in Peripheral Nerves

In animal studies, androgen receptors are found in peripheral nerves that appear responsible for mediating penile erections [18]. Baba et al. showed that NADPH diaphorase staining of nerve fibers in the rat corpus cavernosum and dorsal nerve are dependent on androgens [19, 20]. In a rat model, Armagan et al. demonstrated that T has a neuroprotective role in the nerve fibers of the dorsal nerve, as T deficiency led to nerve degeneration, resulting in anatomic alterations, and erectile dysfunction [21].

Rogers et al. showed that castration altered the dorsal nerve ultrastructure in the rat. In tissue from castrated rats, the diameter of both the

myelinated and nonmyelinated axons appeared smaller than those of control group. Testosterone treatment of castrated animals restored the nerve fibers and myelin sheath structure similar to that observed in the sham group, suggesting that androgens are important in maintaining the peripheral autonomic and sensory nerve structure and function in the penis [22]. Recently, Traish et al. reported similar results for the cavernous nerve [23].

Giuliano et al. suggested that testosterone enhances the erectile response of the cavernous nerve. The authors suggest that androgen action on nerves may be of even greater importance than its actions on penile erectile tissue. In particular, postganglionic parasympathetic ganglions may be a key site for androgenic proerectile response [24]. In elegant experiments, Meusbürger and Keast [25] and Keast et al. [26], demonstrated the role of androgens in maintaining the structure and function of pelvic ganglion neurons.

In 1992, Rajfer et al. elucidated the role of nitric oxide (NO) as the chemical mediator of penile erection [27]. Burnett et al. localized NO to the cavernosal nerve and suggested that NO was the neurotransmitter that initiated penile erection [28]. More recently, animal studies have shown that nitric oxide synthase (NOS) is regulated by the testosterone metabolite, DHT [29]. These results provide critical evidence supporting

not only the importance of androgens in control of erectile function, but also that its influence is mediated at least in part by its trophic effects on peripheral nerves.

Testosterone and the Vasculature

In 1939, Edwards et al. were the first to report the effects of testosterone on blood vessels. They observed that testosterone treatment in castrated men was associated with an increased arterialization of the cutaneous vasculature [30].

Testosterone deficiency has been shown to be an independent determinant of endothelial dysfunction, thus contributing to vascular pathology and ED [31]. One mechanism by which testosterone may contribute to ED on a vascular basis is via the nitric oxide pathway. Nitric oxide causes relaxation of the vascular smooth muscle, which leads to penile erection [23, 32]. The role of androgens on the expression of NOS isoforms in the penile tissue has been clearly demonstrated [23, 29, 33]. Castrated animals have a greatly diminished erectile response to direct nerve stimulation, and replacement with testosterone or DHT restored erectile function, as well as NOS expression in the corpora cavernosa [23, 34]. Experimental work suggests that androgen deficiency causes injury to the endothelial lining of the vascular bed of the penis, with decreased NO secretion, but increased synthesis of transforming growth factor beta 1 (TGF- β 1), endothelin, and contractile prostanoids [35].

The critical role of testosterone for optimal vascular response with erections was suggested in a study by Aversa et al. This study was comprised of 20 men with arteriogenic ED who had normal sexual desire, but low-normal testosterone (mean total testosterone 368 ng/dl and mean free testosterone 0.75 ng/dl) and who did not respond to the PDE5i sildenafil despite multiple attempts. Men were randomized to receive placebo or transdermal testosterone (5 mg/day) for 1 month. After taking sildenafil 100 mg, the arterial inflow to the cavernous arteries, as measured by dynamic color duplex

ultrasound, was significantly greater in patients receiving testosterone than in those receiving placebo. Moreover, a significant association was found between free testosterone concentration and cavernous vasodilation as assessed by duplex ultrasound in eugonadal men with ED ($r=0.37$, $P<0.01$) [36].

These results provide evidence that testosterone has direct vascular effects on NO-mediated vasodilation [37]. Additional studies have also shown increased penile arterial inflow with testosterone administration together with improved erectile response to both sildenafil and tadalafil [38, 39].

An additional mechanism by which testosterone may enhance erections is by attenuating the α -adrenergic vasoconstrictor activity in vascular smooth muscles of the corpus cavernosum. Reilly et al. showed that the responsiveness to phenylephrine, an α -adrenergic agonist, was nearly six times greater in castrated rats than those with normal testosterone levels [40].

Testosterone in the Penis

There are few publications showing a direct end organ dependency of androgen for erectile function in the human corpora cavernosa, although there is evidence that low or absent androgens affect erection. Much of the knowledge we have today about the effects of androgens in the penis comes from animal models [18]. Testosterone appears to regulate nitric oxide synthase, exert trophic effects on cavernosal smooth muscle and ischiocavernosus and bulbospongiosus muscles, and is necessary for the veno-occlusive response [41].

An interesting question is whether testosterone or its metabolite DHT is the active androgen for erectile function. In an animal model, DHT was as effective as testosterone in restoring the erectile response to nerve stimulation in castrated rats, but treatment with finasteride, a 5 α -reductase inhibitor that impedes conversion of T to DHT, decreased the response to testosterone replacement. This suggests that DHT may play an essential role in maintaining erection in a rat model [29].

Vascular Endothelium

Androgen deprivation in an animal model produced a significant loss of trabecular smooth muscle, increased deposition of connective tissue, and impairment of erectile function [42, 43]. Traish and Guay attributed these changes to: (1) a reduced synthesis of paracrine growth factors (e.g., vascular endothelial growth factor [VEGF], fibroblast growth factor [FGF], and insulin-like growth factor 1 [IGF-1]) necessary to maintain smooth muscle, endothelium, and nerve structure and function; (2) upregulation of paracrine factors (e.g., connective tissue growth factor [CTGF] and TGF- β 1) which increase expression of connective tissue proteins; and (3) downregulation of metalloproteinases and upregulation of tissue inhibitors of metalloproteinases resulting in increased ECM deposition [32].

Trabecular Smooth Muscle

Androgens regulate growth and differentiation of vascular smooth muscle cells. Several researchers have hypothesized that androgens promote the commitment of pluripotent stem cells into a muscle lineage and inhibit their differentiation into an adipocyte lineage [42, 44–46]. The total number of circulating vascular progenitor cells may also be dependent on testosterone levels [47].

Androgen deprivation by surgical castration results in a significant decrease in trabecular smooth muscle content [42, 43], which appear disorganized, with large number of cytoplasmic vacuoles, and decreased amounts of cytoplasmic myofilaments [23, 32, 48, 49]. It is thought that androgen deprivation might initiate tissue degeneration and trabecular smooth muscle apoptosis [50, 51], thus causing an imbalance in the ratio of smooth muscle to extracellular matrix, leading to veno-occlusive dysfunction [52]. Studies suggest that veno-occlusion is modulated by the balance between the smooth muscle and connective tissue content of the corpus cavernosum [48, 53–55].

The smooth muscle content of the corpora cavernosa relative to the connective tissue,

assessed histologically with specific staining is defined as the smooth muscle: connective tissue ratio. A decrease in the trabecular smooth muscle content concomitant with increased deposition of connective tissue matrix is expected to produce tissue fibrosis and ultimately erectile dysfunction [35]. It is interesting to note that because veno-occlusion depends on the compression of the subtunical venules to impede blood outflow during sexual stimulation, it is possible that the presence of fat cells in the subtunical region of the corpus cavernosum may contribute to venous leak in the orchiectomized animal [49, 51, 56]. In men with ED, the severity of symptoms and clinical findings correlate with reduced tissue content of corporal smooth muscle [53, 57–59].

Connective Tissue

Several studies suggested that androgens modulate the extracellular matrix through expression of growth factors [60]. In animal models, androgen deprivation produced significant reduction in trabecular smooth muscle content and increased deposition of extracellular connective tissue matrix [42]. This change in tissue architecture is associated with reduction in intracavernosal pressure in response to pelvic nerve stimulation [10, 14, 42, 43, 61–66]. Androgen treatment of castrated animals results in a reversible increase in smooth muscle, concomitant decrease in connective tissue, and restoration of erectile function [42].

Cavernosal tissues from men with erectile dysfunction have been demonstrated to exhibit reduced lacunar spaces, reduced smooth muscle content, and a concomitant increase in connective tissue deposition [55, 67].

Tunica Albuginea

The veno-occlusive mechanism depends on the integrity and function of the cavernosal smooth

muscle and on the elastic properties and function of the tunica albuginea. In an aging rat model with reduced plasma testosterone levels, Davila et al. used dynamic infusion cavernosometry and cavernosography to demonstrate the presence of veno-occlusive dysfunction (venous leakage) in aged male rats with low plasma testosterone levels compared to young adult rats [68]. In a rat model, Shen et al. found that 4 weeks after castration the elastic fibers in the tunica albuginea were replaced by collagen fibers resulting in a loss of its elasticity [69]. The authors concluded that androgens are essential for maintaining the normal structure of the tunica albuginea and corpus cavernosum.

These studies provide ample evidence of a direct effect of androgens on penile structures involved in erectile function.

Evaluation of Androgen Status in Men with Erectile Dysfunction

Medical History

The diagnosis of TD requires the presence of characteristic symptoms or signs combined with blood tests confirming low androgen concentrations. The symptoms of TD are listed in Tables 12.1 and 12.2. Signs and conditions associated with TD are listed in Table 12.3. Although it is generally agreed that reduced libido is the hallmark symptom of TD, this symptom may be difficult to assess in some men, and it is important to note that TD is frequently present even in the absence of diminished libido. ED is a prominent symptom of TD. Additional sexual symptoms include difficulty achieving orgasm, diminished intensity of orgasm, reduced ejaculatory volume, and diminished sexual genital sensation. Non-sexual symptoms of TD include chronic fatigue, reduced energy and vitality, depressed mood, irritability, reduced muscle performance or mass, increased abdominal fat.

Table 12.1 Sexual symptoms associated with testosterone deficiency

Erectile dysfunction
Reduced, absent, or infrequent sexual desire (libido)
Delayed or absent orgasm
Reduced genital sexual sensation

Table 12.2 Non-sexual symptoms associated with testosterone deficiency

Depressed mood
Irritability
Diminished sense of well-being or vitality
Chronic fatigue
Reduced muscle mass or strength
Increased abdominal fat

Table 12.3 Signs and conditions associated with testosterone deficiency

Anemia
Reduced bone mineral density
History of low-trauma fractures
Abdominal/visceral obesity
Gynecomastia

A recent additional symptom suggestive of TD is the failure of men with ED to adequately respond to oral PDE5i medications, based on a number of studies that have shown improved responsiveness when TD has been corrected with testosterone therapy [37, 39].

TD is also associated with a number of signs, or objective measures. These include reduced bone mineral density, anemia, decreased height, and the presence of gynecomastia.

A number of validated screening questionnaires for the diagnosis of hypogonadism are available. These tend to have varying degrees of sensitivity, but all suffer from low specificity. These include Androgen Deficiency of the Aging Male (ADAM) [70]; The Aging Male Scale (AMS) [71], the low testosterone screener of Smith and colleagues [72] and ANDROTEST, a structured interview for the screening of androgen insufficiency in men with sexual dysfunction [73]. Questionnaires may be useful for screening, but should not replace a detailed history if ED is present or TD is suspected.

Physical Examination

The following items may be noted on physical examination for men with TD, although it should be noted that the physical exam will usually be unremarkable in the majority of men who develop TD associated with aging. The absence of abnormalities on physical examination does not exclude the diagnosis of TD.

- One or both testes with reduced volume, or soft consistency
- Gynecomastia
- Penile plaque (a high percentage of men with Peyronie's disease have TD) [74]
- Varicocele. Although the literature suggesting an association between varicocele and TD is equivocal, multiple studies have demonstrated improvement in serum T and free T with varicocele repair, suggesting that untreated varicoceles may suppress T production. In addition, varicoceles are often associated with smaller testes, which in turn may indicate suboptimal testicular function
- In addition, it is recommended that a digital rectal examination be performed for men 50 years or older to establish a baseline regarding prostate size, and to exclude the presence of a nodule [6].

Laboratory Study of Hypogonadism

It is generally agreed that the diagnosis of TD requires a confirmatory blood test result once symptoms or signs have been established. However, there is considerable confusion regarding diagnosis, since a number of blood tests are available, and there is no value for any of them which reliably distinguishes between those with TD and those without [6, 75]. As a general rule, the lower the testosterone value, the more likely a man is to have symptoms that will resolve with treatment. Laboratory-provided reference values should be regarded as nothing more than a rough guide as to what is "normal," since upper and lower limits are established based on population

statistics and are unrelated to clinical symptoms or treatment outcomes [76].

Total Testosterone

The most commonly used blood test for determination of TD is total testosterone. However it is widely agreed that total testosterone is often an inaccurate measure of androgen status since a large portion of circulating total testosterone is tightly bound to sex hormone binding globulin (SHBG), rendering it biologically unavailable. Nonetheless, the FDA has established a value of less than 300 ng/dl to define TD. A collection of international agencies have proposed 348 ng/dl as the recommended threshold value.

Free Testosterone

Free testosterone comprises only 1–2% of total testosterone, but represents a reasonable surrogate for bioavailable testosterone. There is general consensus that free T is a more useful indicator of androgen status for a given individual than total T, but controversy exists regarding which assay is best. Threshold values suggested by the Endocrine Society are less than 50 pg/ml by equilibrium dialysis or calculated free testosterone [6], and the international groups have suggested 65 pg/ml [3]. The direct analog assay for free testosterone yields values considerably lower than for equilibrium dialysis or calculated free T, and a clinically recommended threshold value indicating TD is less than 15 pg/ml for this assay [77]. Since equilibrium dialysis is labor-intensive and not widely available, calculated free T is generally recommended in its place. Although the direct analog free T assay has been criticized in the literature as unreliable [6], it correlates strongly with equilibrium dialysis and calculated free T results [78–80], has been shown to correspond with important biological endpoints [36, 74, 81], and has proven to be a useful clinical test [77].

Additional Blood Tests

Luteinizing hormone (LH) is an important test in young men (<40 years) with TD, and may be useful in older men as well. LH is a pituitary hormone that directly stimulates Leydig cell production of testosterone in the testis. Low values indicate a central cause of TD, such as pituitary insufficiency, or tumors of the hypothalamus or pituitary. High LH values in association with TD indicate a testicular etiology, such as seen with Klinefelter's, or with a history of mumps orchitis.

Follicle stimulating hormone (FSH) is considered a "sister" hormone to LH, and is often obtained together with LH as a separate indicator of pituitary function, although it has no definite role in testosterone physiology.

Serum prolactin is another test recommended for younger men with TD due to the association of hyperprolactinemia with TD.

Hematocrit and/or hemoglobin should be obtained in men with clinical suspicion of TD, at baseline and at follow-up, since these values are often depressed with TD, and usually rise with treatment, sometimes exceeding the normal range.

Finally, it is recommended that men with TD undergo testing for PSA at baseline and at follow-up once treatment has been initiated. This test may be eliminated for younger men.

Sex hormone binding globulin is an optional test, but is a required element if one desires to determine the calculated free testosterone (www.issam.ch/freetesto.htm). Albumin is also required for rigorous determination of calculated free T; however, the use of a constant value of 4.3 g/dl does not appear to significantly reduce accuracy in healthy men [78].

Hypothyroidism and hyperthyroidism may both be associated with ED, but usually only when these disorders are flagrant. The recommended screening test for thyroid disorders is thyroid stimulating hormone (TSH), and this test may be considered elective in the work-up of ED.

Treatment of the Hypogonadal Man with Erectile Dysfunction

In the man presenting with ED who is also T-deficient, treatment with T therapy is indicated for improvement in erectile function, and may be expected to improve other aspects of sexual function also. In some cases T therapy may be a primary treatment, and in others it may be used in combination with other ED therapies, such as the oral ED medications. Whereas in the past, treatment would have been discontinued if sexual symptoms were not relieved; today there is growing appreciation of the general health benefits of testosterone therapy in men with TD, and after appropriate discussion with the patient, testosterone therapy may still be continued in these cases with medical monitoring.

Patient and Partner Education

Patient and partner education is an essential component in the management of TD and ED. Educations includes an overview of pertinent anatomy and physiology, relevant pathophysiology, full disclosure of risks and benefits, and appropriate discussion of expectations regarding treatment [23].

Modifying Reversible Causes

Both TD and ED are potentially reversible if reversible etiologic factors can be changed. Weight loss has been shown to improve testosterone levels, reducing fat mass, and estrogen levels [82, 83]. Also, modification may apply to changing prescription or nonprescription drug use and/or altering psychosocial factors [84]. Opiate therapy for chronic pain syndromes have been associated with severe depression of serum T. Individuals should be questioned regarding the use of anabolic steroids for non-medical purposes, since these may negatively impact the hormonal axis regulating testosterone production.

Hormonal Treatment

Many urologists may lack appreciation of the relative merits of treating hypogonadism compared with oral PDE5i for erectile dysfunction. Testosterone-replacement therapy (TRT) may be the best treatment for men with ED when the presentation includes diminished libido or other sexual symptoms, or when non-sexual symptoms such as depressed mood, decreased sense of vitality, and increased fatigue also exist. The health benefits of TRT also include improvements in body composition, bone density, cognition, and sense of well-being [6]. Thus, there may be good reasons to use TRT as first-line therapy for the man with ED [85]. Also, men with sexual symptoms of hypogonadism respond well to TRT across a wide range of initial total testosterone values, including men with low-normal total testosterone levels. These men may have low bioavailable levels of testosterone that are not reflected in total testosterone values [86].

Isidori et al. conducted a meta-analysis evaluating the effects of testosterone on sexual function in men. Testosterone treatment moderately improved the number of nocturnal erections, sexual thoughts and motivation, number of successful intercours, scores of erectile function and overall sexual satisfaction, whereas testosterone had no effect on erectile function in eugonadal men compared to placebo [87]. In another meta-analysis, Boloña et al. showed a moderate nonsignificant and inconsistent effect of testosterone use on satisfaction with erectile function and a large effect on libido in men with low testosterone levels [88].

Combination treatment with oral PDE5i and testosterone in hypogonadal men may ensure improvement in erectile function [89]. Shabsigh et al. in a placebo-controlled study investigated the effect of testosterone gel in combination with sildenafil in men with ED and hypogonadism who had previously been unresponsive to sildenafil alone. A mild, but significant improvement in erectile function was noted in the group receiving testosterone and sildenafil combination

whereas there was no significant change in erectile function in the group treated with placebo and sildenafil. Additionally, the group treated with testosterone gel and sildenafil showed significant improvements from baseline in orgasmic function, overall satisfaction, and in total scores of sexual function questionnaires [90]. In another study, the synergistic effect for testosterone therapy and efficacy of PDE5i therapy in hypogonadal men with ED showed that when testosterone treatment alone failed, combination therapy with a PDE5i and testosterone gel improved sexual function [91]. Hwang et al. treated TD men who had failed sildenafil at 100 mg with testosterone therapy. One third of these men were able to achieve successful intercourse without sildenafil, another third required the combination of sildenafil and testosterone therapy, and the last third remained unsuccessful [92]. These results indicate that testosterone therapy may be useful in restoring adequate erections in TD men as primary therapy for ED, or in men who have previously failed PDE5i treatment.

The objectives of testosterone therapy are to restore concentrations of testosterone to the physiologic range in order to improve symptoms and possibly optimize general health outcomes, such as bone density, body composition, mood, and vitality [93]. A number of formulations are available for testosterone therapy, and these are described below.

Forms of Testosterone Therapy

Topical Gels

Transdermal application of testosterone-containing gel is the most commonly used form of T therapy. These require daily application. Advantages include convenience, ease of use, and minimal rates of skin reaction. Disadvantages include lack of adequate absorption in approximately 15% of men, and concerns regarding virilization of women and children via skin-to-skin transfer to women and children.

Transdermal Patches

Patch development preceded gels, and offered the first non-invasive form of treatment. However, use of patches has largely been superseded by gels, due to a rate of skin reaction as high as 40% [94] and relatively poor testosterone absorption relative to other treatment modalities.

Testosterone Injections

Two esters of testosterone are commonly used for injection-therapy, testosterone cypionate and testosterone enanthate. Injections are performed intramuscularly every week or 2 weeks. Longer injection intervals are suboptimal due to complete metabolism in nearly all individuals by 14 days. Advantages include universal attainment of adequate testosterone concentrations. Disadvantages include the discomfort associated with injections, and frequent visits to health care facilities, although this latter issue can be circumvented by teaching self-administration of injections to men.

Implantable Pellets

Implantable pellets of crystalline testosterone are placed subcutaneously, usually in the buttock region, and may provide normal testosterone levels for periods of up to 6 months, although 3–5 months is more common. Advantages include convenience, and improved compliance. Disadvantages include the minor discomfort associated with the in-office procedure to place the pellets. Cases of pellet extrusion or infection are uncommon.

Buccal Pellets

A pellet or pastiche of testosterone is available that can be applied to the gumline above the incisors. It must be changed twice daily. Clinical experience reveals good serum T concentrations, but this mode of therapy lacks broad appeal.

Oral Forms of Testosterone

A number of alkylated testosterone preparations have been available since the 1940s. These preparations are associated with relatively poor absorption, as well as significant liver toxicity, and lipid abnormalities. Their use is thus strongly discouraged. As a rule, discussion of T therapy excludes use of oral testosterone. However, a non-alkylated oral T formulation, testosterone undecanoate, is available outside the US, and this formulation does not appear to have hepatotoxicity.

Anti-estrogenic Oral Agents

Oral medications shown to increase endogenous serum testosterone via the hypothalamic-pituitary feedback regulation include agents with anti-estrogenic properties. These include clomiphene citrate, tamoxifen, and aromatase inhibitors such as anastrozole. These agents increase LH, and thus serum T. Although these treatments have been shown to reliably increase serum T, clinical experience suggests that symptomatic response to these agents is less than that seen with exogenous forms of T. It should also be noted that the use of these agents for this purpose is off-label. However, this mode of treatment has been used for several decades to promote testicular function in men with impaired fertility, whereas exogenous T tends to reduce sperm concentrations, sometimes to zero.

Human Chorionic Gonadotropin

Injections of human chorionic gonadotropin (HCG) three times weekly increases serum testosterone by mimicking the effects of LH. This treatment is rarely used as a treatment of T deficiency due to the requirement for frequent injections, but is an excellent treatment for men with TD and infertility due to central causes of TD.

Monitoring Patients in Testosterone Replacement Therapy

Men receiving TRT must be monitored at regular intervals with digital rectal examination and blood testing for prostate-specific antigen, as well as hematocrit or hemoglobin due to the risk of erythrocytosis [94]. Men on transdermal therapies should also undergo early (1 month or sooner) determination of serum testosterone to determine adequacy of absorption and dosage, and at occasional intervals thereafter. There is no need to monitor serum lipids, liver function tests, or renal function with standard (non-oral) formulations. Evaluation of the clinical response to TRT should include assessments of physical and sexual function and bone mineral density, especially in patients who have documented osteoporosis or osteopenia at baseline [93, 95].

Risks of Testosterone Therapy

Overall, T therapy is well tolerated. In the past, the greatest concern regarding T therapy has been the fear that higher serum T will lead to greater prostate cancer (PCa) growth. This fear was based on historical studies in which castrated men with metastatic PCa were administered T injections, with rapid and frequent negative outcomes [96]. However, studies in the modern era of PCa research, often defined by the introduction of the serum *PSA* test in the mid-1980s, have almost uniformly failed to indicate any significant relationship between PCa risk and T therapy, or higher endogenous serum T [97, 98]. A distinction should be made between the T therapy in the androgen-deprived individual versus the man with saturation of the androgen receptor (AR) due to maximal androgen-AR binding. Saturation of AR appears to occur in the human prostate in the near-castrate range [97].

Nonetheless, in the absence of large controlled intervention studies, it is impossible to state definitively that T therapy is safe with regard to PCa, and for this reason most authors recommend routine monitoring with *PSA* and digital rectal exam in the individual receiving T therapy.

Other risks include erythrocytosis, gynecomastia, acne, and edema [94]. All of these resolve with discontinuation of therapy. Sleep apnea has been linked to T therapy; however, a causative relationship has not been proved. Oral agents are associated with hepatotoxicity, hence the universal recommendation to avoid the oral forms of T therapy available in the US. Standard T therapy does not appear to influence renal or liver function results, or lipid profiles, and there is no need to monitor men with those studies.

Other Hormones and Erectile Dysfunction

Prolactin

Decreased desire or erectile dysfunction is the most common symptom on presentation in men with hyperprolactinemia [99]. A direct role of prolactin in male libido has been proposed [100]. However, hyperprolactinemia is an uncommon cause of TD and ED [2, 101]. Hyperprolactinemia has been noted in 1–5% of men who present with ED [102]; however, prolactin is considered a stress hormone and mild elevations occur with a number of conditions without clear impact on sexual function. Medications, notably the antipsychotic class, are also associated with hyperprolactinemia, sometimes to a severe degree. It is unclear whether such elevations impact sexual function.

Serum prolactin levels should definitely be obtained in young men with ED and symptoms of testosterone deficiency, or men of any age with gynecomastia [103]. Hyperprolactinemia may be caused by prolactin-secreting tumors of the pituitary, termed prolactinomas. These are associated with substantially elevated concentrations of serum prolactin. In a study of pituitary MRI's obtained in men with TD, pituitary masses consistent with prolactinomas were found only when serum prolactin was greater than double the upper limit of normal [104].

Standard treatment of hyperprolactinemia includes medical therapy with cabergoline, or

bromocriptine. Rarely, surgical resection is performed for large prolactinomas. Treatment with cabergoline, a dopamine agonist, has been reported to improve erectile function in 97% of hyperprolactinemic men versus 13% of controls after 6 months [105]. Testosterone and semen parameters returned to the normal range in most hyperprolactinemic men by 24 months [106]. Nonetheless, it is important to note that some men with TD and hyperprolactinemia will still require testosterone therapy to achieve an optimal result even after successful treatment of the elevated prolactin.

Estradiol

In aging and obese men, estradiol values increase over time [107], and high values are considered detrimental to male sexual function. Estradiol has been shown to inhibit LH secretion in men and to increase the liver synthesis of SHBG [2, 101]. Estradiol values have been noted to be significantly higher in ED patients with venous leak than in controls, supporting the hypothesis that estradiol level can adversely influence penile smooth muscle function [108]. However, it remains to be determined whether elevated or reduced concentrations of estradiol alone can induce ED directly. Testing for estradiol should be obtained in men who present with gynecomastia, or develop gynecomastia during testosterone therapy. Mild elevations in serum estradiol are not uncommon during testosterone therapy, but are not known to cause adverse effects other than gynecomastia, which is uncommon [94].

Thyroid Hormone

Sexual dysfunction is commonly seen in individuals with significant thyroid hormone disorders. However, thyroid disease is a rare contributor to ED when it is discovered incidentally, or without classic symptoms of hyper- or hypothyroidism.

Carani et al. reported an ED prevalence of 14.7% in men presenting with hyperthyroidism and 64.3% in men with hypothyroidism. It is postulated that ED in hyperthyroidism might be precipitated by increased adrenergic tone that leads to insufficient smooth muscle relaxation within the corpora cavernosa required for the normal erectile response [107]. An increase in estrogen and SHBG levels have been observed in hyperthyroid men, which may theoretically contribute to ED as well [109], although evidence for this is lacking. High prolactin levels observed in hypothyroid individuals may possibly affect the central machinery of sexual drive [107, 110]. Most men with hypothyroidism or hyperthyroidism will return to their baseline level of sexual functioning after normalization of thyroid hormone.

The recommended initial test for thyroid disease is serum TSH. Elevated concentrations indicate thyroid deficiency, and low concentrations suggest hyperthyroidism. Testing for TSH is not required in the absence of classic manifestations or symptoms of thyroid disease [107].

Cortisol

Adrenal diseases cause sexual disturbances only in severe cases of adrenal hypo- or hypercortisolism. Hypercortisolism may suppress gonadotropins production affecting normal sexual activity. On the other hand, primary or secondary hypocortisolism or suspension of substitutive therapy may cause reduced libido or sexual dysfunction. Adequate treatment of cortisol excess or deficiency restores normal sexual function in most patients [109].

Growth Hormone

Growth hormone (GH) hypersecretion can cause male sexual dysfunction. Increased libido may be seen initially followed by a successive and

progressive decline, and the appearance of ED [110]. The resulting acromegaly may also contribute to sexual dysfunction due to negative self-image [111]. Although there is currently great interest in the treatment of acquired GH deficiency in older men, there is as yet little information regarding the impact of this condition on male sexuality [112, 113].

Conclusions

- Hormonal causes of ED are common.
- The most common endocrinopathy contributing to ED is testosterone deficiency.
- Routine testing for serum total and free testosterone is a reasonable approach to men with ED of any age, but should definitely be obtained in men with additional symptoms, such as reduced libido, difficulty achieving orgasm, chronic fatigue, or a history of osteoporosis.
- Testing for serum testosterone should also be considered in men with ED who have failed treatment with PDE5i's, since treatment may "rescue" an adequate response in a large number of these men.
- Treatment of TD may restore normal sexual function.
- Indications for testing for other hormones depend on clinical circumstances.

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Chapter 13

Cardiovascular Issues in the Treatment of Erectile Dysfunction

Graham Jackson

Abstract The cardiovascular response to sexual activity worries a lot of men and women, particularly if a coronary or vascular event has already occurred. The fear of inducing another cardiac episode is fuelled by many myths including the assumption that sex is an extreme stress to the heart, driven to some extent by media/internet distortion. Adding the anxiety that treating ED may increase cardiac risk, and we have a recipe for relationship stress or breakdown and couple frustration. Many agree with the concept that ED is “a man’s problem but a couple’s concern” because it invariably is, though at times is not managed as such. Though this chapter addresses an organic condition, it is important not to compartmentalize ED too rigidly – men with organic ED may, and often do, have psychological problems as well, and men with a predominantly psychological etiology may also have organic issues.

Keywords Cardiovascular disease • Coronary artery disease • Endothelial dysfunction, myocardial infarction • Exercise stress test • Androgen replacement therapy • Phosphodiesterase inhibitors • Intracavernous injection therapy

Introduction

The link between erectile dysfunction (ED) and cardiovascular disease (CVD), specifically coronary artery disease (CAD), is now well established [1]. We recognize that ED may be a marker for silent CAD as the common denominator in the majority of men over 30 years of age is endothelial dysfunction [2]. In addition, up to 75% of men with CAD have some degree of ED, often presenting before the coronary event. The Second Princeton Consensus Conference, which focused on sexual dysfunction and cardiovascular risk, concluded that ED is a warning sign of vascular disease with the practical recommendation that a man with ED and no cardiac symptoms is a cardiac or vascular patient until proven otherwise [3]. From these observations came the idea that ED in the absence of CAD symptoms offered an opportunity to reduce the risk of a coronary or vascular event by addressing the recognized CAD risk factors shared by ED and CAD. This proposal was strengthened by a series of publications pointing to an average time window of 3 years between ED and a CAD event [4].

The cardiovascular response to sexual activity worries a lot of men and women, particularly if a coronary or vascular event has already occurred. The fear of inducing another cardiac episode is fuelled by many myths including the assumption that sex is an extreme stress to the heart, driven to some extent by media/internet distortion. Adding the anxiety that treating ED may increase cardiac risk, and we have a recipe for relationship stress or breakdown and couple

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frustration. I have always liked the concept that ED is “a man’s problem but a couple’s concern” because it invariably is, though at times is not managed as such.

Therefore the cardiovascular issues that need to be addressed are:

- Is sex safe statistically, but more importantly for the individual being counseled?
- Can ED be safely treated in cardiac patients?
- Can ED be a means of preventing subsequent CVD?

Though this chapter addresses an organic condition, it is important not to compartmentalize ED too rigidly – men with organic ED may, and often do, have psychological problems as well, and men with a predominantly psychological etiology may also have organic issues.

Cardiovascular Response to Sexual Activities

The cardiovascular response to sexual activity is the combination of mild-to-moderate physical activity and a state of sexual arousal. Sexual arousal is the major determinant of the cardiovascular response to sex. Several studies have been performed using ambulatory electrocardiography and blood pressure monitoring comparing heart rate, electrocardiographic, and blood pressure responses during sexual activity and other normal daily activities. Nemec et al. [5] evaluated ten healthy males, comparing heart and blood pressure responses during sexual intercourse with their wives in their homes. They recorded only modest changes whether the male was on top or underneath. In the on top position, the peak heart rate was 114 ± 14 beats/min, returning to 69 ± 12 beats/min by 12 s post orgasm, and when the male was underneath, a similar peak heart rate of 117 ± 4 beats/min was recorded. The peak blood pressure responses were similar for both positions with a systolic reading at orgasm of 160 mmHg. Bohlen et al. [6] evaluated the hemodynamic and metabolic response to sexual activity in ten healthy men

(mean age 33 years). Four different types of sexual activity (self stimulation, partner stimulation, orgasm with man on top, and with woman on top) were tested. The response was compared with that of a symptom-limited treadmill test. During sexual activity, the heart rate progressively increased with a peak value during orgasm greater with man on top than with woman on top (127 ± 23 bpm vs. 110 ± 24 bpm, $p < 0.02$). During orgasm, the heart rate increase varied to 54–67% of the peak heart rate achieved during the treadmill, with little difference between the four types of sexual activity. Similar results were obtained when oxygen consumption (VO_2), expressed as the metabolic equivalent of the task (MET) where 1 MET is equivalent to the VO_2 consumption in the resting state, was calculated. During orgasm, the VO_2 consumption varied by 11–22% of that obtained at peak treadmill test. The mean METs value was 3.3 for coitus with man on top. Thus, sexual activity poses no excess cost to the heart compared to ordinary daily activities and much less than maximal exercise. Sexual arousal more than physical exertion is the major determinant of VO_2 consumption.

The cardiovascular responses during sexual activity in patients with CAD elicit qualitative changes similar to normals (Table 13.1). In a study of 30 men and 5 women with stable angina, patients assessed by 24-h ECG monitoring, the heart rate response averaged 122 beats/min (range: 102–137 beats/min) during intercourse compared to a maximum of 124 beats/min during the rest of the day [7]. I concluded “there is no reason why most patients with angina cannot have a normal sex life, and physicians should ask and advise routinely.”

Some general considerations should be kept in mind. Firstly, the cost of intercourse is lower (3–4 METs) for couples in a long-standing relationship compared with extramarital intercourse with an unfamiliar partner. In this latter setting, the higher heart rate achieved during sexual intercourse, mainly due to a high degree of sexual arousal, performance anxiety, ingestion of alcohol and food, or social disapproval, accounts for the higher cardiac workload, and the risk of an acute cardiac event [8]. Secondly, younger couples may be

Table 13.1 Cardiovascular response during sexual activity in normals and CAD

	No. of patients	Mean peak heart rate (beats/min)	METs
<i>Normals</i>			
Nemec [5]	10	114	
Larson [52]	17	115	
Masini [53]	10	126 (M) – 137 (F)	
Bohlen [6]	10	102–127	3.3
<i>CAD patients</i>			
Hellertsein [54]	14	117	3.4
Stein [55]	16	127	
Jackson [7]	35	122	
Garcia-Barreto [56]	23	111 (M) – 104 (F)	
Drory [9]	88	118	

M male, *F* female

more vigorous in their sexual activity than older ones, expending up to 5–6 METs. Finally, the concomitant use of cardiovascular medication such as beta-blockers and/or calcium-antagonist may lower sexual activity cost even in CAD patient with reduced coronary reserve, limiting the risk of effort-induced acute coronary events.

Thus, an exercise stress test is the most valuable tool to check functional reserve before sex. Drory et al. [9] assessed the cardiovascular response to sex by exercise-testing and Holter monitoring in 88 CAD patients with stable angina when off-therapy. In the 34 patients with negative exercise testing, none had ischemia on Holter monitoring during sex, whereas positive exercise testing was associated with ischemic changes by Holter monitoring during sex in 50% of patients. Therefore, CAD patients with any doubt about their exercise ability should perform an exercise stress test before initiating or resuming sexual activity. If they can exercise up to 3–6 METs (4 min of the standard Bruce treadmill protocol is 5–6 METs) without evidence of myocardial ischemia, fall in blood pressure or complex arrhythmias, they can generally safely engage in sexual activity without experiencing cardiac symptoms.

In an asymptomatic subject, tolerance to sexual activity may be assessed by simple everyday guidelines (Table 13.2). If he/she can tolerate walking 1 mile (1.5 km) briskly on the level in

Table 13.2 Metabolic equivalent of task units (METs) as a guide to relating daily activity to sexual activity

Daily activity	METs
Sexual intercourse with established partner	
Lower range (normal)	2–3
Lower range orgasm	3–4
Upper range (vigorous activity)	5–6
Lifting and carrying objects (9–20 kg)	4–5
Walking 1.6 km (1 mile) on the level in 20 min	3–4
Golf	4–5
Gardening (digging)	3–5
Do-It-Yourself, wallpapering, etc.	4–5
Light housework; e.g. ironing, polishing	2–4
Heavy housework; e.g. making beds, scrubbing floors, cleaning windows	3–6

20 min (3–4 METs) or climb up and down two flights of stairs without limiting symptoms (6 METs), it is highly probable that sexual activity can be tolerated without cardiac symptoms.

However, because there may be a significant variation in the physiologic response to sexual activity, it is important to individualize the advice. If sexual activity leads to angina pectoris because of a disproportionate myocardial oxygen demand relative to the supply, the effect of exercise training can decrease the myocardial oxygen demand for the same amount of total body work and may decrease or obviate the occurrence of angina pectoris.

Sexual Activity as a Cardiac Risk Factor

Overall, the risk of myocardial infarction during sexual activity is negligible [10]. Although maintaining sexual activity has been reported to have potential health benefits, it can trigger myocardial infarction (MI), arrhythmia, or sudden death in a very small minority of patients [11, 12]. The Myocardial Infarction Onset Study (MIOS) enrolled 1,712 patients with a first episode of MI [13]. Sexual activity was the potential trigger for MI in 1.5% of cases. Among 858 sexually active in the year before MI, 70 (9%) reported sexual activity in the 24 h preceding the acute coronary event, and 27 (3%) in the 2 h preceding the onset of symptoms. The relative risk of MI was assessed by “case-crossover” methodology. Table 13.3 shows the figures for different categories of patients developing MI during sexual activity. Overall, the relative risk of MI was increased by two to three times and confined to the 2-h period after sexual activity. After correcting for chance occurrence, 0.9% of cases could be attributed to sexual activity within the 2-h period before MI onset. Of paramount importance was the observation that the risk decreased to none if the subject engaged in regular physical activity (at least three times per week) at moderate workload (5–6 METs). A similar study from Sweden reported identical findings [12].

A more important concept is the absolute risk of MI during sex. In the Framingham Heart Study, the baseline risk of MI for a 50-year-old non-smoking, non-diabetic man is 1% per year

or one chance in a million per hour. As sexual activity increases the relative risk by two to three times, this subject will have a 1.01% risk per year or two to three chances in a million per hour, but only for a 2-h period. In patients who have had a previous MI, the baseline risk of reinfarction for death is: 10% per year, or 10 chances in a million per hour increasing to 1.1% per year, or 20 chances in a million for a 2-h period after sexual activity. Once again, the risk decreases to <3% if the patient could exercise >7 METs.

Coital sudden death is very rare. In three large studies, death related to sexual activity was 0.6% in Japan, 0.18% in Frankfurt, and 1.7% in Berlin [14]. Extramarital sex was responsible for 75%, 75%, and 77% respectively, and the victims were men in 82%, 94%, and 93% of cases, respectively. The partnership of an older man with a younger woman was the most common setting. Excessive drinking and sex too close to a large meal were frequently associated.

Key Points

- Sex between couples in a long-standing relationship is not stressful to the heart.
- Casual sex may lead to exaggerated cardiac responses.
- Simple advice related to normal daily activities is reassuring to the patient and partner.
- An exercise ECG is a valuable method of clarifying uncertainty.

Table 13.3 Relative risk of myocardial infarction during the 2 h after sexual activity: physically fit equals sexually fit

Patient type	Relative risk (95% confidence interval)
All patients	2.5 (1.7–3.7)
Men	2.7 (1.8–4.0)
Women	1.3 (0.3–5.2)
Previous myocardial infarction	2.9 (1.3–6.5)
Sedentary life	3.0 (2.0–4.5)
Physically active	1.2 (0.4–3.7)

Treating ED in Patients with CVD

Introduction

Recognizing the need for advice on management of ED, two consensus panels (UK and the USA) have produced similar guidelines dividing cardiovascular risk into three practical categories with management recommendations [15, 16].

The Princeton consensus guidelines have recently been updated (Table 13.4) [3, 16]. It is recommended that all men with ED should undergo a full medical assessment (Fig. 13.1). Baseline physical activity needs to be established and cardiovascular risk graded low, intermediate, or high. Most patients with low or intermediate cardiac risk can have their ED managed in the outpatient or primary care setting.

There is no evidence that treating ED in patients with cardiovascular disease increases cardiac risk; however, this is with the proviso that the patient is properly assessed and the couple or individual (self-stimulation may be the only form of sexual activity) are appropriately counseled. Oral drug therapy is the most widely used because of its acceptability and effectiveness, but all therapies have a place in management. The philosophy is to always be positive during what, for many men and their partners, is an uncertain time.

Lifestyle Factors

Lifestyle factors have been associated with ED in both cross-sectional and longitudinal studies. In particular, obesity and sedentary lifestyle are clear cut risk factors for ED, both in men with comorbid illnesses such as hypertension and diabetes, and especially in men without overt CVD [17]. Other lifestyle factors such as smoking and alcohol consumption have been implicated in some, but not all, studies to date. Intervening on cardiovascular lifestyle factors may have broader benefits beyond restoration of erectile function. This important concept needs careful consideration, as recent studies have implicated the roles of the metabolic syndrome, obesity, insulin resistance, and lack of exercise as independent risk factors for both ED and CVD [18, 19].

The role of obesity in ED has been confirmed in large scale, cross-sectional, and longitudinal studies [19–21]. In a study in The Netherlands, 1,700 Dutch men between the ages of 50–75 were evaluated for the presence of ED and other

health conditions [22]. Body mass index (BMI) was found to be a significant predictor of ED, both as a single factor and in combination with other risk factors (e.g. lower urinary tract symptoms (LUTS), hypertension, and diabetes).

Lack of physical activity is another lifestyle factor strongly linked to the occurrence of ED in aging men. In the Health Professionals Follow-Up Study [20], ED was associated with both increased BMI and decreased level of physical activity. Participants were categorized according to their level of exercise or physical activity. Higher levels of sedentary behavior (less physical activity) were found to be a strong independent predictor of ED in this study. Frequent vigorous exercise was associated with an approximate 30% reduction in the risk for ED.

The effects of weight loss and exercise were examined further in a randomized intervention trial of lifestyle modification in men with obesity-related ED [23]. This study compared 2 years of exercise and weight loss with an educational control in 110 obese men (mean BMI = 36.4 kg/m²) with moderate to severe ED. Approximately, one third of men in the intervention group achieved normal levels of erectile function following treatment, compared with <5% of men in the control group. Changes in weight loss and exercise were shown to affect endothelial function as measured by forearm brachial Doppler assessment, and were highly correlated with improvements in erection. Taken together, these studies strongly support the role of adverse lifestyle factors in the development and maintenance of ED. Obesity and lack of exercise, in particular, have been strongly implicated in a number of cross-sectional and longitudinal studies. At least one long-term prospective study has shown that lifestyle intervention can effectively restore erectile function in a substantial number of men with obesity-related ED, at least among those without significant medical comorbidities. For clinicians, the implications are clear that men with ED and other cardiovascular risk factors (e.g. obesity, sedentary lifestyle) should be counseled on lifestyle modification.

Table 13.4 Risk from sexual activity in cardiovascular diseases

Low risk: typically implied by the ability to perform exercise of modest intensity without symptoms

Asymptomatic and less than three major risk factors (excluding gender)

Major cardiovascular disease risk factors include age, male gender, hypertension, diabetes mellitus, cigarette smoking, dyslipidemia, sedentary lifestyle, and family history of premature CAD

Controlled hypertension

Beta-blockers and thiazide diuretics may predispose to ED

Mild, stable angina pectoris

Non-invasive evaluation recommended

Antianginal drug regimen may require modification

Post-revascularization and without significant residual ischemia

ETT may be beneficial to assess risk

Post-myocardial infarction (MI) (6–8 weeks), but asymptomatic and without ETT-induced ischemia, or post-revascularization

If post-revascularization or no ETT induced ischemia, intercourse may be resumed 3–4 weeks post-MI

Mild valvular disease

May include selected patients with mild aortic stenosis

LVD (NYHA class I)

Most patients are low risk

Intermediate or indeterminate risk: evaluate to reclassify as high/low risk

Asymptomatic and ≥ 3 CAD risk factors (excluding gender)

Increased risk for acute MI and death

ETT may be appropriate, particularly in sedentary patients

Moderate, stable angina pectoris

ETT may clarify risk

MI > 2 weeks but < 6 weeks

Increased risk of ischemia, reinfarction, and malignant arrhythmias

ETT may clarify risk

LVD/congestive heart failure (CHF) (NYHA class II)

Moderate risk of increased symptoms

Cardiovascular evaluation and rehabilitation may permit reclassification as low risk

Non-cardiac atherosclerotic sequelae (peripheral arterial disease, history of stroke, or transient ischemic attacks)

Increased risk of MI

Cardiological evaluation should be considered

High risk: defer resumption of sexual activity until cardiological assessment and treatment

Unstable or refractory angina

Increased risk of MI

Uncontrolled hypertension

Increased risk of acute cardiac and vascular events (e.g. stroke)

CHF (NYHA class III, IV)

Increased risk of cardiac decompensation

Recent MI < 2 weeks

Increased risk of reinfarction, cardiac rupture or arrhythmias, but impact of complete revascularization on risk is unknown

High risk arrhythmias

Rarely malignant arrhythmias during sexual activity may cause sudden death

Risk is decreased by an implanted defibrillator or pacemaker

Obstructive hypertrophic cardiomyopathies

Cardiovascular risks of sexual activity are poorly defined

Cardiological evaluation (ETT and echocardiography) may guide patient management

Moderate to severe valve disease

Use vasoactive drugs with caution

Second Princeton Consensus Conference. Adapted from Kostis et al. [3, 16]

CAD coronary artery disease, CHF congestive heart failure, CV cardiovascular, CVA cerebrovascular accident, ED erectile dysfunction, ETT exercise tolerance test, LVD left ventricular dysfunction, MI myocardial infarction, NYHA New York Heart Association

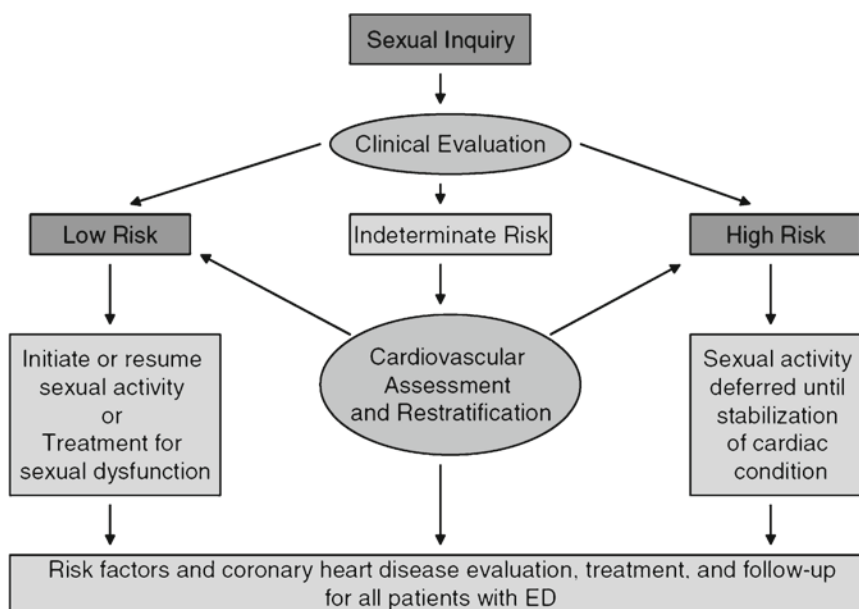


Fig. 13.1 Princeton II evaluation algorithm [16]

Androgens

The use of testosterone replacement therapy for the treatment of hypogonadism and ED may assist phosphodiesterase (PDE5) inhibitors if they have failed to be effective [24]. Testosterone levels within the normal range have neutral or potentially beneficial effects on the cardiovascular system [25]. Androgen replacement therapy should be offered to men with CAD and hypogonadism if symptomatically appropriate. The absence of long-term studies needs to be addressed in terms of possible preventive properties on the vascular wall, reduction in low-density lipoprotein levels, and the reduction of insulin resistance in contrast to the increase in hematocrit and risk of exacerbating prostate cancer.

Phosphodiesterase Inhibitors

To say that sildenafil has transformed the management of ED would be a substantial understatement [26]. Its mechanism of action by blocking the degradation of cGMP by PDE5 promotes blood

flow into the penis and the restoration of erectile function. Vardenafil and tadalafil have been added to this family of drugs [27, 28]. Because their mechanism of action is the same, there is no reason to assume that there will be any significant differences in ED effectiveness, but their half-life may be of cardiac clinical importance.

Hemodynamically, PDE5 inhibitors have mild nitrate-like actions (sildenafil was originally intended to be a drug for stable angina) [29]. As PDE5 is present in smooth muscle cells throughout the vasculature and the NO/cGMP pathway is involved in the regulation of BP, PDE5 inhibitors have a modest hypotensive action. In healthy men, a single dose of sildenafil 100 mg transiently lowered BP by an average of 10/7 mmHg with a return to baseline at 6 h post dose. There was no effect on heart rate [26]. As NO is an important neurotransmitter throughout the vasculature and is involved in the regulation of vascular smooth muscle relation, a synergistic and clinically important interaction with oral or sublingual nitrates can occur. A profound fall in BP can result. The mechanism involves the combination of nitrates increasing cGMP formation by activating guanylate cyclase and PDE5 inhibition decreasing cGMP breakdown by inhibiting

PDE5. The concomitant administration of PDE5 inhibitors and nitrates is a contraindication to their use and this recommendation also extends to other NO donors such as nicorandil. Clinical guidelines regarding timing of sublingual nitrate use post PDE5 inhibitors are 12 h for sildenafil and vardenafil [3, 29]. Tadalafil, with its long half-life, did not react with nitrates at 48 h post use [27, 30]. Oral nitrates are not prognostically important drugs and can therefore be discontinued and, if needed, alternative agents substituted [31]. After oral nitrate cessation, and provided there has been no clinical deterioration, PDE5 inhibitors can be used safely. It is recommended that the cessation time interval prior to PDE5 inhibitor use is five half-lives which equals 5 days for the most popular once-daily nitrate agents. Sildenafil and vardenafil both have a short half-life, which makes them the drugs of choice in patients with more severe CVD, allowing early use of support therapy if an adverse clinical event occurs.

In contrast, because of its long half-life, tadalafil may not be the first choice for the patients with more complex cardiovascular disease. However, as 80% of patients with cardiovascular disease stratify into low risk, it is an alternative for the majority. Tadalafil 10 mg is equivalent to sildenafil 50 mg and 20 mg to 100 mg.

Of particular interest is the daily use of tadalafil 2.5 and 5 mg. In on-demand failures, a regular dosing regime has been successful in 60% without increased adverse effects. This has increased the chance of success with important implications for the more difficult cases such as cardiac failure. There is no evidence of increased cardiovascular risk with on-demand, three times weekly, or daily dosing [32, 33].

Other Therapies

When oral agents are not effective, intracavernous injection therapy, transurethral alprostadil, or a vacuum pump are alternatives requiring specialized referral and advice [3]. Warfarin is not a contraindication to vacuum pump or injections,

but specialized training is needed. There is no evidence of increased cardiovascular risk from using any of these therapeutic options. If surgical intervention with general anesthetic is being anticipated, a full cardiological risk evaluation is recommended.

Non-arteritic Anterior Ischemic Optic Neuropathy

The reports of risk of “blindness” following PDE5 inhibitor use has caused concern [26]. Several case reports have linked PDE5 inhibitors to Non-arteritic Anterior Ischemic Optic Neuropathy (NAION). No explanation as to the mechanism currently exists and it is most likely coincidental, given the widespread use of PDE5 inhibitors in men who are at risk, being older and with vascular disease. The only identifiable risk factor is a small cup-disc ratio. It seems sensible to avoid PDE5 inhibitors in those previously suffering NAION in one eye.

Key Points

- Cardiac disease is not a contradiction to sexual activity.
- High risk cases require a cardiac assessment, not a negative attitude.
- PDE5 inhibitors are safe and effective drugs if used correctly.
- Alternative therapies to PDE5 inhibitors are available and do not increase cardiac risk in properly assessed patients.

ED as a Predictor of Occult CAD

Erectile dysfunction is now a recognized marker for cardiovascular disease as a result of several studies [34]. The artery size hypothesis has been used to explain how ED acts as a silent marker of vascular disease elsewhere in the body, and more significantly as a marker of CAD [35].

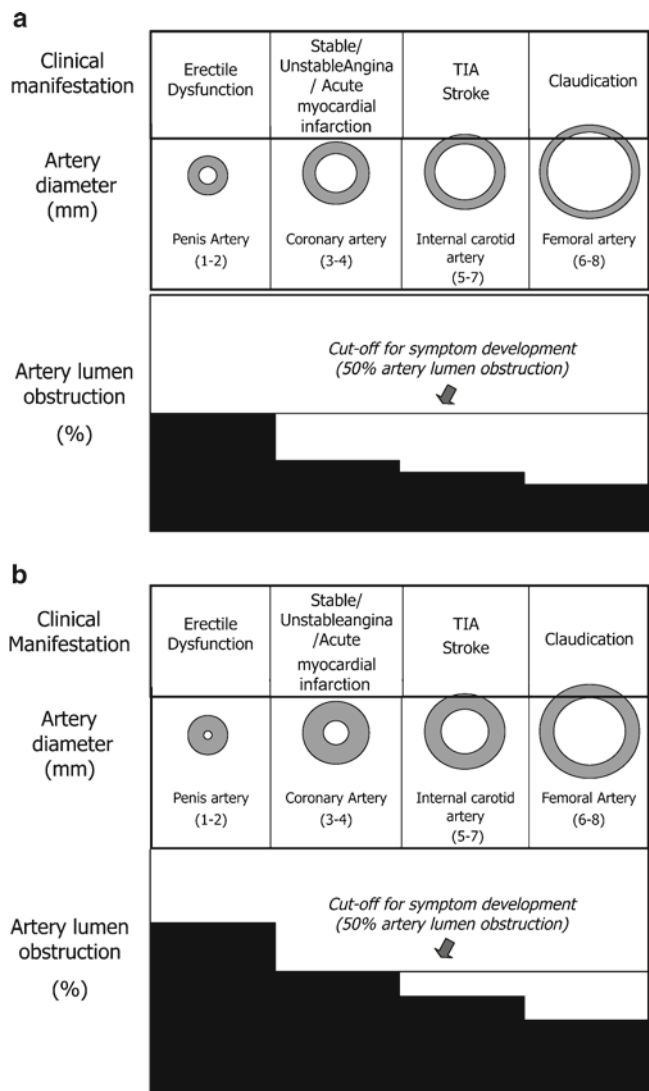


Fig. 13.2 (a) A patient with isolated ED due to >50% obstruction of the penile artery. The same plaque burden would be less likely to cause significant obstruction to blood flow in coronary, carotid or femoral arteries due to their larger sizes. (b) When atherosclerosis increases, a significant

obstruction will develop in coronary circulation, leading to angina pectoris. Due to the relative artery size, coronary circulation is likely to be the second region to become involved. By that time, penile circulation will be severely damaged (modified with permission from reference [35])

Artery size varies considerably according to location within the vascular system (Fig. 13.2). For example, the lumen of the penile arteries is considerably smaller (1–2 mm) compared with that of the coronary (3–4 mm), carotid (5–6 mm), and femoral (6–8 mm) arteries. Because of their smaller size, the same level of plaque burden and/or endothelial dysfunction has a greater effect on blood flow through the penile arteries

than through the coronary, carotid, and femoral arteries. Therefore the clinical manifestations of penile endothelial dysfunction (ED) may become evident before the consequences of coronary or peripheral vascular disease. By the time the lumen of the larger arteries become significantly obstructed (>50%), the penile blood flow may have already decreased considerably, which explains why so many men with CAD have ED.

Thus on the basis of artery size hypothesis and the fact that the endothelium is the same throughout the arterial tree, a malfunction in the penile arteries causing ED may be a predictor of silent subclinical cardiovascular disease (CVD). Furthermore, because an acute coronary syndrome often arises as the result of the rupture of a subclinical plaque, the presence of ED may also be an early warning sign of an acute event as well as being a manifestation of advanced obstructive CAD [36].

In 1999, Pritzker presented a preliminary report entitled “The penile stress test: A window to the hearts of man” [37]. He reviewed the results of exercise stress testing, risk factor profiles, and, in selected cases, angiography in 50 men with ED, who had no cardiac symptoms or past history. Multiple cardiovascular risk factors were present in 80%. Exercise tests positive for ischemia were found in 28 of the 50 men. Coronary angiography was performed in 20 men and revealed left main stem or severe three-vessel disease in 6 men, moderate two-vessel disease in 7 men, and significant single-vessel disease in 7 men. This study identified the significant incidence of occult coronary disease in cardiologically asymptomatic men presenting with ED to a urological service. Others have reported similar findings and noted the occurrence of ED before cardiac symptoms developed [3]. In a study comparing the velocity of cavernosal artery blood flow with the presence of ischemic heart disease in men with ED, a low peak systolic velocity (PSV) predicted the presence of CAD [38]. A PSV below 35 cm/s was associated with CAD in 41.9% of men and above 35 cm/s in only 3.7% of men.

In support of this concept, a series of 300 patients with acute chest pain and angiographically proven CAD were evaluated with a semi-structured interview to assess their medical and sexual histories prior to presentation [36]. The prevalence of ED among these patients was 49% ($n=147$). In these 147 men with both ED and CAD, ED was experienced before CAD symptoms in 99 patients (67%). The mean time interval between the occurrence of ED and the occurrence of CAD was 38.8 months (range: 1–168 months). Interestingly, all men with ED and type 1 diabetes developed sexual dysfunction before the onset of

CAD symptoms. The authors do point out the absence of a control group with CAD and normal erections, but their findings clearly identify the need to assess cardiovascular risk in all males presenting with ED without obvious psychosexual etiology, especially in patients with diabetes.

Speel et al. evaluated 158 men aged 40–69 years with penile pharmaco-duplex ultrasonography in order to determine whether there was cavernous arterial insufficiency and related these findings to the Framingham risk with the results extrapolated to the Dutch aging male population [39]. Cavernous insufficiency identified a significantly increased risk of CAD in the group aged 50–59 years, but not in the age groups 40–49 years and 60–69 years. Overall, it was predicted that one in four men with ED aged 40–69 years and without known CAD would have developed CAD over the next 12 years.

Roumeguère et al. compared 215 patients with ED and 100 patients without ED in order to evaluate undiagnosed hyperlipidemia and coronary risk [40]. The prevalence of hypercholesterolemia was 79.6% versus 52% in the ED and non-ED groups ($p=0.06$). Increased 10-year CAD risk was 56.6% versus 32.6% (ED vs. no ED; $p<0.05$). Low HDL cholesterol and high total cholesterol to HDL ratio, both established important risk markers for CAD, were identified as predictors of ED. This study suggested that ED might serve as a “sentinel event” for coronary heart disease.

ED is also more frequent in diabetic patients with silent CAD than in those without. In a study of men with type 2 diabetes ($n=260$), the incidence of ED (IIEF questionnaire) was significantly higher in the population with asymptomatic CAD than in the population without CAD (33.8 vs. 4.7%; $p<0.001$) [41]. ED not only predicted CAD independently of other risk factors, but also was the strongest predictor of silent CAD in this study.

The large Prostate Cancer Prevention Trial provided the first evidence of a strong association between ED and the subsequent development of clinical cardiovascular events [42]. ED at entry or that developed during follow-up was found to significantly predict any cardiac event with a hazard ratio of 1.45 ($p<0.001$; 95% confidence interval (CI): 1.25–1.69). The data also

showed that the cardiovascular risk associated with incident ED (i.e. developed during follow-up) was at least as great as the risk associated with a family history of myocardial infarction, current smoking, or hypercholesterolemia.

A similar strong correlation between ED and increased cardiovascular risk was also reported in a health screening project using the IIEF-5 questionnaires [43]. In this analysis of 2,561 patients, the presence of moderate to severe ED (IIEF-5 score 5–16) was calculated to increase the 10-year relative risk of developing CAD by 65% ($p < 0.001$) and of stroke by 43% ($p = 0.04$). Although mild ED (IIEF-5 score 17–21) was associated with increased risk (18–24%), this observation was not statistically significant.

In a recently reported population-based study (the Krimpen study), a single question on erectile rigidity (from the International Continence Society male sex questionnaire) was shown to be a predictor for the combined outcome of acute MI, stroke, and sudden death, independently of risk factors in the Framingham risk profile [44]. Men (aged 50–75, free of prostate and bladder disease) were followed up for an average of 6.3 years. Of those men who did not have CVD at baseline ($n = 1,248$), 258 (22.8%) had severely reduced erectile rigidity. Fifty eight cardiovascular events occurred in the 7,945 person-year follow-up. After adjusting for age and CVD risk score, the hazard ratios (95% CI) were 1.6 (1.2–2.3) and 2.6 (1.3–5.2) for reduced and severely reduced erectile rigidity, respectively.

Recent findings suggest there is a strong temporal relationship between ED and CAD, with ED preceding a cardiovascular event by at least 2–5 years. This temporal relationship was investigated in a questionnaire-based study that included 207 patients with CVD attending cardiovascular rehabilitation programs and 165 age-matched controls from general practice in the United Kingdom [45]. Patients completed up to four questionnaires including the IIEF. Of the individuals with CVD, 56% were experiencing symptoms of ED at the time of the study and had done so for a mean of 5 ± 5.3 years. In contrast, 37% of individuals in the control group had ED symptoms for a mean of 6.6 ± 6.8 years. Of particular concern, the study highlighted that only 53% of the CVD group and 43% of the

control group had actually discussed their ED symptoms with a health professional.

In a study of 147 men presenting with acute coronary syndrome (plaque rupture), documented ED and CAD, Montorsi et al. reported the presence of clinically evident ED symptoms in 99 patients (67%) developed ~3 years (mean 38.8 months, range 1–168 months) prior to the acute event [36].

In the subsequent Association Between eRectile dysfunction and coronary Artery disease (COBRA) trial, 93% of patients with a chronic coronary syndrome reported ED symptoms before the onset of angina pectoris, with a mean interval of 24 (range 12–36) months [46]. This finding further reinforces the concept of a lead time of at least 2–5 years between the development of ED and symptomatic CAD. The time intervals (range) for patients with one, two and, three vessel disease were 12 (9.5–24), 24 (16.5–36), and 33 (21–47) months, respectively. There was a significant relationship between the length of time from ED to CAD onset and the number of vessels involved ($p = 0.016$). Importantly, given that men with ED may be at cardiovascular risk, this “long” lead time provides an early opportunity for cardiovascular risk reduction [4].

Key Points

- ED may be a marker for asymptomatic CAD.
- ED can occur 3–5 years before a cardiac event.
- ED should trigger a cardiac risk assessment and aggressive cardiac risk factor reduction.

Cardiovascular Risk Reduction in Patients with ED

Currently there are no long-term follow-up data confirming that intervention reduces the risk of developing symptomatic CAD in men with ED. However, the findings from two major cardiovascular studies, the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) and the Collaborative Diabetes Atorvastatin Study (CARDS) may serve

as a useful guide to risk reduction intervention in men with ED until such data become available [47, 48]. Both studies showed that men of a similar age and cardiovascular risk benefit significantly from cardiovascular risk reduction.

The large randomized ASCOT study ($n > 19,000$) tested the primary hypothesis that a newer antihypertensive treatment regimen (calcium channel blocker $\pm$ an angiotensin converting enzyme inhibitor) is more effective than an older regimen (β -blocker $\pm$ diuretic) in the primary prevention of CHD in patients with at least three pre-specified cardiovascular risk factors [47]. The second primary hypothesis evaluated whether lipid lowering therapy with atorvastatin would provide further benefit against CHD endpoints in asymptomatic, well-controlled, hypertensive patients who were not considered dyslipidemic (total cholesterol ≤ 6.5 mmol/L) [49]. Although follow-up was planned for a mean of 5 years, the lipid arm of the study was terminated early after a median follow-up of 3.3 years because of a highly significant reduction in the incidence of non-fatal MI and fatal CHD (combined primary endpoint) and stroke. At the time of study termination, 100 primary events had occurred in the atorvastatin group compared with 154 events in the placebo group (hazard ratio 0.64; 95% CI: 0.50 to 0.83; $p = 0.0005$) and 89 cases of fatal and non-fatal stroke had been reported with atorvastatin compared with 121 cases in the placebo group (hazard ratio 0.73; 95% CI: 0.56 to 0.96; $p = 0.024$).

In common with ASCOT, CARDS was also stopped 2 years early at 3.9 years, for similar reasons. CARDS was a randomized, double-blind, placebo-controlled trial designed to evaluate statin therapy for primary prevention of CVD in patients with type 2 diabetes, without elevated LDL cholesterol ($n = 2,838$). The results showed a 37% reduction in the incidence of major cardiovascular end points, and a 48% reduction in the incidence of stroke [48]. A reduction in the primary endpoint of major CVD events was apparent and statistically significant as early as 18 months after treatment initiation [50].

Although both ASCOT and CARDS did not include ED as a risk factor, given the numbers

evaluated, it is highly likely that ED coexisted in a significant number of men enrolled in the two studies, highlighting the importance of cardiovascular risk reduction in men with ED.

Exercise Electrocardiography or Cardiac Computed Tomography?

Exercise electrocardiography (ECG) has been widely advocated for the identification of ED patients with an increased cardiovascular risk. However, this procedure has limitations in that it can only be used to identify flow-limiting lesions. Consequently, exercise tolerance tests are often normal in patients in the early stages of atherosclerosis. This limitation means that subclinical lipid-rich plaques that have the potential to rupture and precipitate an acute cardiac event frequently go unidentified.

Findings from a recent study indicate that multi-detector computed tomography (MDCT) may be able to address this shortcoming and be used to identify early subclinical plaque disease in patients with normal maximal exercise tests [51]. In this study, 20 men aged 39–69 years with ED and no cardiac symptoms were evaluated. ED was confirmed using the Sexual Health Inventory for Men (SHIM) questionnaire. Eight patients were hypertensive and controlled on medication, 18 patients had elevated LDL cholesterol levels (> 3.0 mmol/L), and 9 patients had a waist circumference ≥ 94 cm. Coronary calcium scores exceeded 50 in 11 men (range 54–1,234). All of these 11 patients had significant nonobstructive angiographically confirmed CAD on MDCT. However, 9 of these 11 patients had normal maximal exercise ECGs. Of particular note was the fact that one of the men (age 50 years; SHIM score of 16, calcium score 1,234) with a significantly abnormal MDCT was able to exercise for 13 min and 26 s to a heart rate of 173 bpm with no chest pain and no ECG changes. Another four men in the study had low calcium scores (< 20), single plaque disease, and normal exercise ECGs. Five patients had normal MDCT scans and were

diagnosed as having ED of a predominantly psychological origin.

Key Points

- No prospective comparative studies of risk reduction in men with and without ED have been performed.
- Evidence exists from risk reduction trials that would have included men with ED that intervention reduces CVD events.

Conclusion

With the recognition that ED is an early warning sign for silent coronary and vascular disease, screening for men presenting with ED and no cardiac symptoms is widely advocated. According to the second Princeton Consensus Guidelines, all men with ED and no cardiac symptoms should be considered as cardiac (or vascular) patients until proven otherwise. Such patients should undergo a full medical assessment with stratification of cardiovascular risk as high, medium, or low. Those patients at low risk should receive lifestyle advice regarding physical activity and weight control and undergo regular monitoring by their general practitioner. Patients at increased risk for cardiovascular events should ideally undergo stress testing and referral for risk reduction therapy.

Although an exercise ECG is advocated to identify patients at increased cardiovascular risk, this method will identify only those people with obstructive flow-limiting CAD. Wherever possible, intermediate and high-risk patients should be considered for elective computed tomography coronary angiography to identify the presence of nonflow-limiting lipid plaques that are potentially vulnerable to rupture. By implementing these measures, it should be possible to initiate early aggressive cardiovascular risk reduction in “at-risk” patients, thereby taking advantage of the 2- to 5-year window of opportunity between

the development of symptomatic ED and CAD. However, for the full potential of this approach to be realized, comprehensive education programs are required to encourage men with ED to present to their general practitioner as soon as possible. In addition, a multidisciplinary approach is required, involving teamwork between the family doctor, nurse, pharmacist, urologist, diabetologist, and cardiologist.

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Chapter 14

The Penile Prosthesis Option for Erectile Dysfunction

Fikret Erdemir, Andrew Harbin, and Wayne J. G. Hellstrom

Abstract Erectile dysfunction (ED) treatment can be divided into three main categories. These are oral agents, intracavernosal and intraurethral therapies, and local devices, such as vacuum and penile prosthesis. The first-line treatment for ED is oral phosphodiesterase type 5 inhibitors (PDE5Is); second-line treatment options include any combination of intracavernosal agents, such as papaverine, phentolamine, PGE1, or transurethral alprostadil. For this reason, penile prosthesis continues to be an important form of treatment for ED. Penile prosthesis implantation is a highly effective treatment option which yields high success rates, increased patient satisfaction, and low complication rates for men who fail first- and second-line treatment. Penile prostheses are indicated in a variety of conditions which cause ED, such as diabetes mellitus (DM), Peyronie's disease, corporal fibrosis following priapism, ED following radical prostatectomy for prostate cancer and spinal cord injury.

Keywords Corpus cavernosum • Semirigid penile implants • Inflatable penile implants • Detumescence • Doppler ultrasonography

Introduction

Erectile dysfunction (ED) treatment can be divided into three main categories. These are oral agents, intracavernosal and intraurethral therapies, and local devices, such as vacuum and penile prosthesis [1]. The first-line treatment for ED is oral phosphodiesterase type 5 inhibitors (PDE5Is); second-line treatment options include any combination of intracavernosal agents, such as papaverine, phentolamine, PGE1, or transurethral alprostadil. The success rate of PDE5Is and intracavernosal agents ranges between 40 and 80% [2–6]. For this reason, penile prosthesis continues to be an important form of treatment for ED.

Penile prosthesis implantation is a highly effective treatment option which yields high success rates, increased patient satisfaction, and low complication rates for men who fail first and second-line treatment. The main reason of this increased patient satisfaction is related to their ease of use, reliability, and the ability to provide excellent rigidity [7]. They are indicated in a variety of conditions which cause ED, such as diabetes mellitus (DM), Peyronie's disease, corporal fibrosis following priapism, ED following radical prostatectomy for prostate cancer and spinal cord injury.

Penile implants were introduced to the market over 40 years ago. The Egyptian surgeon Beheri was the first to place a penile implant into the corpus cavernosum [8]. There are two major classes of penile implants; semi-rigid and inflatable (Table 14.1). The inflatable consists of the two-piece inflatable and the three-piece inflatable

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Table 14.1 Penile prosthesis options [8]

Prosthesis type	Prosthesis name	Advantages	Disadvantages
Semirigid	AMS Malleable 650M™	Easy to implant	Permanent erection
	Mentor Acu-Form	Low chance of failure	In pain/erosion increased chance of pain/erosion
Two-piece inflatable	AMS 700 CX	Partial rigidity	Erection and flaccidity compromised
Three-piece inflatable	AMS 700 CX	More natural erection	More technically difficult to implant and flaccidity
	AMS 700 CXR	Less chance of pain/erosion narrow base	
	AMS 700 Ultrex Mentor Alpha I		

Fig. 14.1 AMS 700 CX™ three-piece inflatable penile prosthesis. Image courtesy of American Medical Systems, Minneapolis, MN, USA



[9]. In the three-piece inflatable group, there are two vendors, Coloplast (Minneapolis, MN, USA) and American Medical Systems (Minneapolis, MN, USA). The AMS 700 CX, developed by Scott and colleagues, consists of a pair of inflatable cylinders, a reservoir, a pump, and connecting tubes (Fig. 14.1). The cylinders are implanted within both corpora cavernosa, the pump within the scrotum, and the reservoir behind the rectus abdominis muscle in the anterior lateral aspect of the perivesical space (Fig. 14.2). Pump compression actively transfers fluid from reservoir into the inflatable cylinders resulting in a rigid erection, whereas compression of the release valve allows passive flow of fluid back into the reservoir and achieves detumescence. The reservoir is filled with a sterile

saline solution and consists of a polyurethane elastomer shell and silicone elastomer tubing adapter, which are bonded together using a silicone elastomer adhesive. The Titan from Coloplast is similar in appearance (Fig. 14.3). While both semirigid and inflatable prostheses are options, the three-piece inflatable prosthesis is currently the standard of surgical therapy for ED in the USA, mostly due to patient choice.

Preoperative Period

Before choosing a procedure, all patients who are candidates for a penile implant need to be assessed with a detailed systemic and sexual

Fig. 14.2 Illustration depicting the appearance of the AMS 700 CX™ three-piece inflatable penile prosthesis after implantation. Image courtesy of American Medical Systems, Minneapolis, MN, USA

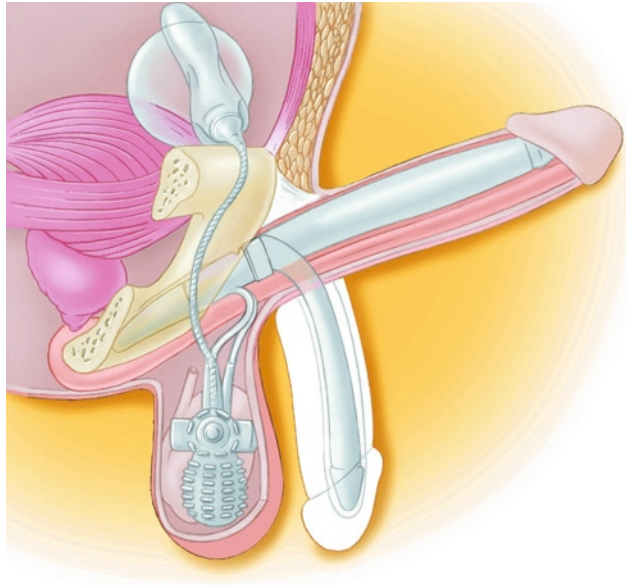


Fig. 14.3 Coloplast Titan™ three-piece inflatable penile prosthesis. Image courtesy of Coloplast Group, Minneapolis, MN, USA



medical history. All candidates should be assessed for the following criteria:

- Good general health
- Failure of other therapeutic options
- Psychological stability
- Patient and partner fully informed
- Complete medical assessment: including the International Index of Erectile Function

(IIEF), penile color Doppler ultrasonography (optional), and nocturnal penile tumescence testing (optional).

Patients need to be aware that penile implants only produce prosthetic erections and they do not restore libido, sensation, orgasm, or ejaculation if these are absent. It is important to exclude any urinary tract infection prior to insertion of

the penile prosthesis. Additionally, care should be taken that there is no irritation in the perineal or genital skin.

Infections associated with implants are most often caused by skin pathogens, therefore most authorities recommend that the patient use a chlorhexidine-based wash 2–3 days before surgery to reduce the overall bacterial count on the skin surface. Patients are shaved in the operating room, just prior to surgery, to minimize abrasion and trauma to the perineal skin which can also increase the risk of infection. A prolonged scrub of the perineal and suprapubic skin with chlorhexidine or iodine-based soap, followed by the application of alcohol-based disinfectant reduces intraoperative colonization [10]. Preoperative antibiotics are routinely administered and should ideally be broad-spectrum, cover both aerobic and anaerobic organisms, and be given prophylactically.

In addition, decreasing operating room traffic during the procedure may limit the number of airborne bacteria that land in the surgical field during the operation.

Operative Procedure

There are a number of approaches to the implantation of a penile prosthesis. The majority of procedures conducted in the USA are via the penoscrotal approach. Following the induction of anesthesia, patients are placed in the supine or lithotomy position. Although local anesthesia has been used for special situations for penile prosthesis implantation, most patients receive spinal or general anesthesia. The basic surgical approaches for three-piece inflatable penile prosthesis implantation are the infrapubic and the penoscrotal [11, 12]. The penoscrotal approach provides easier corporeal exposure and avoidance of trauma (especially during revision surgery) to the sensory dorsal nerves of the penis. Furthermore, the scrotal pump can be anchored in a dependent position with this approach. The disadvantage of the penoscrotal approach is the blind placement of the fluid reservoir into the retropubic space. The urethra is easily observed

and avoided in this approach. The advantages of the infrapubic approach are the implantation of the fluid reservoir under direct vision and concealment of tubing under Scarpa's fascia. Disadvantages of the infrapubic approach include limited corporeal exposure, possible damage to the dorsal nerves of the penis with sensory loss, and the inability to anchor the pump in the scrotum. If a prosthesis is placed through an infrapubic incision on the dorsal surface of the corpora cavernosa, care must be taken to avoid damaging the neurovascular bundles which run between 11 o'clock and 1 o'clock positions on the upper surface of the corporal bodies. Making corporotomies at the 10 o'clock or 2 o'clock positions circumvent this possible complication.

Before initiating a penoscrotal approach, most surgeons place a Foley catheter. A 3-cm incision is made at the penoscrotal junction either vertically or horizontally and carried down to the superficial/dartos fascia. Once the dartos fascia is divided, hook elastic retractors can be used to expose the surgical field (Fig. 14.4). The next step is to identify the corpus spongiosum and dissect laterally exposing the corpora cavernosa on each side. Later, a 1–2 cm corporotomy incision is made after the placement of 2-0 polyglactin (Vicryl) stay sutures. This exposes the corporal spongy tissue.

Successive curved Heger or Brooks dilators are used to dilate the spongy tissue of the corpus cavernosa proximally and distally (Fig. 14.5). Accurate measurement of the length of the corporal bodies is key to long-term satisfaction. Meanwhile, throughout the operation, copious antibiotic solution is irrigated over the surgical site and instruments at regular intervals. The appropriate three-piece prosthesis is selected; the package is opened and soaked with antibiotic solution (unless the prosthesis contains impregnated antibiotics (Inhibizone™, AMS)). A critical aspect of the surgery is appropriate cylinder sizing. If a cylinder is larger than the corporal body that can accommodate, the patient may have persistent pain, protrusion, or erosion of cylinders into the glans or curvature of the penis when it is erect. The cylinder and pump are checked for integrity, and all air is removed by

Fig. 14.4 Exposure of the penoscrotal approach of penile prosthesis implantation with elastic hook retractors

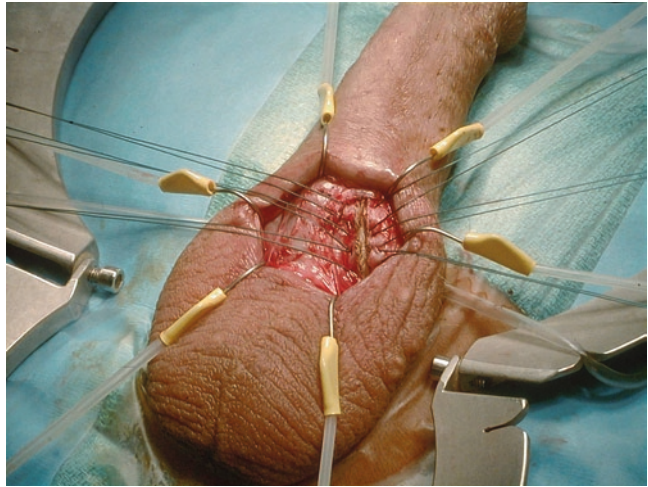
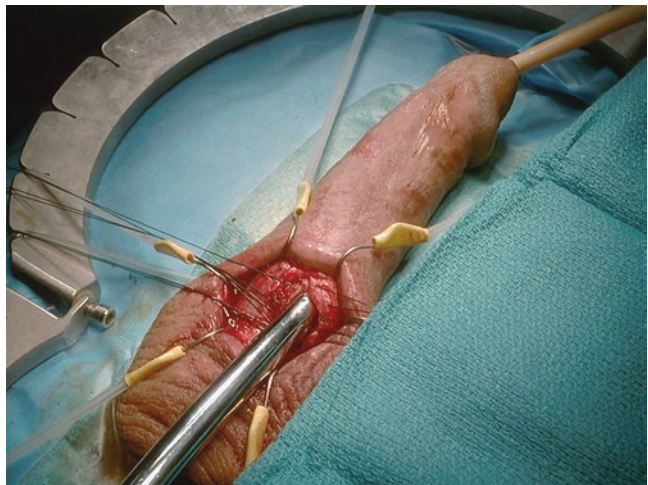


Fig. 14.5 Dilation of corpus cavernosum using Hegar dilator



infusing sterile sodium chloride solution and then back-suctioning to collapse the cylinders. The proximal cylinder is placed gently into the proximal cavernosal body and seated down into its position next to the pubic bone.

The distal half of the cylinder is brought through the distal corporal body with a Furlow inserter. This instrument passes a needle through the glans penis and is designed to avoid the urethra. The needle is removed, and the accompanying suture is used to pull the cylinder snugly against the distal glans. This procedure is repeated for the contralateral side. The open

corporal bodies are closed using 2-0 absorbable polyglactin stay sutures, carefully reapproximating the tunica albuginea. After closure is complete, the tubing from the cylinders is visible coming from inside the corpora and connected to the control pump.

The next consideration is the placement of the abdominal reservoir. If the patient has received prior pelvic radiation treatments or has undergone pelvic surgery, placing this through a separate abdominal incision may be prudent. Otherwise, the reservoir can be tunneled from the scrotal area through the external inguinal

ring and transversalis fascia to place the reservoir into the space of Retzius. The reservoir is filled to the correct volume of sterile saline solution (60–100 mL). The prosthesis is tested for inflation, deflation, and leaks. It is left in a semirigid state overnight to help tamponade potential corporal bleeding. The pump is inserted in a dependent scrotal subdartos position for future ease of access [13].

If necessary, the process of penile modeling can take place at this juncture for patients with asymmetric penises or Peyronie plaques with deformities. In the inflated state, rubber shods are clamped on the prosthesis tubing to take up the extra pressure that would compromise the control pump valves. The surgeon torques and bends the asymmetric penis into a more symmetric shape. The dartos fascia is closed in two layers with medium polyglactin sutures, and the skin is approximated with absorbable suture. Any potentially irritating iodine paint is washed off of the patient. The urethral catheter can be removed later in the recovery room or on the following morning before discharge. The cylinders are deflated; the patient receives oral antibiotic therapy for 7–10 days and is instructed to pull down on the pump daily for the first week. After approximately 4–6 weeks, the patient is instructed on how to inflate and deflate the device every other day. Sexual activity is usually permitted from 6 weeks after the procedure. Diabetic patients may experience neuropathic pain for a longer interval after the procedure.

Complications

Survival of implants ranges between 78 and 95% after 10 years [13–17]. In a long-term study involving 2,384 patients who underwent penile prosthesis implantation, estimated 10-year revision-free survival was 68.5% and the 15-year revision-free implant survival was 59.7%. In 1992, the Mentor Alpha-1 (now the Coloplast Titan) device added pump reinforcement to forestall mechanical breakage which improved 10-year survival from 65.3% to 88.6% [18].

In January 2001, AMS CX added parylene coating to the cylinders that has increased 3-year mechanical survival from 88.4% to 97.9% [18].

Since 1973, improvements have been made in penile prosthesis design. Notwithstanding these improvements, complications or adverse events can still occur, including infection, hematoma, urethral perforation, persistent pain, mechanical failure, malposition of components, and patient dissatisfaction. Extremely rare complications include erosion of reservoir into the bladder or bowel, penile gangrene, sepsis, glans necrosis, and hernia [19–22]. The complication rate has decreased substantially from approximately 50% in the earliest models to 1–12% in the more recent devices. Regardless of the type of prosthesis used, meticulous surgical technique and surgeon's experience are important factors in determining the final outcome.

A major postoperative concern for most implanting surgeons is the development of infection (Table 14.2). Signs or symptoms of infection include a purulent exudate, increasing pain instead of gradual improvement, worsening erythema and induration, or low-grade fever. Most infections present within the first 3 months after surgery and the vast majority manifest within the first year, although delayed infections beyond 1 year occasionally occur [29]. The literature lists several risk factors for infection, such as inadequate perioperative antibiotic prophylaxis prolonged hospitalization, concurrent urinary tract infection, prolonged operative time, repeat implantation procedures, and combined operations (hernia repair, circumcision, artificial urinary sphincter implanation) with penile prosthesis surgery. Some patients, such as diabetics, and patients with spinal cord injury may

Table 14.2 Infection rates after penile prosthesis implantation

Authors	Infection rates
Quesada [23]	0.5%
Goldstein [24]	2%
Govier [25]	6.5%
Jensen [26]	11%
Wolter [27]	1.06%
Minervini [28]	8%

have a decreased host defense [30]. Local factors which increase infection risk include capsule formation around a foreign body, which diminishes blood supply to the area, and biofilm production. These factors provide a protective cavity in which bacteria may remain in a low metabolic state with no systemic antibiotic contact. The severity of infections may range from simple superficial infections that can be managed by conservative measures and wound care, to penile gangrene and sepsis which may be life-threatening. Penile gangrene is rare and may be due to gram-negative organisms with or without anaerobic superinfection [19]. Standard antibiotic prophylaxis is administered 1 h prior to surgery using agents effective against common organisms, such as *Staphylococcus epidermidis* and *aureus*, as well as *Escherichia coli*. Many authors use an aminoglycoside and vancomycin or a first-generation cephalosporin. Fluoroquinolones have also been shown to be equally effective against these organisms and may be administered orally. Gram-negative bacterial infection tends to become clinically manifest within a month after implantation, compared with 5.75 months for staphylococcal infections.

Bacterial adherence to the penile prosthesis is the first event in biofilm formation. Standard penile prostheses have been constructed with hydrophobic materials (polyurethane for Mentor alpha-1 and silicone for AMS 700-CX) which favor bacterial attachment. Both prosthesis companies have responded by making changes to their implant materials. In 2000, AMS introduced their inflatable penile prosthesis with Inhibizone™ to prevent bacterial growth during surgery. In this prosthesis, the surface is coated with antibiotics (rifampin and minocycline) against the most common Gram-positive bacteria, *S. aureus* and *S. epidermidis*. In a large retrospective comparison of 4,205 patients, use of the Inhibizone™ coating reduced the infection rate at 180 days from 1.6% to 0.7% [31, 32]. In experimental studies, it has also been shown that coating silicone graft material with antibiotics, particularly rifampin/minocycline, reduced the incidence of graft colonization in contaminated wounds [33]. Another local strategy to prevent

bacterial colonization and infection was instituted by Mentor (now Coloplast, Minneapolis, MN). They developed a proprietary hydrophilic coating that inhibits bacterial adherence and absorbs antibiotics from the soaking solution just before implantation. Early reports showed that this device is similarly effective in reducing infection rates [27].

In the case of infection, the surgeon has two options. The first is to remove the prosthesis and reinsert it, usually 3–6 months later. If this option is chosen, the penis will be noticeably shorter, the reinsertion procedure more difficult because of the scar tissue that forms during that interval, and the overall satisfaction of both patient and his partner will understandably be diminished because of a shorter phallus. A second option is the use of a salvage procedure, which entails removing the prosthesis and all foreign materials, irrigating the wound with a series of antiseptic solutions, and reinserting a new prosthesis at the same operation [34]. Mulcahy et al. reported a success rate of 84% using a series of irrigating solutions starting with kanamycin (80 mg/L) and bacitracin (1 g/L) in normal saline, followed by half-strength hydrogen peroxide, half-strength providone/iodine solution, vancomycin (1 g), and gentamicin (80 mg) in 5 L of pressurized normal saline, half-strength hydrogen peroxide again, and another round of kanamycin/bacitracin solution [35].

Placement of prosthesis into fibrotic corporal bodies may require extensive surgical expertise in order to leave the patient with a functional device. Fibrosis of the corpus cavernosum may be the result of prosthesis infection, intracavernosal infections, Peyronie's disease, or priapism [36, 37]. The main risks encountered during prosthesis implantation into fibrosed corpora cavernosa are injuries to the urethra due to forceful instrumentation against resistance, perforation of the tunica albuginea, and a higher infection rate. The higher rate of infection is probably the result of devitalization of tissues, need for vigorous manipulation, extensive exposure (generous corporotomies) and prolonged operative times. In men with mild fibrosis, dilatation may be accomplished in a standard

fashion. In cases with more severe fibrosis, more advanced surgical techniques may be required to create a satisfactory channel, including shaft dissection or use of Rosello Carrion cavernotome [38–40]. When attempting to place penile prosthesis cylinders in these difficult conditions, a narrow diameter penile prosthesis cylinders (Coloplast narrow-base or AMS CXM) can be extremely helpful.

Mechanical failure has always been a major concern for any implanted device. Mechanical failures in inflatable prostheses have been reported from 4% to 15% at 10 years, and lower with malleable penile prosthesis models [15, 22, 41, 42]. Mechanical failures include leakage from the cylinders, tubing fracture, cylinder or reservoir leak, connector disruption, tube kinking, connector problems, and cylinder aneurysm (Table 14.3). If a mechanical problem develops soon after surgery, replacing the malfunctioning component is usually satisfactory, while the replacement of the whole device is customary after an interval of 2–3 years.

Reservoir herniation is an unusual complication of three-piece inflatable prosthesis surgery cases and is almost exclusively limited to the penoscrotal approach [46]. This may be caused by vigorous postoperative coughing or failure of proper initial reservoir placement under the transversalis fascia. Reservoir protrusions through an unrecognized existing hernia or a large transversalis defect created intraoperatively are other possible causes. Decreased spontaneous autoinflation of the cylinders in the immediate postoperative period may result in a lower incidence of this adverse event. The herniated reservoir may be repositioned through the original penoscrotal incision when recognized in the immediate postoperative period, or alternatively

a small inguinal incision can be used to place the reservoir in the perivesical space, and the defect is closed from above.

Supersonic transport (SST) deformity may be secondary to short prosthesis cylinder sizing or incomplete distal dilation of the corpus cavernosum [31]. If the problem is recognized intraoperatively and adequate distal dilation achieved, additional rear-tip extenders may be placed to lengthen the cylinders. If the problem is noted in the early postoperative period, it may be beneficial to wait a period of time to allow for complete healing and scar formation, which may result in glans fixation and resolution of the SST deformity. Refractory cases may be surgically corrected by revising the prosthesis or placement of two 3-0 PDS or permanent prolene sutures on the underside of the glans on each side through a circumcoronal incision (glanuloplasty) [31]. By tying these sutures to the tunica albuginea near the cylinder tip and away from the neurovascular bundle, the glans is effectively secured against the cylinder tip.

Device extrusion beneath the penile skin may occur on occasion as an isolated phenomenon, but prosthesis erosion is often a telltale sign of device infection. Semirigid prostheses are more prone to erosion; similarly, those with distressed tissue and vascular supply, such as brittle diabetics or patients who have undergone “redo” implant surgery. Erosion has also been witnessed as a complication of prolonged or difficult urethral catheterization [22, 47, 48].

The incidence of this complication may be reduced significantly by using an inflatable rather than semirigid prosthesis. Mulcahy has described a distal corporoplasty or natural tissue repair for lateral extrusion or penile prosthesis cylinders. In this procedure, the cylinder is repositioned in a

Table 14.3 Long-term results of penile prostheses

	Follow-up period (years)	Mechanical failure	Prosthesis type
Daitch [43]	5	9.1%	AMS CX three-piece
		17.1%	Ultrex
Wilson [15]	5	5.6%	Alpha 1
Ferguson [44]	5.7	9%	Malleable
Deuk Choi [45]	8	7.3%	AMS CXM
Levine [45]	5	2.3%	Ambicor

more medial and secure position under the glans penis by creating a new cavity for the cylinder behind the back wall of the fibrotic sheath [48].

A variety of techniques have been described for addressing perforation problems intraoperatively, including direct repair of a lateral perforation, placement of a windsock patch at the proximal end of the cylinder, anchoring of the cylinder tubing to the tunica, or the placement of an absorbable polyglycolic acid patch over the defect [22, 49]. Continued dissection to the level of the rear-tip extenders and anchoring the extender to the tunica is an alternative approach. Attachment of the rear tip to the tunica prevents retrograde cylinder migration back into the perforation.

Management of a distal corporal perforation or urethral perforation involves termination of the procedure and return at a later date, particularly if distal perforation occurs during dilation of the first side. If corporal dilation has been successfully accomplished on one side and the second side is perforated, a single cylinder may be placed on the nonperforated side. The tubing from the unused cylinder is removed and plugged with a standard deactivation plug provided by the manufacturers. A single functioning cylinder may provide adequate rigidity for penetration, and the patient may elect not to undergo a second procedure for contralateral cylinder placement. Similarly, if urethral perforation occurs after one side has been successfully dilated, the cylinder from the perforated side is removed and its tubing plugged.

Patient and Partner's Satisfaction

Numerous studies have shown high satisfaction rates with penile prosthesis implantation for both patients and their partners. In a series of 185 patients from a number of institutions, the authors reported a 98% patient and 96% partner satisfaction rate [50]. Lower success rates have been noted in situations where there is an overall loss of penile length [34, 51]. In a multi-institution report from Italy surveying patients

with penile implants and Peyronie's disease, 79% of the patients were satisfied and 75% of the partners reported satisfaction with the result [50]. In another study of 146 recipients of a two-piece penile prosthesis, the authors reported 85% satisfaction among the recipients, and 76% satisfaction among their partners [52]. In some studies, inflatable and other prosthesis had been compared. Beutler et al. found increased satisfaction in men using an inflatable penile prosthesis compared to men receiving a noninflatable penile prosthesis, and, in another study, they showed greater satisfaction among female partners of men using inflatable compared to noninflatable prostheses [53]. As previously noted, satisfaction domain scores for patients with corporal fibrosis and shortened penises undergoing revision prosthesis surgery are reported to be lower than other revision implant groups [54].

Patient satisfaction is a multifactorial issue and includes the degree of postoperative pain and swelling, postoperative complications, cosmetic outcome, device function, ease of use, and partner acceptance. The rapid development of erections and the consistently excellent rigidity obtained with a prosthesis are two major factors contributing to high levels of satisfaction. The major reason for dissatisfaction with penile prosthesis placement is shorter length of the penile erection. Other explanations for dissatisfaction include not feeling natural by the partner, reduced sensitivity and diminished drive, and the partner not having the same role in creating an erection as she once did. Another common patient complaint is the lack of adequate engorgement of the glans during sexual activity. Typically, the patient reports that the corpora cavernosa provide satisfactory rigidity after activating the implant but notes the glans that remains soft. One recent study reported on the beneficial effect of sildenafil on glans engorgement in patients having undergone penile implant [55]. By using the IIEF, researchers documented that sildenafil caused a statistically significant improvement in implant-assisted intercourse. Similar results were reported in a case report which showed the benefits of administering 500 µg of transurethral alprostadil (MUSE, Vivus Inc, Mountainview,

CA) on demand in patients with self-contained inflatable penile prostheses [56].

It is recognized that patients with Peyronie's disease, radical prostatectomy, or a BMI >30 kg/m² have a statistically significant reduction in their level of satisfaction compared with the general implant population [57]. It is likely that penile length issues play a large role in the Peyronie's disease and radical prostatectomy patients in this regard. It has not been clearly delineated why a BMI >30 kg/m² should be associated with reduced satisfaction, but mechanical issues relating to the prepubic fat pad size have been noted in many of these men.

Summary

Penile prosthesis is a safe and effective therapy for ED of various causes, including ED refractory to first and second-line therapies. Current options for prosthesis include malleable and inflatable, and the inflatable option includes various two- and three-piece models. Preoperative preparation requires meticulous sterilization procedures, including prophylactic antibiotics and chlorhexidine scrub. Implantation can be accomplished either penoscrotally or infrapubically, with the advantages of the penoscrotal approach being avoidance of the dorsal nerves of the penis and ease of pump anchoring. There are a variety of complications that can occur postoperatively, but infection is the most concerning. If infection does occur, the surgeon can elect to remove and replace the prosthesis at a later date or attempt a salvage procedure. Patient and partner satisfaction have been reported to be high in many studies.

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Chapter 15

The Effect of Radical Prostatectomy on Erectile Dysfunction

John P. Mulhall

Abstract Prostate cancer is the most common form of cancer in American men other than skin cancer. The American Cancer Society had estimated that about 185,000 new cases of prostate cancer would have been diagnosed by 2008 in the USA alone. Almost 30,000 men will die of the disease in 2008 alone in this country. It is the second leading cause of cancer death in men after lung cancer. While a man has a 15% chance of being diagnosed with prostate cancer during his lifetime, only 3% actually dies of the disease. The use of PSA as a screening tool has resulted in a far greater number of men being diagnosed with prostate cancer at the earliest stages. Thus, in the modern era, the vast majority of men live for a long time after diagnosis and treatment. This has translated into younger men being diagnosed with prostate cancer and long-term sexual function becoming an even bigger issue given these factors.

Keywords Radical prostatectomy • Erectile dysfunction • Rehabilitation • PDE5 inhibitors • Intracavernosal injections

Introduction

Prostate cancer is the most common form of cancer in American men other than skin cancer.

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The American Cancer Society had estimated that about 185,000 new cases of prostate cancer would have been diagnosed by 2008 in the USA alone. Almost 30,000 men will die of the disease this year alone in this country. It is the second leading cause of cancer death in men after lung cancer. While a man has a 15% chance of being diagnosed with prostate cancer during his lifetime, only 3% actually dies of the disease. The use of PSA as a screening tool has resulted in a far greater number of men being diagnosed with prostate cancer at the earliest stages. Thus, in the modern era, the vast majority of men live for a long time after diagnosis and treatment. This has translated into younger men being diagnosed with prostate cancer and long-term sexual function becoming an even bigger issue given these factors.

The incidence of an ED after RP is tremendously variable, ranging from anywhere from 20 to 90% [1–5]. The reasons for this are complex but include issues such as variability in patient populations studied, variation in the means of data acquisition, and most importantly variability in the definition of adequate erectile function postoperatively. Of note, the rate of ED in the literature is higher in multi-surgeon, multicenter series compared to single-surgeon, single-center series. The determinants of erectile function recovery include patient age at the time of surgery, pre-operative erectile function, degree of nerve sparing, postoperative erectile hemodynamics and finally the health of erectile tissue [6].

The Pathophysiology of Erectile Dysfunction after Radical Prostatectomy

The pathophysiology of ED after radical prostatectomy involves three factors (Fig. 15.1): namely, neural injury, vascular injury, and smooth muscle damage. It is well appreciated by every urologist that thermal injury to the cavernous nerves result in permanent loss of erectile function after surgery. What is less appreciated is the concept that traction on the nerves may in fact be just as deleterious. In a recent study, Masterson et al. demonstrated that alteration in technique, whereby the Foley catheter is no longer used as a retired retraction tool to maximize tension on the lateral pedicles, resulted in a significant improvement in erectile function post-prostatectomy [7]. Furthermore, Mullerad et al. demonstrated in the cavernous nerve injury model that exposure of the cavernous nerves without any direct injury results in an ED in a rat model. Thus, it appears that even the most minor neural trauma may in fact result in at least short-term erectile problems. The consequences of neuropraxia are several fold: it has been well documented by several centers that smooth muscle and endothelium undergo structural changes in response to cavernous nerve injury. User et al. have shown that bilateral and unilateral cavernous neurectomy resulted in early smooth muscle apoptosis [8]. In this analysis, apoptosis was maximal at 2–7 days after surgery. Of note, in this analysis the smooth muscle apoptosis appeared to be clustered in the subtunical area. It was suggested by the authors that this may in fact be a contributor to the development of

venous leak postprostatectomy. We have shown in our cavernous nerve crush injury model that crush injury can cause apoptosis in both smooth muscle and endothelium in a more delayed fashion compared to neurectomy model [9]. Another consequence of neuropraxia is alterations in smooth muscle:collagen ratios. In response to nerve injury, the smooth muscle undergoes collagenization. Neural injury has been shown to be associated with upregulation of collagen types I and III as well as upregulation of fibrogenic cytokines, such as TGF-beta [10]. Klein et al. showed using electron microscopy that cavernous nerve injury results in endothelial cell retraction [11]. Given the importance of both corporal smooth muscle and endothelium for the purposes of erection, it is easy to see how neuropraxia-induced erectile tissue alterations may be deleterious to long-term erectile function recovery.

Vascular injury revolves around damage to accessory pudendal arteries (APAs). These arteries are variable in their incidence in the literature depending on what kind of series is assessed, whether it is an operative series, an angiographic series, or a cadaveric series [12–17]. APAs are super diaphragmatic arteries that lie above the levator ani and are predisposed to injury at the time of radical prostatectomy. Their origin is variable coming from femoral, obturator, vesicle, or iliac arteries. These arteries can be visualized on preoperative endorectal MRI or on preoperative CT scan. Cadaveric studies have the highest incidence of APAs. Probably, the most important study is that of Breza et al. [13]. In this study, 10 cadavers underwent extensive pelvic dissection, and the arterial anatomy was defined

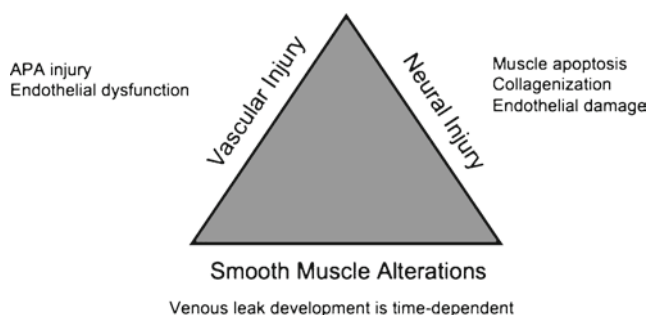


Fig. 15.1 Schematic illustrating pathophysiology of erectile dysfunction after radical prostatectomy

in detail. In this analysis, 7 of the 10 cadavers had APAs found. In seven cadavers, the APAs were the major source of arterial inflow into the penis, and one cadaver had APAs as the sole source of inflow into the corpora cavernosa. Droupy et al. have shown in a small study using transrectal and transperineal ultrasound that these arteries are functional [14]. Nine of 12 patients studied had periprostatic arteries coursing forward toward the penis. Upon intracavernosal injection the hemodynamic changes that were seen in the cavernosal arteries were mirrored in the periprostatic arteries suggesting that the APAs were functional. Rogers et al. have shown that APA preservation at the time of open radical prostatectomy translates into an improvement in an erectile function recovery and possibly even shortening of the time to recovery of erections.

I have already alluded to the concept that neuropraxia results in smooth muscle alterations. It is likely that this is amplified by the absence of erections. If one thinks of muscle within the body, whether it is skeletal or smooth in nature, muscles require some form of exercise to maintain integrity and health. Given the fact that we obtain three to six erections each night, it is easy to see how going a prolonged period of time without erections may in fact lead to erectile tissue damage.

Cavernosal Oxygenation

This is the concept that the penis is a large vein in the flaccid state and a large artery in the erect state (Fig. 15.2). In the flaccid state, the pO_2 is

approximately 35–40 mmHg. It has been postulated that this results in upregulation of fibrogenic cytokines including TGF-beta. TGF-Beta results in collagen production which may eventually lead to fibrosis and venous leak. During erection the penis is oxygenated with pO_2 rising to 75–100 mmHg. In vitro evidence demonstrates that oxygenation upregulates the production of endogenous prostanoids as well as cyclic AMP [18]. Moreland et al. have shown in a series of in vitro experiments that the exposure of cultured corporal cavernosal smooth muscle cells that low oxygen levels suppress PGE_1 and cAMP production. Upon returning oxygen environment to normoxia, levels of both normalized. In a further series of experiments, the same authors showed that in the in vitro setting that prostanoids inhibit TGF-beta activity and thus reduce collagen production [19]. Therefore, in a healthy male there is a balance between the flaccid and erect states and as long as men obtaining erections with some degree of regularity, erectile tissue health is preserved. However, after radical prostatectomy in a state of unantagonized flaccidity everything is shifted in favor of fibrogenic cytokine production leading to structural changes and venous leak development.

In a recent study, Mueller et al. demonstrated the potential benefit to hyperbaric oxygen therapy (HBOT) in the cavernous nerve injury model [20] (Fig. 15.3). Animals with bilateral nerve crush injury were divided into the treatment with room air within a hyperbaric chamber versus hyperbaric O_2 (3 atm) for 90 min. Animals were treated for a period of 10 days consecu-

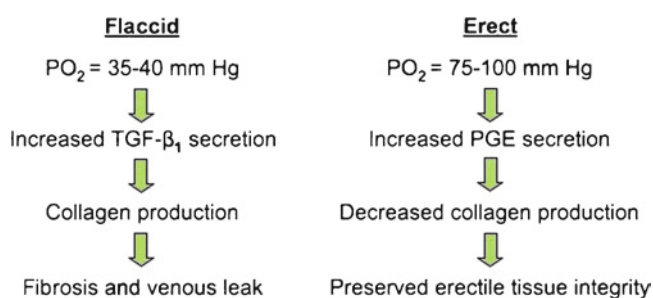


Fig. 15.2 Diagram highlighting the concept of cavernosal oxygenation

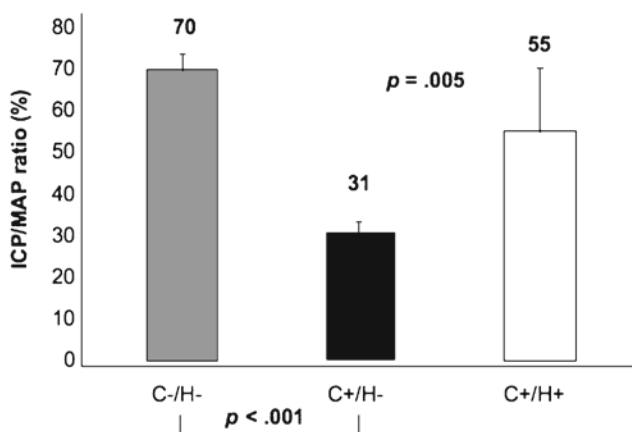


Fig. 15.3 The effect of hyperbaric oxygen on erectile function preservation in the cavernous nerve injury model. C- No crush injury, C+ Crush injury; H- Room air, H+ Hyperbaric oxygen. Adapted from

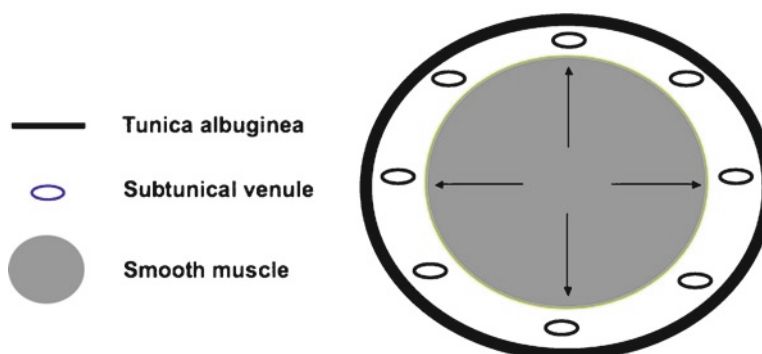
Muller A, et al. The effect of hyperbaric oxygen therapy on erectile function recovery in a rat cavernous nerve injury model. *The Journal of Sexual Medicine*. 2008

tively and at 28 days after bilateral nerve crush, animals underwent functional assessment. Using intracavernosal pressure/mean arterial pressure (ICP/MAP) ratios the animals treated with HBOT had an ICP/MAP ratio of 31%. This compared with ICP/MAP ratio of 55% in animals exposed to 10 days of HBOT ($p < 0.005$). This is not to suggest that patients after prostatectomy be encouraged to enter a decompression chamber for HBOT. However, I do believe that these data support the concept that cavernosal oxygenation is critical to the recovery of erectile function. In unpublished data, emanating from Pfizer Central labs in the UK, a canine model was used to explore the impact of hypoxic conditions on erectile function [21]. In the anesthetized, ventilated dog with the cavernous nerve exposed, cavernous nerve stimulation resulted in progressively poorer ICP/MAP ratios as the FiO_2 was dropped from 21% to 18%. In a second series of experiments, the pretreatment of the animals with sildenafil citrate resulted in the preservation of erectile response following cavernous nerve stimulation even under profoundly hypoxic conditions. This suggests that sildenafil at least and perhaps PDE5 inhibitors in general are capable of preserving erectile tissue relaxation profiles even under hypoxic conditions.

Venous Leak

I tell patients to think of their penis like a tire, with a hose and a valve being present. The hoses are represented by the left and right cavernosal artery while the valve mechanism is the veno-occlusive mechanism. Figure 15.4 is a schematic of a cross-section of one of the corpora cavernosa. Positioned between a tunica albuginea externally and the corporal smooth muscle internally are a series of subtunical venules. As the smooth muscle expands in a three-dimensional fashion under nitric oxide control, the subtunical venules are compressed against the tunica. This is the veno-occlusive mechanism. In conditions where the muscle fails to expand adequately some or all of the subtunical venules are left in a noncompressed state, and this results in the concept we know as venous leak (synonyms: corporovenocclusive dysfunction, venogenic erectile dysfunction). The two things that lead to failure of the corporal smooth muscle to expand are adrenaline, the world's most potent antierection chemical and structural changes such as fibrosis.

Nehra et al. have shown in human corporal tissue biopsy taken at the time of cavernosometry that once smooth muscle content in the penis



Adapted from Mulhall JP et al. *Int J Impot Res.* 2001;13:236-239.

Fig. 15.4 Schematic of the erectile veno-occlusive mechanism. Adapted from Mulhall JP, Damaser MS. Development of a mathematical model for the prediction of the area of venous leak. *International Journal of Impotence Research.* 2001;13: 236–9

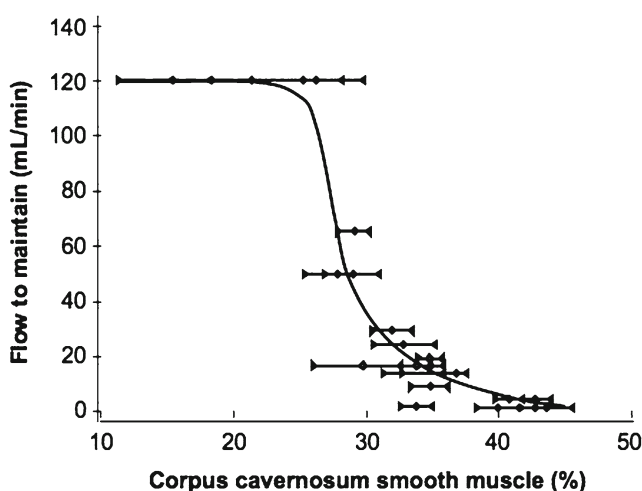


Fig. 15.5 Relationship between cavernosal smooth muscle content (X-axis) and venous leak as measured by flow-to-maintain values during cavernosometry (Y-axis). Adapted

from Nehra A, et al. Mechanisms of venous leakage: a prospective clinicopathological correlation of corporeal function and structure. *The Journal of Urology.* 1996;156: 1320–9

drops below 40% venous leak occurs [22] (Fig. 15.5). Indeed, the further this figure dropped below 40%, the greater the magnitude of leak is. Iacono et al. have shown that as early as 2 months after radical prostatectomy in an untreated man there is a marked increase in collagen deposition and a marked increase in elastic fiber content in erectile tissue [23]. This is in keeping with the animal data outlined above that suggest even in the earliest stages after cavernous nerve injury,

structural changes occur. Mulhall et al. have shown in a series of 16 patients who had preoperative and postoperative hemodynamic assessment that more than half of the men had venous after surgery [24]. In a more recent analysis by Mulhall et al. [25], in men who had partner corroborated excellent erectile function prior to surgery, who underwent duplex Doppler penile ultrasound after surgery, there was an increase in the incidence of venous leak (based on elevated

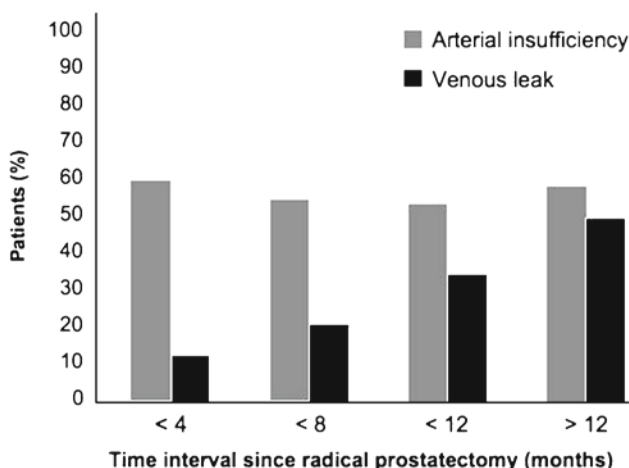


Fig. 15.6 The incidence of hemodynamic alterations after radical prostatectomy. Venous leak increased in incidence with time postoperatively. Adapted from Mulhall JP, et al.

Erectile dysfunction after radical prostatectomy: hemodynamic profiles and their correlation with the recovery of erectile function. *The Journal of Urology*. 2002;**167**: 1371–5

and diastolic velocities) as time progressed after surgery (Fig. 15.6). The incidence of venous leak less than 4 months after surgery was approximately 10% and rose to 35% between 8 and 12 months after surgery and 50% after 12 months. The importance of this information is that in the same series, men with normal erectile hemodynamics were more likely to have recovery of natural erectile function. However, only 8% of men who had venous leak had recovery of natural functional erections after surgery. We also know from other data that men with venous leak are far less likely to respond to PDE5 inhibitors than men with arterial insufficiency.

Animal Data Supporting the Concept of Penile Rehabilitation

There currently exist a total of six studies published in the literature demonstrating a positive effect of regular PDE5 inhibitor use after cavernous nerve injury. Three of these studies pertain to tadalafil, two sildenafil, and one vardenafil [26–30]. Mulhall et al. analyzing animals exposed to bilateral cavernous nerve injury treated with sildenafil compared to no treatment

(control) demonstrated significant improvement in ICP/MAP ratios in rats treated for 28 days in a row with sildenafil commencing the day of cavernous nerve injury [31]. In the control group, the ICP/MAP ratio dropped from 70% to 30% and this rose to 48% in animals treated with 20 mg/kg sildenafil citrate administered daily subcutaneously. On structural analysis, sildenafil treatment resulted in the preservation of corporal smooth muscle content, preservation of endothelial factors (as evidenced by the preservation of CD31 staining), in the reduction of apoptosis, and an increased phosphorylation of AKT and eNOS. In normal corporal smooth muscle in the rat model apoptotic indices measure approximate 10%. In the bilateral cavernous nerve injury models, this rises to 60%, however, with sildenafil treatment these indices dropped to 20%. Phosphorylation of AKT and eNOS are critical to endothelial function for penile erection. In data presented at the AUA meeting in 2007, Mueller et al. have shown that pretreatment of a rat for 3 days prior to cavernous nerve injury resulted in even greater improvement in ICP and AP ratios [32].

In work by Kovanecz et al., long-term continuous sildenafil treatment resulted in the improvement in venous leak following cavernous nerve resection in the rat model [27] and a

number of authors have shown that with chronic tadalafil dosing in a cavernous nerve injury model corporal fibrosis can be prevented, collagen production is reduced, and smooth muscle content is preserved [27, 29]. It has also been shown by Lysiak et al. tadalafil increases AKT and extracellular signal-related kinase activation resulting in reduced apoptotic cell death in the penis following cavernous nerve injury.

Human Data Supporting the Concept of Penile Rehabilitation

Penile rehabilitation is defined as the use of any drug or device at or after RP to maximize erectile function recovery. The purpose of penile rehabilitation is the prevention of corpus cavernosal smooth muscle structural alterations not only to maximize the chances of a man having recovery of functional erections, but also returning him to his preoperative erectile function level [33].

In 1997, Montorsi et al. published a randomized trial, comparing men using intracavernosal injections three times a week for 12 weeks after radical prostatectomy compared to men who used no treatment [34]. Twelve of the Fifteen patients using injection therapy completed the trial and eight in the injection arm (67%) had natural erections sufficient for intercourse by 6 months after surgery. This was compared to 20% of men (all 15 finished) in the control arm who had the recovery of natural erections. Interestingly of those patients failing to have recovered erectile function, the majority had

venous leak on duplex Doppler penile sound. While this study was significantly underpowered to address this question, this was the first study to suggest that early erections postprostatectomy are critical to the recovery of long-term erectile function. In 2005, Mulhall et al. in a nonrandomized study of 132 patients compared patients who opted for penile rehabilitation versus those who did not do rehabilitation [35] (Fig. 15.7). Rehabilitation patients were told to obtain three erections/week whether sildenafil or penile injections. Those in the rehabilitation group averaged 1.9 erections/week. The patients opting for the rehabilitation had significant improvement in natural response, sildenafil response, and intracavernosal injection response. While short of being definitive, there is a signal from both of these studies that early erections after radical prostatectomy may be important for the recovery of long-term or a function.

At the AUA in 2003, a randomized controlled trial was presented. Seventy-six patients were randomized in a three-way fashion to Viagra 50 mg or 100 mg or placebo nightly starting 4 weeks after bilateral nerve sparing radical prostatectomy and continuing for 36 weeks [36]. Unfortunately, at this point in time, this paper has not yet been published in peer-reviewed literature. Twenty-seven percent all patients using Viagra (there was no significant difference between 50 or 100 mg Viagra) had the recovery of erections similar to their baseline erections compared to 4% of those patients in the placebo group. If we conduct a critical analysis of bilateral nerve sparing radical prostatectomy patients across all ages, it is likely that we will find that no more than 10% or so who will have returned to baseline erection rigidity after surgery.

	Rehabilitation group (n = 58)	No rehabilitation group (n = 74)	P value
Patients with functional erections (nonmedication assisted) ¹	52%	19%	<0.001 ¹
Patients responding to sildenafil ²	64%	24%	<0.001 ¹
Patients responding to intracavernosal injections	95%	76% ³	<0.01 ¹

Fig. 15.7 Outcomes with penile rehabilitation in a non-randomized trial. Adapted from Mulhall J, et al. The use of an erectogenic pharmacotherapy regimen following

radical prostatectomy improves recovery of spontaneous erectile function. *The Journal of Sexual Medicine*. 2005;2: 532–40; discussion 40–2

One of the questions asked following the presentation of these data was how might PDE5 inhibitors improve long-term erectile function. We have much data from animal studies suggesting that they are myoprotective and endothelial protective. This is supported by human data. All three PDE5 inhibitors in phase II–IV trials have demonstrated a lower incidence of myocardial infarction compared to those patients in the placebo groups of the trials. We know that PDE5 inhibitors are potent endothelial protectants in the diabetic patient population as well as in patients with increased cardiovascular risk [37, 38]. All three PDE5 inhibitors have been shown to improve flow-mediated dilation at low doses and for a significant period of time after the cessation of the medication. Thus, it would appear that PDE5 inhibitors result in cellular events that protect endothelium beyond the presence of drug within the blood. Furthermore, there is elegant evidence in humans and animals that PDE5 inhibitors generate the production of endothelial progenitor cells from the bone marrow. These cells may be critical for the reparation of injured endothelium and may themselves be proerectile in nature. The second mechanism that has been explored, albeit to a lesser extent, is the concept of PDE5 inhibitors may in fact be neuromodulatory. Zhang et al. have shown with both sildenafil and tadalafil that a rat middle cerebral artery occlusion model of stroke that dosing with medication compared to saline results in significant functional recovery [39, 40]. Finally, it has been suggested that the PDE5 inhibitors work by inducing cavernosal oxygenation during erection after radical prostatectomy. However, in the early stages after surgery the majority of men do not respond with erections in response to any of the PDE5 inhibitors, thus it is not likely that cavernosal oxygenation is a major mechanism by which PDE5 inhibitors protect erectile tissue. There is, however, a randomized controlled trial comparing all three PDE5 inhibitors in the pulmonary hypertension literature demonstrating that increased oxygenation occurs in pulmonary artery in response to sildenafil citrate.

Schwartz et al. in a randomized controlled trial comparing the impact of sildenafil on

corporal smooth muscle integrity in men after radical prostatectomy [41]. Twenty-one patients used sildenafil every other day at 50 mg or 100 mg. They had corporal biopsy performed prior to radical prostatectomy and 6 months postoperatively. Histopathological analysis showed significant preservation of smooth muscle content with sildenafil use at both the 50 and 100 mg level. These data are supported by the previously mentioned animal data where all six studies demonstrated the ability of PDE5 inhibitors to be myoprotective and in some cases even myotrophic. Finally, at the AUA 2008 meeting Bannowsky et al. reported on a nonrandomized study of sildenafil postradical prostatectomy [42]. In 41 patients who used 25 mg of sildenafil every night starting 2 weeks after radical prostatectomy compared to a control group (no treatment), they showed using SHIM scores that 24 months after surgery there was a six-point difference in the score between sildenafil and control groups.

In summary, as practicing physicians we appreciate that the consequences of ED are profound for many men. In a 55-year-old men who was asymptomatic prior to his prostate biopsy, who had a mildly elevated PSA and ends up having a radical prostatectomy long-term ED is a major source of psychological distress in his life. I believe that the above data shows that cavernosal smooth muscle alterations are common early after prostatectomy; that venous leak imparts a poor prognosis for recovery of natural and PDE5 inhibitor-assisted erections; that the animal evidence is robustly supportive of the concept that erectile function preservation can be achieved using PDE5 inhibitors; that there is a signal from human data that early erections after surgery and regular sildenafil use is of some benefit to the recovery of erectile function. Despite this, there is yet to be conducted at large randomized controlled trial that definitively answers the role of injection therapy versus PDE5 inhibitors.

More recently, two other strategies have been explored for the purposes of penile rehabilitation postprostatectomy. Vacuum device therapy has been around for more than a century and has

continued to assume a role in the management of men with erectile dysfunction. A number of centers have studied the role of vacuum device therapy for the preservation of penile length postprostatectomy as well as for rehabilitation. It has been well documented that the pO_2 and pCO_2 levels in the cavernosal sinusoids following the application of a vacuum device remain in the venous range [43]. Indeed the oxygen saturation is approximately 80%. If one believes that cavernosal oxygenation is critical to erectile tissue health and penile rehabilitation outcomes, this finding would undermine the role of vacuum device therapy as a rehabilitation strategy. Raina et al. study 109 patients who were randomized to vacuum device use daily for 9 months versus observation [44]. Thirty-two percent of patients in the vacuum device rehabilitation group versus 37% in the observation group had recovery of natural erections at 9 months after surgery. Seventy percent of the vacuum device patients and 29% of those not using vacuum device were able to have sexual intercourse at that time. Dalkin et al. studied 39 men with good preoperative erectile function who underwent nerve sparing radical prostatectomy [45]. Stretched flaccid penile length was evaluated preoperatively and at 3-month postoperatively by a single examiner. The vacuum device was used daily starting the day after catheter removal and was continued for 90 days. In men using the vacuum device on more than 50% of the possible days, only 3% had a decrease in stretched flaccid penile length of greater than 1 cm. Of the three men with poor vacuum device compliance 67% had a penile length reduction of more than 1 cm. Kohler et al. analyzed 28 men who were randomized to early vacuum device or a control group [46]. The vacuum device group had therapy commenced 1 month after radical prostatectomy while the control group had vacuum therapy instituted 6 months after radical prostatectomy. Postoperative SHIM scores were higher in the treatment group at 6 months 12.4 versus 3.0. Furthermore in the treatment group, no significant changes in stretched flaccid penile length were measured at 3 or 6 months postoperatively. In the control group, the mean penile length loss

at 3 and 6 months was approximately 2 cm. Based on these small studies, there is a solid rationale for the conduct of a large multicenter analysis of vacuum device in a randomized controlled trial as a rehabilitation strategy. The current evidence in my opinion does not support the role of vacuum devices as monotherapy in penile rehabilitation.

Recently, there has been resurgence in the interest in transurethral prostaglandin (MUSE) as a treatment strategy in ED as well as a penile rehabilitation strategy. Costabile et al. in a retrospective analysis of all MUSE clinical trial data analyzed 384 patients who were postprostatectomy [47]. In this population, 40% had sexual intercourse on at least one occasion at home, and 18% of patients had urethral pain and burning. The limiting factor in the use of MUSE in the treatment of men postprostatectomy, particularly in the first year after surgery, is penile pain due to PGE_1 hypersensitivity. It is our experience that doses of 500 mcg and 1,000 mcg of MUSE are associated with penile pain rates in excess of 50%. Raina et al. studied 54 patients using MUSE postradical prostatectomy [48]. 55% of patients were capable of having sexual intercourse using MUSE and 48% continued long-term therapy. The compliance with MUSE was 63% at a mean follow-up of 2.3 years. Mean SHIM scores went from 19 preoperatively to five immediately postoperatively and this increased to 16 with the use of MUSE. While a score of 16 on the SHIM questionnaire is not by normal, although there appears to be a signal that there may be some benefit to MUSE as a rehabilitation strategy. The same authors studied 91 men who had undergone nerve sparing radical prostatectomy with a mean follow-up of 6 months. 56 men were treated with MUSE at 125 or 250 mcg three times/week for 6 months. MUSE was started 3 weeks after surgery. The control group was allowed to use erectogenic agents on-demand for sexual intercourse. Fifty percent of the MUSE rehabilitation patients had sexual intercourse without the use of any aides versus 37% of the untreated patients. Hundred percent had penile pain and 32% discontinued treatment. Once again, given the small number of studies

and the small population sizes studied, while there is a signal that there may be of value to transurethral PGE₁ administration as a rehabilitation strategy, there is a distinct need for the conduct of a large multicenter, randomized controlled trial to define its role.

The Role of Penile Rehabilitation

The arguments against penile rehabilitation are threefold. It is common for rehabilitation naysayers to talk about the lack of level I evidence-based medicine. While it is true that there exists only two randomized controlled trials, one of which was likely grossly underpowered, which present inconsistent results, there is a signal from the studies as a whole that early erections and PDE5 inhibitors early after surgery is of some benefit. The magnitude of this benefit is difficult to gauge at this time. I believe that many antagonists are somewhat nihilistic in their approach. Indeed, our daily urologic practice is replete with strategies and procedures that do not have level I evidence-based medicine behind them.

The second argument against penile rehabilitation is that animal data does not necessarily always translate into the human model. This is most certainly true, however, we have for two decades now in the field of sexual medicine translated evidence from animal models into humans. Much of the studies assessing the impact of hyperlipidemia on erectile function are based on the hyperlipidemic rabbit model. Furthermore, most of the work conducted on nitric oxide and its role in penile erection has been conducted in eNOS and nNOS knockout mice. Finally, an argument for both patients and physicians against rehabilitation is cost. Using the Memorial Sloan-Kettering algorithm (Fig. 15.8) we have estimated that the average patient who has zero coverage for his medications will pay between \$1,500 and \$2,500 over 24 months after radical prostatectomy to accomplish pharmacological penile rehabilitation. For the 55-year-old male who has 25 years of sex ahead of him this translates into less than \$100

per annum for preservation of his future sex life. That is not to say that efforts should not be made to convince the insurance industry or Congress to cover medications in this unique population. Indeed, there are many parallels between women who have had a mastectomy for breast cancer who subsequently undergoes breast reconstruction and men postradical prostatectomy who are left with erectile problems and require regular use of medication to preserve erectile tissue to promote the recovery of natural erections.

The principal arguments in favor of penile rehabilitation are that ED is associated with a significant reduction in health-related quality of life. Litwin has shown that poor function after radical prostatectomy translates into a high level of distress, while good function is associated with a low level of distress. Secondly, in this patient population, venous leak development is time-dependent. It is not known definitively what time period after radical prostatectomy is required to pass before irreparable structural damage to erectile tissue occurs. It is likely that this is related to such factors as age prior to surgery and preoperative erectile function. It is known, however, that 4–6 months after surgery the incidence of venous leak starts to rise sharply therefore, I and others believe that rehabilitation is ideally instituted within 4 months of surgery, and in our hands we start our program immediately following surgery. I reiterate that I believe that the signals from the animal and human studies are clear and robust on the animal side and thought-provoking on the human side. Finally, sexual medicine experts are routinely performing rehabilitation postradical prostatectomy. Eighty-seven percent of members of the International Society for Sexual Medicine when surveyed are performing pharmacological rehabilitation after radical prostatectomy.

The data from the REINVENT study are still being digested, but at this time, to me the data infer one of three things: (1) that penile rehabilitation is a waste of time: it is difficult to ignore the robust animal data and several other human studies using sildenafil or injection therapy suggesting a benefit; (2) that the design of this study was inadequate to define such an outcome: the

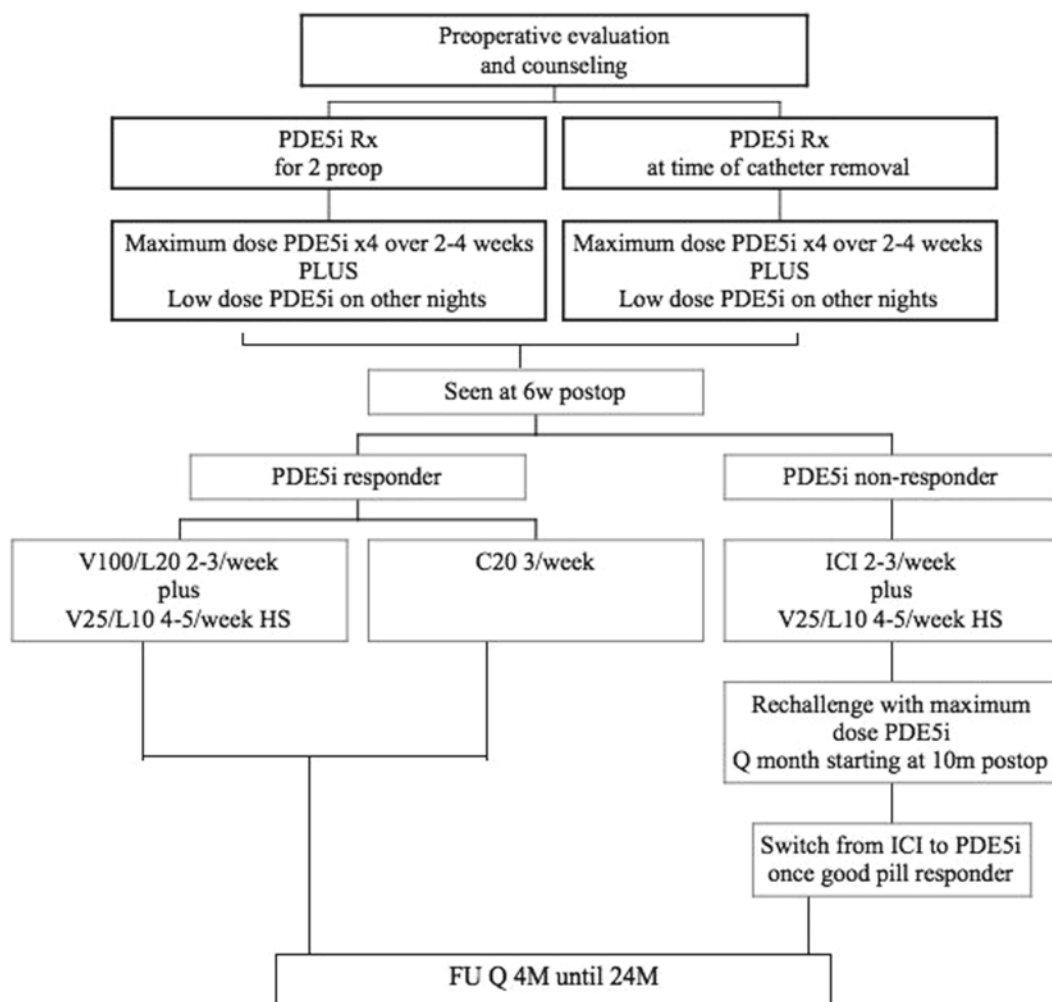


Fig. 15.8 The memorial sloan-kettering penile rehabilitation algorithm

ideal study design is debated, but it is likely that this study was flawed enough so as to make its interpretation difficult; and finally (3) that vardenafil is inferior to sildenafil in penile rehabilitation: without a head-to-head trial, it is impossible to answer this issue.

Structure of a Rehabilitation Program

In my practice, such patients are divided into two groups (Fig. 15.8). Group 1 are patients who present to see me prior to radical prostatectomy,

and Group 2 are patients who come to see me following radical prostatectomy. These patients are treated in a different manner in the early stages pre- and postsurgery. When patients see me prior to surgery, I encourage them to use low-dose PDE5 inhibitors on a nightly basis for the 2 weeks prior to their operation. This strategy is based on animal data supporting pretreatment (presented but not yet published) [32]. These patients are then told that with the catheter in place they should continue low-dose PDE5 inhibitor on a regular basis. When they are given permission by their prostatectomist to resume attempts at obtaining erections, they switch to low-dose PDE5 inhibitor six nights a week

and a maximum dose pill one night a week. The maximum dose pill needs to be used in an appropriate fashion with sexual stimulation. The patients are encouraged to return to the office 6 weeks after surgery, which allows them approximately 4 weeks to try maximum dose medication. For patients who have not seen me prior to surgery, the day the catheter is removed they are given a prescription by the practice nurse for a PDE5 inhibitor and are told to use low-dose agent nightly, 6 days a week and maximum dose medication one night a week with sexual stimulation. On return to the office at 6 weeks, patients are asked about their response to the maximum dose PDE5 inhibitors. If the patient is a responder (defined as penetration hardness), they will use PDE5 inhibitors alone for the purpose of penile rehabilitation: maximum dose sildenafil/vardenafil two nights/week and low-dose on the other five nights. Alternatively, they can use tadalafil 20 mg three times a week. The patients are encouraged to get at least two erections/week. The major issue with this approach is cost, as a sildenafil responder uses thirteen 1,000 mg pills per month (8 full doses and 20+ quarter pills). A tadalafil responder uses twelve 20 mg pills per month. We have not yet explored the tadalafil 5 mg/day strategy for this population. The reason for this is that after 5 days of continuous use of 5 mg daily, serum levels equivalent to a single 8 mg dose are achieved. This serum level is not likely good enough for intercourse in the early stages after RP.

Those patients who present at 6 weeks after surgery who have not responded to a PDE5 inhibitor, and this is the majority of patients in my practice who are driven directly to intracavernosal injection therapy. They are encouraged to undergo penile injection therapy training and to use injection therapy at least two times a week. On noninjection nights, they are told to use low-dose PDE5 inhibitors going to bed as previously outlined. We discourage patients who are using regular injections from using tadalafil because of its long half-life. Toward the end of the first year after surgery, if patients are still using penile injection therapy they are encouraged to use maximum dose PDE5 inhibitor at least once per month. This is performed in an effort to define if

the patient is responding to oral medication, as this will facilitate them ceasing injection therapy. We tell our patients that it usually takes 10–14 months after surgery to start seeing some improvement in erectile function but that it is 18–24 months before we see optimization of erectile function recovery. This is also a time-frame for best response to a PDE5 inhibitor.

Penile rehabilitation after RP is a highly labor-, cost-, and space-intensive strategy. It is impossible for an individual physician to run this program alone. A nurse practitioner or physician assistant is critical to the success of the program. The sheer volume of injection patients, their training, their monitoring, and follow-up alone would be overly burdensome to any given physician. Saying this, in multiphysician practices, resources can be shared and an NP or PA can cover several physicians' patients rendering this a more cost-effective program. With the pay-for-performance initiatives looming, I believe that long-term complications of RP become increasingly focused upon and the role of penile rehabilitation after this surgery to optimize sexual function outcomes may become critical to this goal.

Finally, it is my personal philosophy that given the devastating consequences of acute onset, long-term ED after radical prostatectomy, we should be giving greater consideration to rehabilitation for these men while we await definitive evidence confirming or refuting its benefit.

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Chapter 16

Peyronie's Disease: Natural History, Diagnosis, and Medical Therapy

James F. Smith, William O. Brant, and Tom F. Lue

Abstract Peyronie's disease (PD) is an acquired disorder of the tunica albuginea of the penis resulting in varying degrees of penile curvature and sexual dysfunction. The diagnosis of the disorder is usually straightforward after a detailed sexual history and focused physical exam. Although a wide range of medical treatments have been employed to treat the disorder, data from randomized trials support only a few. The administration of intralesional verapamil has provided generally consistent and positive results, while some evidence exists to support the use of colchicine, Potaba™, l-carnitine, and superoxide dismutase. Other promising therapies, but not yet verified by randomized trials, include penile extender devices and pentoxifylline.

Keywords Tunica albuginea • Penile curvature • Intralesional verapamil • Penile extender devices • Penile plaque • Ultrasonography

Introduction

Peyronie's disease (PD) typically defined as penile erection deformity, penile pain, or mass, generally results from a fibrosis of the tunica

albuginea of the penis [1]. While the disorder has been named after François Gigot de la Peyronie (Fig. 16.1), surgeon to King Louis XIV of France and descriptions in the literature suggest that the disorder was recognized as early as 1265 [2]. This chapter considers the epidemiology, natural history, diagnostic evaluation, and current medical and nonsurgical interventions for PD. Special emphasis is placed upon the quality of evidence underlying current treatment options, although, as in numerous other fields, many treatments thought to be generally efficacious have not been subjected to the most rigorously designed studies. Surgical treatments of PD are described in a separate chapter.

Epidemiology

PD has been reported in 3–9% of men aged 50 years or older. It is a common misperception, supported by historical reports of prevalence as low as 0.4% [3, 4], that PD is an uncommon disorder. Among 1,100 men screened for prostate cancer in southern Brazil, 3.7% of men over 50 reported symptoms of penile deformity or plaque [5]. Penile plaques were seen in 8.9% of men presenting to another prostate cancer screening program [6]. Data from a population based cohort of 8,000 German men revealed that 3.2% of this population endorsed symptoms consistent with PD [7]. This data revealed a significant age-related linear trend in the prevalence of these findings as 1.5% of 30- to 39-year-old men and 6.5% of men over 70 described findings

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Fig. 16.1 François Gigot de la Peyronie, surgeon to King Louis XIV of France

consistent with PD. Although the prevalence of PD has been reported to be as high as 16% in one report from a tertiary referral center [8], a selection bias could very well explain this finding, as these were men being evaluated for erectile dysfunction in that center. Despite these findings, further research is necessary to convincingly characterize the incidence and prevalence of PD among the general population.

Natural History

Contrary to popular belief, Peyronie's disease is frequently a progressive disorder, as nearly half of untreated men have worsened curvature or increased plaque size. Among 246 men newly diagnosed with PD and followed for 1 year without treatment, 12% improved, 40% remained stable, and 48% worsened [9]. Clinicians often separate the disease into an active and a quiescent phase based upon the clinical and diagnostic evaluation [10]. The quiescent, or chronic, phase is generally considered to be a time of disease stability without further

progression in plaque size, penile deformity, or curvature. In contrast, the active phase is characterized by increasing plaque size or penile curvature and penile pain. While it may be true in many men that the active phase lasts from 12–18 months from the onset of disease, a significant proportion of men experience continued progression after this time point [4]. Medical therapy offers the promise of shortening the acute phase of disease by stabilizing the underlying penile lesion and minimizing progression of disease.

Etiology of Peyronie's Disease

Inflammation is a characteristic finding within Peyronie's plaques [11]. Because of this finding, sources of inflammation, such as that resulting from penile injury, have been implicated as causal factors underlying the development of PD. These findings also underlie the search for anti-inflammatory treatments (e.g., vitamin E) that may minimize inflammation and treat penile lesions. Further support for this hypothesis comes from pathologic studies that have demonstrated tunica albuginea scarring secondary to vascular inflammation between the tunica albuginea and the corpora cavernosa [12]. Anatomically, an outer, longitudinally oriented layer of connective tissue overlies an inner, circularly oriented layer [13]. Fibers from the inner layer radiate outward to serve as a support structure to reinforce the corporal septum. Insertions of these fibers may separate with minimal trauma leading to bleeding and inflammation.

If this model of trauma is indeed correct, why are younger men much less likely to develop PD, when they are more likely to have sex more often and more vigorously than older men? It has been suggested that in older men, even mild diminution of erectile rigidity may increase susceptibility to buckling forces [14]. The subsequent trauma to the tunica albuginea may be more likely to result in injury given that an older man's tissues are less elastic and more prone to disruption. Once a traumatic event has occurred, edema may limit the dispersion of cytokines and related

inflammatory mediators, thus perpetuating the local injury [15]. A combination of inflammation and less effective wound healing among some men may lead to fibrosis, a loss of elasticity, and excessive collagen deposition. PD lesions have a higher ratio of collagen type III to type I than in healthy tunica albuginea, a loss of elastic fibers, and increased fibrin deposits [13, 16]. Furthermore, early in the disease process, fibroblasts are found in greater concentration along with inflammatory cells. Calcified ossification of these lesions can occur in up to one-third of these cases [17]. These pathophysiological factors may explain the initial pain experienced by many men with PD that is followed by subsequent penile deformity, curvature, and plaque.

In general, tunical plaques are found on the dorsal aspect of the penis; however, the abnormal tissue may extend beyond the palpable lesion [18, 19], or even into the corporal tissue or intercavernosal septum [20]. Among the minority of men with PD who do not have palpable plaques, penile ultrasound often demonstrates septal defects, intracorporal fibrosis, or subtunical calcifications [17]. When the normally elastic tunica albuginea fibers are replaced by relatively non-compliant collagen-rich tissue, this relative inelasticity and contracture of the tunica albuginea leads to decreased penile length/girth and ipsilateral penile deviation. Further, this inelasticity of the tunica albuginea may impede the normal vasoocclusive mechanism of erection and thus lead to venous leak [21]. This hypothesis would provide an explanation for the erectile dysfunction seen in some men with PD.

Studies that suggest abnormal wound healing in men with PD lend support to the model of trauma as a necessary step in the pathophysiology of PD [2]. Enzymes in the matrix metalloprotein family have important antifibrotic properties, while TGF- β has been shown in cell culture and animal models to be an important profibrotic mediator of plaque formation [11, 22]. These factors in addition to the effect of plasminogen activator inhibitor type 1 [23] and osteoblast-stimulating factor 1 [15] may help explain the balance between pro- and antifibrotic enzymatic processes that likely contributes

significantly to the development of penile lesions and subsequent penile abnormalities.

Abnormal wound healing resulting from underlying genetic abnormalities may contribute to some cases of Peyronie's disease. The presence of Dupuytren's contractures among some men with Peyronie's disease suggests that a genetic predisposition to scarring and fibrosis may be associated with tunica albuginea fibrosis and scarring [24]. Another example is the Kelami syndrome, also known as urethral manipulation syndrome, described as ventral penile curvature occurring after urethral manipulation [25–27]. Sonographic evidence suggests that the underlying mechanism for penile curvature in this setting is one of periurethral scarring [27], perhaps secondary to inflammation from urethral manipulation. It has also been demonstrated that among men with Paget's disease, a chronic skeletal condition leading to painful bony deformities, 32% had penile lesions consistent with PD [28].

Clinical Manifestations

Loss of flexibility of the tunica albuginea results in differential expansion of the tunica during erection with subsequent penile curvature or deformity. The degree of curvature and volume of plaque is highly variable upon presentation (Fig. 16.2). Curvature can range from nearly straight (15°) to 180° in the most severe cases. Plaques can be single or multiple and are associated with a variety of penile deformities (Figs. 16.3 and 16.4). While the most common direction of curvature is dorsal, ventral, lateral, and complex curvatures are frequently seen (Fig. 16.5). Noncurvature deformities range from “notching” to circumferential “hourglass” defects. Penile shortening is a commonly reported symptom and causes great concern to patients [29].

Although some men with PD have erectile dysfunction, this may be related to age or chronic disease rather than representing a causal relationship. Multiple reports have described a prevalence of erectile dysfunction as high as 80–100% among men with PD [30–32]; however, a recent study

Fig. 16.2 Dorsal penile curvature, demonstrated with intraoperative pharmacologic erection



Fig. 16.3 Exam of flaccid penis, demonstrating dorsal penile plaque



suggests that only one-third of men with PD also have erectile dysfunction [33]. Further, given that PD is associated with diabetes and erectile dysfunction among older men with PD [34], chronic medical conditions may explain the observed relationship between PD and erectile dysfunction.

There are several publications that highlight the emotional and psychosocial impact of PD. Patients often have a variety of psychosexual complaints, including poor self-image [35], emotional, and relationship difficulties [29]. It has also been shown that almost half of men with PD had clinically significant depression [36]. A challenge for

clinicians and researchers is the lack of a validated quality of life measure for men with PD; however, these measures are being developed [35].

Patient Evaluation

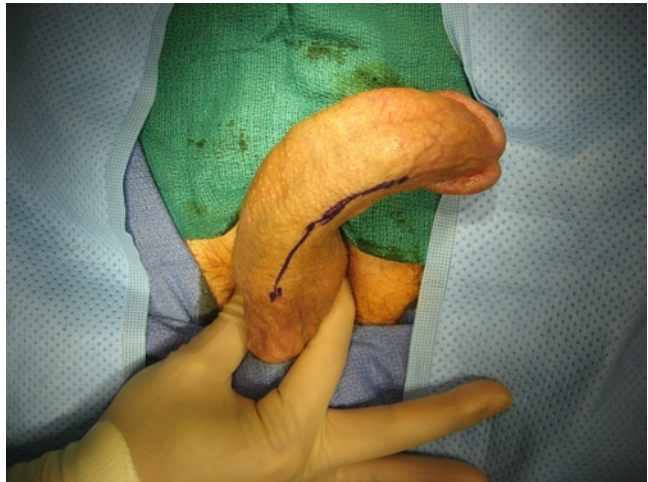
History

The evaluation of a man suspected of having PD should begin with a thorough medical history that probes the etiology (e.g., inciting

Fig. 16.4 Right-sided curvature with associated indentation deformity, demonstrated with intraoperative pharmacologic erection



Fig. 16.5 Left-sided curvature with associated penile torsion/corkscrew deformity, demonstrated with intraoperative pharmacologic erection. The pen mark demonstrates the median raphe overlying the corpus spongiosum



events or trauma), level of disability (i.e., the ability to have intercourse, erectile function, and psychosocial effects), duration of disease, and degree of curvature. Risk factors for severe PD and general medical concerns should be identified with this evaluation [2]. This data collection can be facilitated by utilizing a disease-specific questionnaire [37]. A patient-supplied photograph of the erect penis can be beneficial in characterizing the degree of deformity, although the measurement of curvature

from this image may underestimate the degree of curvature [38].

Physical Exam

A directed physical examination is critical to confirm the diagnosis and determine disease severity. The key components of the exam include the genitalia and extremities. Loss of

penile length is a common complaint and can worsen over time. Given this, the measurement of stretched penile length provides key information. Plaque characteristics should be noted for their position, size, tenderness to palpation, texture (i.e., calcifications), and number. The hands and feet should be examined for the cord-like thickening of Dupuytren’s contractures or Lederhose’s disease. Other findings may be non-specific; for example, plantar fasciitis is a common complaint in the general population [4].

Measurement of Erectile Function and Degree of Curvature

Several validated questionnaires (SHIM, SEAR, QEQ, etc.) can evaluate erectile function in men with PD. In situations of uncertainty regarding a patient’s erectile function, a cavernosal injection and self-stimulation (CIS) test should be performed using vasoactive agents [39]. The CIS test may also provide the most accurate means of measuring penile curvature [38]. A protractor is useful to determine the degree of penile curvature while calipers or a ruler are used to measure penile plaques and nodules.

Imaging and Vascular Studies

Ultrasound, X-ray, CT, and MRI have been used to identify abnormalities of the tunica albuginea and corpora cavernosa. Generally, B-mode ultrasound is the most useful technique for measuring the extent of fibrosis or calcification of the tunica albuginea, corpora cavernosa, and septum. Although CT scan, X-rays, and MRI have been used for PD, penile ultrasound identifies calcifications more accurately than these techniques [40, 41]. When vascular abnormalities are suspected, a duplex doppler ultrasound after CIS assesses vascular health and provides the best estimate of penile curvature and deformity [42]. While ultrasound is not used in all centers specializing in the care of men with PD, this relatively low-cost and minimally invasive technique quickly and efficiently identifies

Table 16.1 Modern therapy used for Peyronie’s disease (partial listing)

Treatment category	Agent
Oral	Pentoxifylline
	Vitamin E
	Acetyl-L-carnitine
	Propionyl-L-carnitine
	Potassium para-aminobenzoate (Potaba™)
	Colchicine
Topical	Tamoxifen
	Verapamil cream
Mechanical	Superoxide dismutase
	Fastsize penile extender
Intralesional	Collagenase
	Verapamil
	Interferon-alpha 2b
Extragenital	Shock wave lithotripsy

the underlying penile abnormality [20] and provides key information that guides medical management and the choice of surgical intervention. From clinical experience, men with extensive calcifications are unlikely to benefit greatly from medical therapy and may require excision of these calcifications to correct the penile curvature.

Medical and Nonsurgical Therapy

The current list of medical and nonsurgical treatments for PD is long (Table 16.1) and reflects the fact that no treatment has been uniformly successful. Few of these treatments have been subjected to rigorous evaluation with randomized trials (Table 16.2); however, some therapies have shown consistently positive results. New treatments and nonsurgical interventions are under study that may provide significant benefits for men with PD.

Intralesional Therapy

Verapamil

Intralesional injection of calcium channel blockers, such as verapamil, has been shown to decrease plaque size and penile curvature.

Table 16.2 Medical therapy for Peyronie’s disease evaluated by randomized trials (modified and used with permission from Smith et al. IJIR July, 2008)

Treatment/author	Intervention	Treatment duration	Effect
<i>Verapamil</i>			
Rehman (1998) [44]	Saline injections versus verapamil injections	Weekly injections × 4–6 months	Decreased plaque size and ED in treatment arm
Cavallini (2002) [45]	Verapamil + tamoxifen versus verapamil + l-carnitine	Weekly verapamil injections × 10 weeks; Oral medications taken 3 months	Decreased plaque size, curvature, and ED in the verapamil + l-carnitine arm
Di Stasi (2004) [58]	EMDA with lidocaine versus verapamil + dexamethasone	4× per week for 6 weeks	Decreased plaque size and curvature in verapamil arm
Cavallini (2007) [46]	Verapamil at three different dilutions: 10 mg/4 ml; 10 mg/10 ml; 10 mg/20 ml	Treated every other week for 12 total sessions	Decreased plaque size, curvature, penile pain in 10 mg/20 ml treatment arm relative to two other arms
Fitch (2007) [60]	Topical 15% verapamil versus 10% topical trifluoperazine versus placebo	Treatment applied to shaft of penis BID for 3 months	Decreased plaque size, curvature, and ED when comparing topical verapamil to placebo
Greenfield (2007) [59]	Topical 15% verapamil versus topical 10% magnesium sulfate versus placebo		
Greenfield (2007) [59]	Verapamil twice weekly versus saline twice weekly by EMDA	3 months	No benefit in treatment arm
<i>IFN α-2b</i>			
Inal (2006) [52]	IFN-alpha weekly versus vitamin E BID versus IFN-alpha weekly + vitamin E BID	Vitamin E × 6 months; IFN-alpha × 12 weeks	No difference in effect between groups
<i>Potaba</i>			
Weidner (2005) [68]	Potaba QID versus placebo powder QID	12 months	Decreased plaque size in treatment arm
<i>Vitamin E</i>			
Prieto Castro (2003) [83]	Vitamin E BID + colchicine BID versus i bupropfen BID	6 months	Decreased plaque size and curvature in vitamin E + colchicine arm
Inal (2006) [52]	See above	See above	No difference in effect between groups
Safarinejad (2007) [64]	Vitamin E BID versus l-carnitine BID versus vitamin E BID + l-carnitine BID versus placebo BID	6 months	No difference in effect between groups

(continued)

Table 16.2 (continued)

Treatment/author	Intervention	Treatment duration	Effect
<i>Tamoxifen</i>			
Teloken (1999) [87]	Tamoxifen BID versus placebo	3 months	No benefit of treatment arm
Biagotti (2001) [63]	Tamoxifen BID versus L-carnitine BID	3 months	Decreased plaque size and curvature in the L-carnitine arm
<i>Liposomal superoxide dismutase (orgotein, Lipoxysan®)</i>			
Montorsi (2000) [56]	EMDA administration 8 mg orgotein + dexamethasone + lidocaine versus Placebo 3x per week	3 weeks (9 sessions)	Decreased plaque size, curvature, and pain in treatment arm
Riedl (2005) [57]	Gel application of Lipoxysan BID to plaque versus placebo gel	4 weeks	Decreased pain in treatment arm
<i>Colchicine</i>			
Safarinejad (2004) [90]	Colchicine BID versus placebo	4 months	No benefit in treatment arm

They function by inhibiting the production of extracellular matrix proteins and decreasing the production of TGF- β and collagen. Oral verapamil therapy is not utilized because effective oral doses produce serum levels 100-fold greater than the toxic threshold [43, 44]. Several randomized trials have demonstrated improvements in penile curvature, and erectile function, as well as decreased plaque size after the treatment with intralesional verapamil [44–46]; however, a recent systematic review highlighted many methodological weaknesses that limit the strength of conclusions about the effectiveness of intralesional verapamil [47]. Further, this mode of delivery can only be successful for palpable lesions.

Collagenase

Intralesional injection of collagenase effectively decreased plaque size and penile angulation in a case series of 25 men with PD [48]. The primary adverse effects of its use were common (occurring in 80%), but were generally mild, consisting of penile pain, edema, and ecchymosis. No adverse required additional treatment. Another nonrandomized study demonstrated improvements in pain and decreased sexual disability [49]. While promising based upon its mechanism of action, the efficacy of intralesional collagenase should be confirmed by randomized trial data before it can be recommended strongly for men with PD.

Interferon α -2b

As abnormalities in collagen deposition and composition of the tunica albuginea appear to underlie a significant portion of the plaques observed in PD, the discovery that in vitro administration of interferon α -2b (IFN- α) decreased the production of extracellular matrix collagen and increased collagenase in fibroblasts

derived from Peyronie's plaques provided evidence that this could be an effective treatment [50, 51]. A small randomized study with three study arms comparing IFN α -2b in combination with vitamin E to IFN α -2b alone or vitamin E alone did not demonstrate benefit with intralesional IFN α -2b in combination with vitamin E over the 6-month study period [52]. In contrast, a nonrandomized, nonblinded, prospective cohort study did show a significant decrease in curvature and plaque size in men treated with intralesional IFN- α [53]. Other explanations, such as patient age or selection of participants, medical comorbidities, and duration of disease, might have contributed to the significant findings in this study. The administration of IFN- α is commonly associated with flu-like symptoms (fever, chills, and arthralgias), minor penile swelling, and sinusitis; however, these resolved spontaneously within 36 h of treatment with over-the-counter nonsteroidal anti-inflammatory medication.

Iontophoresis and Topical Therapy

Iontophoresis

Superoxide Dismutase (Orgotein, Lipoxysan®)

Collagen abnormalities observed in the tunica albuginea of men with PD may result from the effects of inflammation with subsequent development of oxygen free radicals. This theory has led to the successful use of superoxide dismutase, a potent scavenger of oxygen free radicals, to decrease the inflammation associated with PD [54, 55] and theoretically offers benefit for inflammatory lesions associated with PD. In spite of this theory, a small clinical trial did not demonstrate convincing evidence of therapeutic benefit [56]. A later small, clinical trial using human recombinant superoxide dismutase revealed significantly greater pain relief among treated men [57].

Verapamil

Electromotive verapamil therapy (EMDA) with dexamethasone can significantly decrease penile curvature and plaque size relative to a lidocaine control [58]. Spontaneous resolution of mild erythema at the electrodes site was observed and no other significant side effects were noted. Contrary to these results, a recent randomized, controlled trial of men treated twice weekly with EMDA for 3 months did not reveal a significant clinical improvement [59]. The primary benefit of utilizing EMDA as a drug delivery mechanism arises from the ease of application and minimal side effects.

Topical Verapamil

A double-blind, placebo controlled study evaluating topical verapamil hydrochloride applied twice daily over the entire shaft of the penis resulted in a significant reduction in curvature, plaque size, and improvements in erectile function after 3 months of treatment [60]. This study also assessed the effect of topical verapamil relative to the calmodulin-blocker, trifluoperazine, and placebo. Several methodological flaws compromise the quality of this data and weaken conclusions that can be drawn from it. Further, it was found that trifluoperazine had significant side effects, including anxiety, agitation, blurred vision, insomnia, and depression. While these results suggest a benefit, additional doubt about the effectiveness of this treatment arises from controversy about the ability of topical verapamil to truly penetrate the tunica albuginea [61].

Oral Therapy

L-Carnitine

L-Carnitine increases mitochondrial respiration and decreases free radical formation thus suggesting a mechanism of action to treat PD [62];

however, data from randomized trials have been equivocal. When combined with intralesional verapamil, L-carnitine significantly decreased penile curvature and plaque size relative to verapamil injections and oral tamoxifen [45]. Another trial comparing tamoxifen to L-carnitine demonstrated decreased plaque size and curvature in the L-carnitine arm and found that L-carnitine provided significant pain reduction and fewer side effects than tamoxifen [63]. Conversely, a larger trial comparing vitamin E and L-carnitine to vitamin E alone did not demonstrate significant clinical benefit [64]. Side effects are usually mild but include mild euphoria [63] and gastrointestinal upset with doses greater than 4 g/day [65].

Potaba™

Potaba™ (potassium paraaminobenzoate) may exert its effects through anti-inflammatory and antifibrotic mechanisms. Several observational studies have demonstrated its effectiveness in treating PD [66, 67]. In the lone clinical trial conducted, men randomized to the Potaba™ arm, all of whom had early-stage PD, had a greater reduction in plaque size [68]. Despite the limited data, Potaba™ holds promise in terms of stabilizing preexisting lesions and preventing new plaques from forming; however, frequent dosing, significant gastrointestinal side effects and its relatively high cost limit its use.

Pentoxifylline

Pentoxifylline is a nonspecific PDE-5 inhibitor with anti-inflammatory properties used to treat claudication and symptomatic cerebral atherosclerosis [69], kidney transplants, open heart surgery, dermatologic conditions, and radiation-induced fibrosis as a means of decreasing inflammation and fibrosis [70–75]. The potential benefit of pentoxifylline for the treatment of PD is based upon data from in vitro and in vivo models. Pentoxifylline added to fibroblast culture

resulted in an upregulation of cAMP and decreased collagen I production [76]. These researchers also demonstrated decreased levels of profibrotic factors and decreased size of fibrotic plaques after the treatment with pentoxifylline in a rat model of Peyronie's disease. Additional in vitro evidence revealed an upregulation of osteoclastic activity after the treatment with pentoxifylline [77].

From a clinical standpoint, case reports suggest that pentoxifylline may prevent corporal fibrosis after priapism [78] and decrease calcifications in new-onset Peyronie's disease [79]. The reduction in tunica albuginea calcifications may derive from pentoxifylline's ability to promote osteoclastic activity. In general, side effects are mild and consist of nausea (14%), dizziness (9%), and headache (3.5%) [80]. Despite the potential for benefit based upon its mechanism of action and early clinical data, higher quality data is needed to support the use of pentoxifylline for the routine treatment of PD.

Vitamin E

Although numerous in vitro studies have demonstrated the potent antioxidant properties of Vitamin E (alpha-tocopherol) [81, 82], these properties may not translate into improved clinical outcomes for men with PD [82]. Several randomized studies have shown no benefit [52, 64]; however, when vitamin E was combined with colchicine, a single-blind, small randomized controlled trial in men with mild, early PD demonstrated significantly decreased plaque size in the intervention arm [83]. Despite this lack of efficacy, vitamin E is often prescribed because of its ease of use and the perception of few side effects. Unfortunately, a growing body of literature suggests a possible link between chronic, high dose vitamin E ingestion and significant side effects such as increased heart failure, blood pressure, and all-cause mortality; however, these findings were confined to patients being treated for chronic medical conditions, such as diabetes, cardiovascular disease, and hypertension [84].

Tamoxifen

Tamoxifen, a nonsteroidal antiestrogen, may reduce the production of TGF- β by fibroblasts in the tunica albuginea [2, 85]. Observational studies have demonstrated modest treatment benefits [86]. One clinical trial revealed no significant difference between tamoxifen and placebo [87], while another found that tamoxifen was inferior to l-carnitine in terms of reducing penile curvature and pain, and plaque size during the early stage of PD [63].

Colchicine

Colchicine is often used for the treatment of gout and a variety of malignancies [88, 89] and has been used for the treatment of PD because of its anti-inflammatory properties. One randomized study has shown decreased plaque size in the acute phase of PD [83]; however, these findings could not be repeated in a subsequent, larger clinical trial [90]. Because of the potential for significant bone marrow suppression, a complete blood count should be obtained quarterly. More commonly, gastrointestinal side effects (i.e., diarrhea, nausea, and anorexia) are reported [81].

Other Nonsurgical Treatments

Penile Traction

Two recent studies have reported promising results for penile traction therapy as an adjunct to oral and intralesional therapy for PD. One small observational study using penile traction for men with curvature $<50^\circ$ demonstrated increased penile length (1.4 cm on average) and decreased curvature over 1 year of treatment [91]. A second, recently published prospective, uncontrolled study of 11 men, combined intralesional verapamil with penile traction, applied, on average

for 3.6 h/day, demonstrated subjective and objective decreases in penile curvature [92]. While the small size of this study and the absence of a control group limit the conclusions one can draw from it, this pilot study supports the feasibility of this approach. One of the primary concerns of men with PD is the frequent loss of penile length [29]. These mechanical devices may offer patients an effective way to minimize this feared and psychologically devastating symptom. Larger, controlled studies are necessary to verify these results; however, this therapy presents a novel approach to the treatment of PD that may be beneficial for many individuals.

Shock Wave Therapy

Several groups have utilized shock wave therapy successfully to treat penile plaques and curvature [93–95]. Local and/or regional anesthesia is needed occasionally for the procedure and while minor skin hematomas were very common (76%), both this adverse event and mild urethral bleeding (8%) resolved spontaneously. The only placebo-controlled trial for shock wave therapy demonstrated a reduction in penile pain without the improvement in penile curvature [96].

Summary of Nonsurgical Treatment Options

Data from the randomized trials evaluating intralesional injection or electrophoresis of verapamil are almost uniformly positive; however, their consistently low methodological quality limit the conclusions one can draw from them. Data for many oral medications are often equivocal; however, l-carnitine and Potaba™ suggest some benefit. Penile stretching devices and pentoxifylline are promising therapies that need to be assessed with larger, controlled studies to convincingly evaluate their effectiveness.

Key Points

- Peyronie's disease is an acquired disorder of the penis resulting in varying degrees of penile curvature, deformity, and sexual disability.
- The diagnosis rests on a careful psychosexual history and physical exam.
- Ultrasonography is a useful tool to guide non-surgical treatment choices and plan surgical approaches.
- Numerous medical therapies have been utilized to treat Peyronie's disease with only modest success.
- New therapies are needed that are effective, easy to administer, low-cost, and have few or no side effects.

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Chapter 17

Peyronie's Disease: Surgical Therapy

Peter R. Hinds and Hossein Sadeghi-Nejad

Abstract Peyronie's disease (PD) is characterized by scarring and alteration of the intricate architecture of the tunica albuginea of the penis. This anatomic deformity may cause an abnormal penile curvature toward the site of scarring, cosmetic displeasure, painful erections during the active phase, and erectile dysfunction (ED) that in some may preclude sexual intercourse. The earliest descriptions of the condition in the Western literature are attributed to Guilielmus of Saliceto (1210–1276) and Theodoricus Borgognoni (1205–1298) who are said to have described penile curvature in medical and anatomical textbooks. The symptomatic incidence of PD is estimated at 1–5% while the asymptomatic incidence is at 0.4–1%, mostly affecting men 45–60 years of age with an average age of 53 years. To date, most medical and herbal therapies have achieved suboptimal penile straightening and satisfaction rates in the vast majority of patients. In those with failed medical or conservative therapies, surgical interventions have shown great promise with excellent results.

Keywords Tunica albuginea • Penile curvature • Penile plaque • Intralesional injection therapy • Shock-wave lithotripsy • Short-wave diathermy • Ultrasound therapy • Radiation therapy

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Overview and Historical Perspective

Peyronie's disease (PD) is characterized by scarring and alteration of the intricate architecture of the tunica albuginea of the penis. This anatomic deformity may cause an abnormal penile curvature toward the site of scarring, cosmetic displeasure, painful erections during the active phase, and erectile dysfunction (ED) that in some may preclude sexual intercourse. The earliest descriptions of the condition in the Western literature are attributed to Guilielmus of Saliceto (1210–1276) and Theodoricus Borgognoni (1205–1298) who are said to have described penile curvature in medical and anatomical textbooks. In 1561, a description of PD was reported by Gabriele Fallopio (Fallopius) in the *Observationes anatomicae* during his post as Professor and chair of anatomy and surgery at the University of Padua, Italy. Fallopio (1523–1562) was one of the most illustrious sixteenth century Italian anatomists. He contributed greatly to the field of anatomy and especially to the knowledge of male and female reproductive organs [1]. Despite these early descriptions, credit was given to Francois Gigot de la Peyronie in 1743 who described the penile disorder, after examining a patient with an upward curvature of the penis during erection, as an induration of the corpora cavernosa that can be felt as rosary beads of scar tissue [2]. Peyronie was a French surgeon who cofounded and chaired the Royal Academy of Surgery in 1736 while serving as first surgeon to King Louis XV.

The symptomatic incidence of PD is estimated at 1–5% while the asymptomatic incidence is at 0.4–1%, mostly affecting men 45–60 years of age

with an average age of 53 years. Schwarzer and colleagues [3] published the results of a questionnaire based on the response of 8,000 men with a 55.4% response rate. The authors found a prevalence of 3.2% for the new appearance of a palpable plaque. The prevalence by age was 1.5% for men aged 30–39 years, 3% for men aged 40–49 years, 3% for men aged 50–59 years, 4% for men aged 60–69 years, and 6.5% for men aged 70 or older. In addition, 84% of males reported penile angulation and 47% reported painful erections. A triad of plaque, angulation, and pain was reported in 32% whereas 41% reported ED. All symptoms and signs were associated with penile plaques in this study. The symptoms of Peyronie's disease are quite variable causing minimal symptoms in some and severe debilitating symptoms in others. The natural history and course of the pathology has been studied, and it is now widely accepted that there are two phases of the disease. The first is an inflammatory or active phase that may be accompanied by painful erections and changing deformity of the penis. This is typically followed by the inactive or quiescent second phase that is characterized by the stability of the disease process manifested by a stable penile deformity and resolution of the painful erections if they were present. Gelbard and colleagues reported complete resolution of the plaque without the treatment in 13% of men with Peyronie's disease while 40% had progression and 47% noted no change in the disease process [4]. In addition, about 25% of patients experience end stage PD of those 33% experience disabling penile curvature [5].

The proposed etiology and treatments of PD are frequently described in the literature. The etiologies and associations with Peyronie's disease have included medications such as beta blockers and phenytoin, PDE5 inhibitors, and intracavernosal injections for erectile dysfunction, external genitalia trauma or buckling injury during sexual intercourse with a resultant inflammatory reaction and fibrosis, urethral instrumentation or trauma, diabetes mellitus, tympanosclerosis, plantar fascial contracture, and Paget's disease [6, 7]. However, with the exception of Dupuytren's contracture that is present in 30–40% of men with PD, none of these entities have withstood the test of

time [7]. Medical treatments have focused on plaque disruption, plaque dissolution, immune system modulation, reducing inflammation, and reducing oxidant stress very early in the disease course prior to the onset of plaque fibrosis and calcification that typically occurs after 1–2 years. Some of the medical therapies that have been used for the treatment of PD include oral preparations, such as Vitamin E, colchicine, para-aminobenzoate, tamoxifen, carnitine, or various herbal preparations. Topical therapies include intralesional injection therapy with verapamil, collagenase, interferon alpha-2b or corticosteroids as well as extragenital therapies with shock-wave lithotripsy, short-wave diathermy, laser therapy, and ultrasound or radiation therapy [8–19].

Surgical therapy is usually reserved for men who have failed optimal medical therapy and is not ideally instituted before a minimum of 6 months to 1 year since the onset of signs and symptoms. The time lapse allows for the resolution of the inflammatory phase, the evaluation of medication effectiveness and for spontaneous resolution that can be observed in up to 13% of cases [4]. The surgical options that include excision or incision of the plaque with tissue grafting to the plaque site defect and shortening of the unaffected side to straighten the penis or a penile prosthetic implant are reviewed in more detail later in this manuscript.

Penile Anatomy and Pathophysiology

The penile anatomy is composed of multiple layers that provide protection and strength to withstand intracavernosal buckling forces. Beneath the skin is a thin dartos fascia that overlies Bucks fascia. The latter contains a single corpus spongiosum lying ventrally between the paired corpora cavernosa that are in turn covered by a resilient protective lining of 1.5–3 mm thick tunica albuginea. The tunica albuginea not only has an outer longitudinal and an inner circular layer of connective tissue composed mostly of type I collagen, but also elastin and Types III and V collagen. Collagen and elastin provide

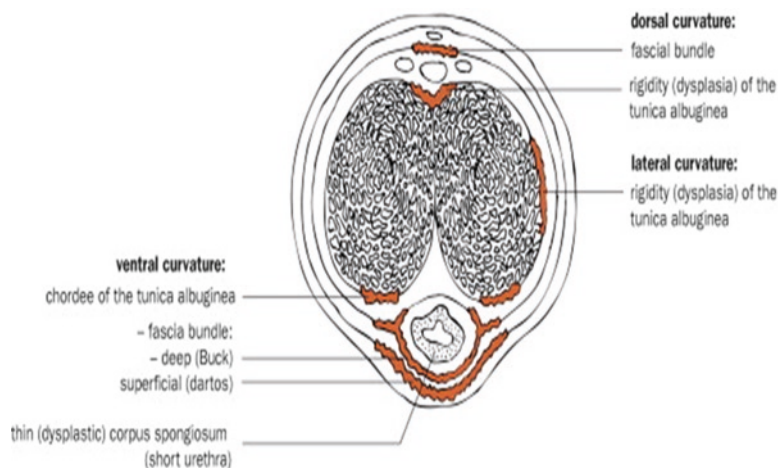


Fig. 17.1 Cross-section of penis showing Peyronie's plaque location and the associated curvature. Reprinted from *The Journal of Urology*, 179, Nyirády, P., Kelemen, Z.,

Bánfi, G., Rusz, A., Majoros, A., Romics, I., Management of congenital penile curvature, pages 1223–1224, 2009, with permission from Elsevier

strength and penile stretch, respectively. It should be noted that the strength layer of the tunica albuginea, the outer longitudinal layer, is the thinnest at the 3 and 9 o' clock positions, the exact location where one is likely to find most traumatic penile fractures [20, 21].

This brief review of penile anatomy allows better understanding of Peyronie's disease as it relates to the distortion of the penile microarchitecture. A cross-section of the penis scarred by PD is shown with various types of penile curvatures is shown in Fig. 17.1. The etiologies may include mechanical stress, microvascular trauma, and inflammation. It has been shown that excessive bending during erection or blunt trauma to the erect penis may result in bleeding into the subtunical spaces or delamination of the tunica at its point of attachment to the inner circular layer of the tunica albuginea, with resultant accumulation of fibrinogen, fibrin, and clot in the subtunical layers and subsequent initiation of an inflammatory reaction [21]. This is then followed by the recruitment of inflammatory cells (neutrophils, platelets, and macrophages) and subsequent release of various cytokines, autocoids, and vasoactive factors that induce a fibrotic reaction [22, 23]. The important factors are platelet-derived growth factors (PDGF-A and PDGF-B) and transforming growth factor- β_1 (TGF- β_1) [21, 24]. PDGF promotes the proliferation of fibroblasts that promote wound healing and macrophages that remove debris from the

wound and release TGF- β_1 . In addition, TGF- β_1 has a pleotropic effect on fibroblast function by increasing transcription and synthesis of collagen, proteoglycans and fibronectin while also increasing synthesis of tissue inhibitors of collagenase thus preventing tissue breakdown. PDGF, on the other hand, potentiates fibroblast proliferation [25].

In summary, Peyronie's disease is a fibrotic disorder of the tunica albuginea involving potential trauma to the penis with an accompanying inflammatory response. The fibrotic plaques that form are most likely produced by tunica fibroblasts in response to cytokine stimulation (i.e., TGF- β_1 and PDGF).

Summary Points

- The tunica albuginea is composed of collagen interlaced with elastin. Collagen provides tensile strength while elastic affords penile stretch and compliance.
- Peyronie's disease involves scarring and alteration of the microarchitecture of the tunica albuginea. Proposed etiologies include penile microvascular trauma and inflammation.
- Peyronie's plaques are produced by the tunica fibroblast, mostly in response to TGF- β .

Patient Presentation and Evaluation

Patients with Peyronie's disease typically present with symptoms within the first 6 months of the disease process (40%). The signs and symptoms may include penile deformity, penile pain, or a penile lump that may be present alone or in combination with these other findings. Penile deformity is the most common initial symptom (52%) and is present in 94% of men with PD. Penile pain and penile lump occur in 40 and 21% of men with PD, respectively [26]. The evaluation of a patient with Peyronie's disease initially includes a thorough history and physical examination. The history should include the presence of comorbid medical conditions especially those that may compromise vascular sufficiency, medication history, social habits, familial diseases, previous surgeries, genital trauma, the presence of painful intercourse, and erectile dysfunction. The physical examination should include careful palpation of the hands (for signs of Dupuytren's contracture) and the genitalia. The latter should be performed with the penis on stretch to allow for optimal examination. Photographs brought in by the patient demonstrating the extent of penile deformity during an erection are also helpful. Radiographic images of the penis may provide additional anatomic information and may show calcified plaques or even severe calcification (i.e., bone) in patients with late stage Peyronie's disease. However, penile X-rays are rarely performed as part of the evaluation. Penile duplex Doppler ultrasound with pharmacologic challenge is strongly recommended as part of the initial evaluation. Grayscale sonographic examination of the penis demonstrates the size and location of the plaque in relation to the corpora cavernosa. The pharmacologic stimulation that is performed in conjunction with the ultrasound (i.e., intracavernosal alprostadil injection) is helpful for the documentation of penile hemodynamics, the degree of curvature, and the quality of the erection prior to medical or surgical intervention.

Summary Points

- Forty percentage of men with PD present with symptoms within 6 months of the disease process.
- The initial signs and symptoms in men with PD, from most to least common, are deformity (52%), penile pain (40%) and a penile lump (21%).
- Evaluation includes a thorough history to elicit the presence of any associated etiology and a physical examination of the genitalia on stretch and all extremities.
- Duplex Doppler ultrasound with intracavernosal injection of alprostadil is recommended as part of the initial evaluation.

Surgical Management

In men with stable disease in whom optimal medical therapy has failed, the goal of surgical intervention is to correct the penile deformity and restore or preserve erectile function. Preservation of maximal penile length when possible and resolution of penile pain are additional aims that are discussed with the patient prior to intervention [27]. To achieve these goals, a number of different surgical approaches have been employed over the years. They include excising and plicating (suturing) of the corpora just opposite to the plaque (Nesbit procedure), suturing of the corpora just opposite the plaque without corporal excision, excision of the plaque with interposition of a tissue graft, incision of the plaque with interposition of a tissue graft and lastly the insertion of a penile prosthesis alone or in combination with penile molding or plaque manipulation in severe cases that are accompanied by erectile dysfunction. The major differences between the above surgical techniques can be classified according to use of a tissue graft, the location of the corporoplasty, shortening of the penis and postoperative outcome.

Summary Points

- Surgery for Peyronie's disease is reserved for males with significant penile curvature who are in the quiescent phase and have failed optimal medical therapy.
- Surgical techniques may include excision or incision of the plaque with the placement of a tissue graft, straightening the penis by suturing the corpora directly contralateral to the plaque site (plication) or the insertion of penile prostheses with penile molding/plaque manipulation.
- The differences in techniques yield variable outcomes in relation to the preservation of erectile function, straightening of the penis, and the loss of penile length.

Nesbit Procedure

The Nesbit procedure was initially described in males with congenital penile curvature requiring

surgical correction and was later used in males with Peyronie's disease. Penile straightening is achieved by excising an elliptical portion of the tunica albuginea just opposite the side of plaque involvement and angulation, followed by approximation and suturing of the defect [28, 29]. The drawbacks and criticism of the Nesbit procedure have included penile shortening, erectile dysfunction, protrusion of the corpora at site of excision, and recurrence of penile curvature [30]. In reality, most men with Peyronie's already perceive their penis to have been shortened by the pathology. There is no debate, however, that plication procedures surely do not *restore* the length loss secondary to the plaque. The use of the Nesbit procedure that declined over subsequent years after the initial publication and has been replaced by a modified Nesbit procedure or one of the other reconstructive procedures are discussed later. The modified Nesbit procedure involves a vertical incision in the tunica albuginea followed by horizontal closure of this incision thus avoiding the excision of the tunica albuginea as shown in Fig. 17.2. Patient

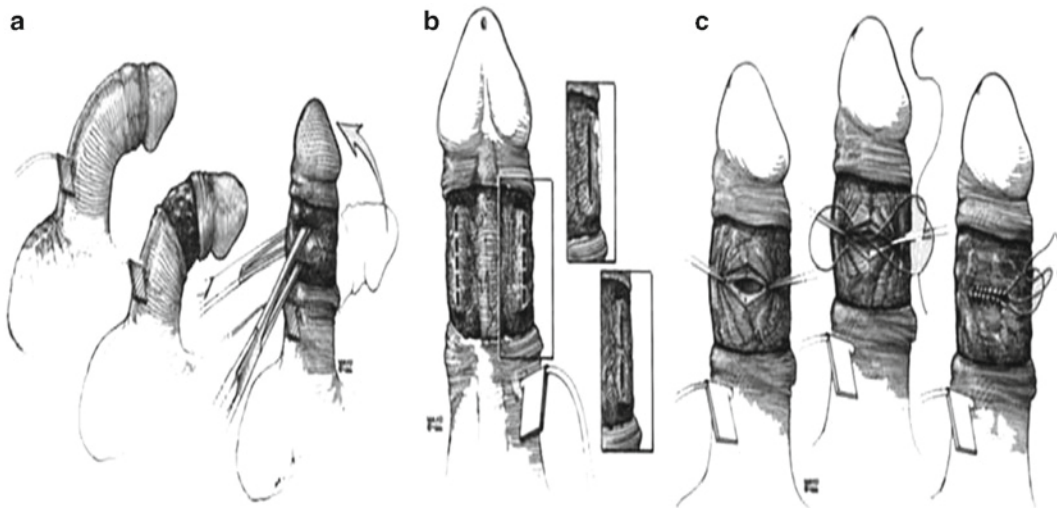


Fig. 17.2 Modified Nesbit: (a) Allis clamps are used to grasp and gather tunica albuginea opposite point of maximum penile curvature during artificial erection. (b) Longitudinal or multiple smaller incisions are made between indentations left by Allis clamp. (c) Incisions are closed horizontally using running

permanent suture with knots buried at both ends. Reprinted from The Journal of Urology, 158, Licht, M., Lewis, R.W. Modified Nesbit Procedure for the treatment of Peyronie's disease: a comparative outcome analysis, pages 460–463, 1997, with permission from Elsevier

satisfaction, need for subsequent surgery, rates of postoperative impotence and the correction of penile curvature were compared for the modified Nesbit, standard Nesbit, and plaque excision with synthetic patch grafting by Light and Lewis [31]. Data on 30 patients who had undergone a modified Nesbit procedure was compared to patients who had undergone either a standard Nesbit procedure or plaque excision with synthetic patch grafting by the same group of surgeons. The modified Nesbit procedure showed no *statistically* significant difference in penile curvature elimination, patient satisfaction, rates of postoperative impotence or need for subsequent surgery. However, there was an overall higher rate of penile curvature elimination (93–79%) and patient satisfaction (83–79%) when compared to standard Nesbit procedure. The plaque excision with synthetic patch grafting group had a lower rate of penile curvature elimination (61%, $p=0.004$) and patient satisfaction (30%, $p=0.00002$), as well as a significantly higher rate of postoperative erectile dysfunction (18%, $p=0.04$) [31]. Rates of decreased penile length postoperatively were 67 (1–2 cm), 37, and 30% in the modified Nesbit, standard Nesbit, and plaque excision groups, respectively [31].

albuginea. The tunica opposite the site of plaque and angulation is sutured in a transverse fashion thus eliminating the penile curvature as shown in Fig. 17.3. Further modification of this procedure has been described by Lue as a “16-dot” technique [33] as shown in Fig. 17.4. The 16-dot technique has minimal morbidity with a relatively short operative time (mean operative time of 45 min), involves no dissection of the neurovascular bundles or the urethra, eliminates the need for tunical incision or excision, and reliably eliminates penile curvature (85%). This procedure can be performed under local anesthesia in the appropriately selected patient. However, it should be noted that it has the same limitations as the Nesbit procedures and as such it may not be suited for males with extensive plaques, bilateral penile indentations or deformities, or an initially short penis. The rate of penile shortening has been reported to be 41–90%. The other complications include postoperative impotence (7–40%), loss of penile sensation (3–48%), and “bothersome” palpable knots at suture site in 12–18% of patients. The rates of patient satisfaction and elimination of penile curvature have been reported as 90 and 71%, respectively [32, 33].

Summary Points

- Modified Nesbit and standard Nesbit procedures are best suited for males without extreme curvatures ($>60^\circ$) or an initial short penile length.
- The Nesbit and modified Nesbit procedures achieve the high rates of patient satisfaction (79–83%) and correction of penile curvature (79–93%).

Plication Procedures

The plication procedure was first introduced by Essed and Schroeder [32]. The technique is similar to that of the modified Nesbit except that it involves a longitudinal incision in the tunica

Summary Points

- Plication procedures may not be suited for males with extensive plaques, bilateral penile indentations/deformities, or an initially short penile length.
- Postoperative complications may include: penile shortening (41–90%), impotence (7–40%), loss of penile sensation (3–48%), and “bothersome” palpable knots at suture site (12–18%).
- The rates of patient satisfaction and elimination of penile curvature have been reported as 90 and 71%, respectively.

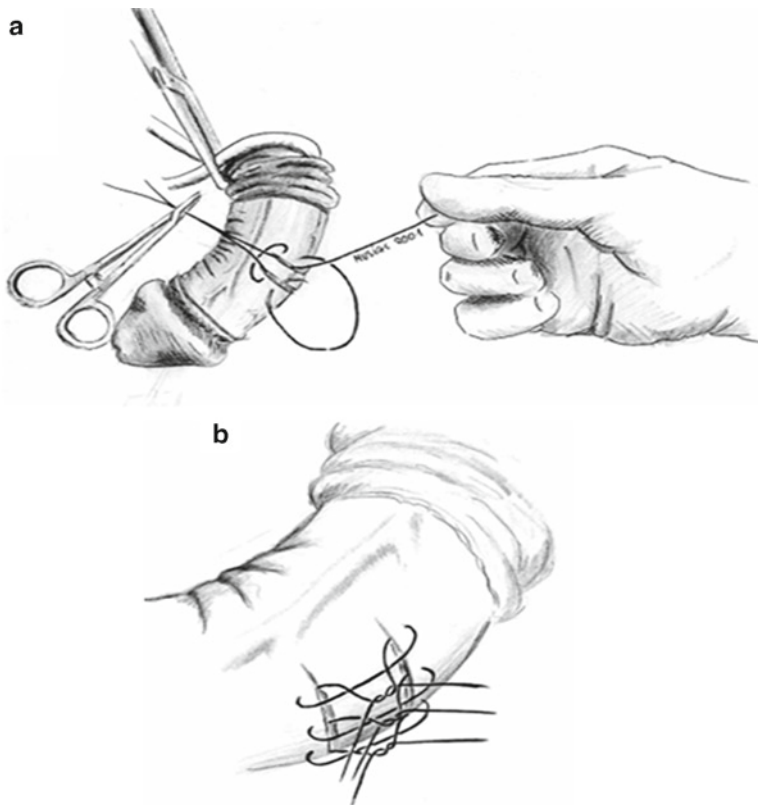


Fig. 17.3 Plication procedure. (a) Reprinted with permission from: Van DerHorst et al. (b) Slightly modified technique of the Original Essed plication procedure for congenital penile deviation. *International Braz J Urol.* 2003; 29, 332–35

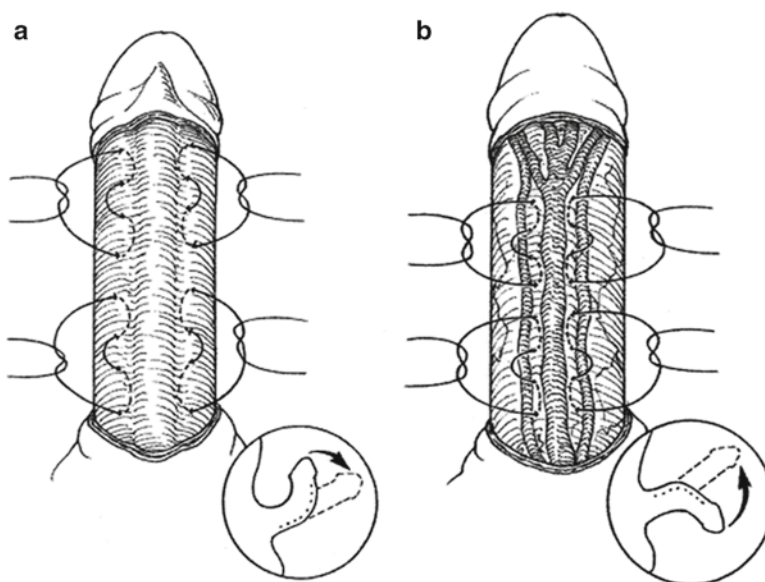


Fig. 17.4 16-dot Procedure: Planned suture entry sites marked with pen. Erection attained throughout operation with papaverine. (a) 16-dot repair of ventral curvature. Peridorsal vein sutures without dissection of neurovascular bundles. (b) 16-dot repair of dorsal curvature with periurethral sutures of 2-0 Ticron. Procedure performed

with midline raphe incision (circumcising incision used for illustration purposes). Reprinted from *The Journal of Urology*, 167, Gholami, S.S. and Lue, T.F. Correction of penile curvature using the 16-dot plication technique: A review of 132 patients, pages 2066–2069, 2002, with permission from Elsevier

Plaque Excision/Incision With Tissue Grafting

The techniques of plaque excision and plaque incision are discussed together as both methods have shown comparable results, and there are no studies directly comparing the two techniques. The basic concept involved in the technique of plaque incision or excision with tissue grafting is the elimination of the angulation by the removal of the plaque and filling the defect at the plaque site with a graft to achieve penile straightening. Figure 17.5 shows incision of the plaque prior to grafting. A synthetic or an autologous graft may be used. Synthetic grafts are known to be less elastic than autologous grafts with a higher predisposition of the recipient to wound infection. An example of an autologous graft is the venous graft providing the greatest elasticity, durability, and less risk of infection compared to synthetic grafts. However, there is some morbidity associated with harvesting. Patient satisfaction has been reported at 86–92% with a penile straightening rate of 59–96% [27]. It should be noted that there has been some skepticism in the long-term outcomes of these techniques in terms of patient satisfaction and durability when a vein graft is used. Follow up studies over a 5-year period have shown a decrease in patient satisfaction from 86

Summary Points

- Penile plaque excision/incision with tissue grafting theoretically eliminates the curvature caused by the plaque by filling the site of plaque defect with a graft thus straightening the penis.
- Penile plaque excision/incision with tissue grafting affords a patient satisfaction of 86–92% and the rate of penile straightening of 59–96%.
- Patient satisfaction may decrease to 60% at 5 years due to ED and perceived penile shortening.
- Erectile dysfunction is a serious adverse effect of graft procedures and should be thoroughly discussed with the patient prior to surgical intervention.

to 60% due to erectile dysfunction (22.5%) and penile shortening (35%) [27, 34]. *Perceived* penile shortening was reported in 40% of patients; however, there were no differences between the mean preoperative penile length and the 32-month postoperative measured penile lengths [35]. The psychological trauma of

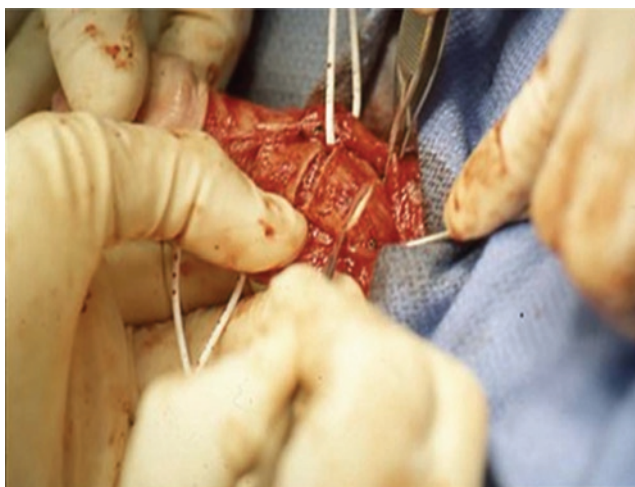


Fig. 17.5 Plaque incision prior to grafting. Reprinted with permission from Tran, V.Q., Kim, D.H., Lesser, T.F., and Aboseif, S.R. Review of the surgical approaches for

Peyronie's disease: Corporeal plication and plaque incision with grafting, *Advances in Urology*, Vol. 2008, Article ID 263450, 4 pages, 2008. doi:10.1155/2008/263450

new-onset postoperative erectile dysfunction in a previously potent patient is such that we rarely resort to graft use unless absolutely necessary.

Penile Prosthesis

The use of penile prostheses in the treatment of Peyronie's disease is quite unique as this is the only technique that simultaneously addresses the two key components of patient satisfaction in males with PD: penile straightening and erectile function. The etiology of ED in males with PD may be a direct result of veno-occlusive disorders (83.9%) or arterial blood flow abnormalities (48.2%) [36]. The operative techniques discussed thus far were all directed at penile straightening in men with PD who presumably do not have preexisting erectile dysfunction. For men with PD who suffer from concomitant ED, however, penile prosthesis surgery can achieve penile straightening through mechanical stretching of the fibrotic tunica albuginea lining the corpora and simultaneously providing a rigid penis for satisfactory sexual intercourse. From a mechanical standpoint, successful outcomes depend on the prosthetic cylinders providing adequate intrinsic rigidity without distal expansion [37]. To fulfill these criteria, the Coloplast Titan penile prosthesis or the American Medical Systems CX type implants are better suited than other models. A high pressure cylinder, such as the Coloplast Titan or AMS 700CX, has higher tensile strengths and allows penile modeling without cylinder aneurysm formation [38]. The cylinders are inserted using standard techniques and principles. In cases of mild curvature, the process of corporal dilation and cylinder placement alone can result in penile straightening. When significant penile curvature persists after cylinder placement as in Fig. 17.6, then the technique of modeling as originally described by Scott and later modified by Wilson and Delk can be employed as follows: the cylinders are inserted into the lumen of the corpora via a longitudinal incision in both corpora

(corporotomy). The corporotomies are closed, the cylinders are inflated to full rigidity and the tubings are clamped [36, 37]. The penile plaques are ruptured by forcibly bending the penis opposite to the curve of the penis and holding for 90 s. The clamps are removed, additional fluid added to the cylinders, clamps reapplied, corporotomies protected, and the modeling procedure is repeated for another 90 s. Two modeling sessions are usually adequate and if a residual curvature of greater than 20° is noted, incision of the central portion of the plaque may be carried out down to the exposed cylinder with modeling repeated or a Nesbit or graft procedure performed [37]. Complications related to penile prosthesis insertion with modeling may include urethral perforation (3%), prosthesis infection (3%), and failure of modeling (8%). We have had great success with this approach and in the original publication, penile straightening was achieved in 86% of males with PD [38]. The results for penile prosthesis insertion alone were reported by Montorsi and colleagues who found that after AMS 700CX insertion alone, penile straightening was achieved in 70% while penile shortening was noted by 30%. The authors reported a 79% patient satisfaction rate and 75% partner satisfaction rate [39]. It is difficult to assess if the reported penile shortening is that seen in a large number of all prosthesis cases or a phenomenon restricted to this particular cohort of patients. Levine and colleagues developed an algorithm for the surgical management of patients with ED and PD that included molding followed by tunica incision for insufficient straightening [40]. In cases where the tunical defect is greater than 2 cm, polytetrafluoroethylene (PTFE) patch grafting can be performed to prevent prosthesis cylinder herniation [40]. Penile prosthesis insertion was performed with modeling in 54%, penile prosthesis and plaque incision in 26%, and penile prosthesis with plaque incision and PTFE in 20%. The authors reported that 100% of their patient population achieved penile straightening, 9% had temporary (<8 months) decreased penile sensation, 7% had penile shortening <2 cm, 2% had delayed

Fig. 17.6 Penile curvature in PD male after prosthesis insertion but prior to penile molding. In this case, the degree of preexisting curvature was such that modeling was needed as the prosthesis insertion alone would not correct the angulation



ejaculation, and 2% developed prosthesis infection [40]. Most experts agree that penile prosthesis insertion with or without modeling is ideally suited to the patient with Peyronie's disease who has concomitant ED.

Summary Points

- Penile Prosthesis implantation with or without modeling may be optimal in males with ED and Peyronie's disease.
- Penile straightening can be achieved in 86–100% of patients by employing penile prosthesis insertion with modeling, plaque incision, and PTFE graft.
- The technique of modeling carries the risk of urethral perforation (3%), prosthesis infection (3%), and failure of modeling (8%).
- Prosthesis insertion alone achieves penile straightening in 70% and penile shortening in 30% with a 79% patient satisfaction rate and a 75% partner satisfaction rate.

Table 17.1 summarizes the outcomes of patients with Peyronie's disease.

Conclusion

Peyronie's disease and its variable effect on male sexual function have prompted numerous researchers and clinicians to seek cure through medical and surgical interventions since its discovery in the sixteenth century. To date, most medical and herbal therapies have achieved sub-optimal penile straightening and satisfaction rates in the vast majority of patients. In those with failed medical or conservative therapies, surgical interventions have shown great promise with excellent results. Spontaneous resolution of Peyronie's disease signs and symptoms may be observed in a small number of patients. With increased knowledge of the natural history of Peyronie's disease, surgeons are now allowing time for the quiescent phase to begin prior to any surgical intervention. Once the disease has reached its stable phase with documented failure of medical or minimally invasive interventions, the surgical option most fitting to the patient can be undertaken. A detailed discussion of all options, expected outcomes, patient expectations, and associated complications should be reviewed. The various plication procedures described in this review are best suited for males with curvatures $<60^\circ$ who do not have extensive plaques,

Table 17.1 Summary of outcomes in PD patients treated with Nesbit procedures, Plication procedure, Plaque manipulation with grafting and Penile prosthesis

	Sensory dysfunction	Risk of ED and/or impotence	Patient satisfaction	Penile straightening	Shortening of penis
Nesbit procedures	<2%	<2%	79–83%	79–93%	37–67%
Plication	3–48%	7–40%	90%	71%	41–90%
Tissue graft with plaque excision/incision	<5%	5–10%	85–92%	59–96%	40%
Penile prosthesis	<5%	–	79–88%	86–100%	<30%

Some differences are attributed to inhomogeneous patient populations in the studies with variable inclusion criteria

hourglass deformity, or an initial short penile length. Graft procedures are best suited for males with complex curvature and deformities, but the patient should be carefully counseled about the high possibility of postoperative ED. Penile prostheses are the preferred option for males with concomitant ED and PD. Excellent outcomes and satisfaction rates are achievable for nearly all patients with PD by adhering to sound surgical principles and thorough patient counseling.

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Chapter 18

Priapism: Medical and Surgical Therapy

Belinda F. Morrison and Arthur L. Burnett

Abstract Priapism is a rare disorder, typified by a persistent penile erection, which is usually painful. Though rare, it is seen commonly in certain patient populations, e.g. sickle-cell disease. Priapism is a true urological emergency. Unfortunately, due to the general rarity of the disorder, many patients delay in seeking medical attention and medical practitioners may also be delayed in initiation of proper management. Priapism can also be quite a frustrating disorder to manage, as available treatment modalities may be unsuccessful in averting the dreaded complication of erectile dysfunction. Much has been learnt recently about the molecular pathophysiology of priapism. This may serve, in the future, as an opportunity for prophylaxis in patients with recurrent episodes of priapism. In addition, new innovations are being described in distal penile shunts, which may improve success rates of treatment. The current chapter outlines the etiology and pathophysiology of priapism, guidelines for management, and evolving treatment modalities.

Keywords Priapism • Penile erection • Compartment syndrome of penis • Urological emergency • Ischemic priapism • Non-ischemic priapism • Stuttering priapism • Phosphodiesterase type 5 inhibitor • Cavernosal blood gas analysis •

Penile aspiration • Penile shunts • Intracavernosal sympathomimetics • Sickle-cell disease

Introduction

Priapism is defined as a persistent penile erection that continues beyond, or is unrelated to, sexual stimulation [1]. It is a pathological process that must be distinguished from normal sleep-related erections (see Fig. 18.1). Priapism generally involves the paired corpora cavernosa. However, there have been reports of involvement of the corpus spongiosum [2]. There have also been reports of involvement of the clitoris, typically in women with advanced pelvic malignancies or on trazodone [3]. Priapism is a true urological emergency which is a consequence of altered haemodynamics in the penile vasculature. It is essentially a compartment syndrome of the penis. As in compartment syndromes elsewhere in the body, a critical time period before permanent pathological sequelae, result is given. This time period is 4 h; however, it is not unusual to find patients presenting with longer episodes without permanent tissue damage [2].

As in many conditions in medicine, the name “priapism” has a historical origin. This name is credited to an ancient Greek god, Priapus. He was depicted as having an abnormally large phallus and as such the name priapism was given. It is said that a spell was cast upon Priapus while in his mother’s womb. He grew up with shepherds on earth. In Greek mythology he is known as the fertility god, protector of livestock, fruits,

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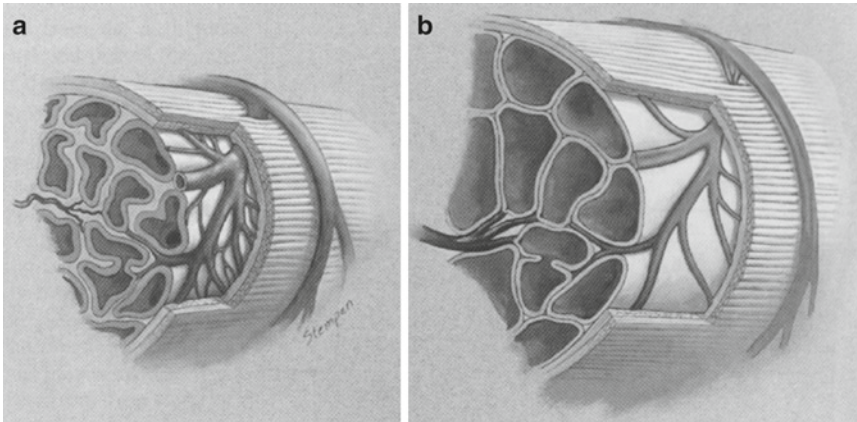


Fig. 18.1 Mechanism of penile erection. (a) In the flaccid state, the arteries, arterioles, and sinusoids are contracted. The intersinusoidal and subtunical venular plexuses are wide open, with free flow to the emissary veins. (b) In the

erect state, the muscles of the sinusoidal wall and the arterioles relax, allowing maximal flow to the compliant sinusoidal spaces. Most of the venules are compressed between the expanding sinusoids

plants, and gardens. Many statues of this god were erected in ancient Greece, and Priapus was seen as a guardian deity [4].

Epidemiology

Several limitations exist in defining the true incidence of priapism in the population. Many patients with priapism may not present due to ignorance about the disorder or spontaneous resolution, which leads to an underestimate of the frequency of the condition. In addition, several population studies are limited by their retrospective nature and diagnosis misclassification. Nevertheless, Eland et al. found an overall incidence in the Netherlands of 1.5 per 100,000 person years (the number of patients with a first episode of priapism divided by the accumulated person-time in the study population) [5].

Certain populations deserve mention due to their high risk of developing priapism. Patients with sickle-cell disease are well studied, and prevalence rates of priapism are reportedly as high as 42% [6]. The probability of experiencing priapism in patients with sickle-cell disease, by age 20 is 89% [7]. The use of intracavernosal therapy for erectile dysfunction has led to an increase in the incidence rates in certain populations.

Etiology

A wide variety of conditions have been associated with priapism (see Table 18.1). These may be classified as hematologic dyscrasias, erectogenic pharmacotherapy, non-erectogenic pharmacotherapy, neurological disorders, trauma, solid organ neoplasms, and idiopathic disorders.

Hematological Dyscrasias

Priapism is a major problem in patients with hemoglobinopathies. Homozygous sickle-cell disease (HbSS) has a strong association with priapism. This disease is quite common in persons of African or Mediterranean ethnicity. Sickle-cell disease occurs in 1 in 150 live births in Jamaica, with the homozygous variant (HbSS) occurring in 1 in every 300 live births [8]. Emond et al. noted a prevalence of priapism of 42% in Jamaican patients with sickle-cell disease, with a median age of onset of 21 years [6]. The underlying risk is thought to be due to abnormal sickle-shaped red blood cells obstructing venous drainage of the penis. These patients tend to have two patterns of presentation. They may present with major attacks, lasting as long as 24 h, or with brief, “stuttering” attacks which are usually

Table 18.1 Common etiologies of ischemic and non-ischemic priapism

Ischemic priapism
<i>Hematological dyscrasias</i>
Hemoglobinopathies, e.g. sickle-cell disease, thalassemia, Hb Olmsted
Thrombophilic states, e.g. lupus, protein C deficiency, polycythemia
Anticoagulant use, TPN, Erythropoietin, hemodialysis patients
Amyloidosis, Fabry's disease, asplenism, Glucose-6-phosphate dehydrogenase deficiency, glucose phosphate isomerase deficiency
Hematological malignancies, e.g. leukemia, lymphoma, multiple myeloma
<i>Erectogenic pharmacotherapy</i>
Papaverine, intracavernosal, and transurethral PGE1, phentolamine
Phosphodiesterase type 5 inhibitors, e.g. sildenafil
<i>Non-erectogenic pharmacotherapy</i>
Anti-hypertensive, e.g. guanethidine, prazosin, hydralazine
Antidepressants – typical and atypical
Cocaine, alcohol, FK506
Tamsulosin, alfuzosin
<i>Neurologic disorders</i>
Lumbar disc disease, cauda equina syndrome
Seizures, cerebrovascular disease, syphilis, brain tumors
Anesthesia – regional, general
<i>Solid organ malignancies</i>
Urological – penile, urethral, bladder, prostate, testis
Non-urological – rectal, renal
<i>Non-ischemic</i>
Trauma
Vasoactive drugs
Penile revascularization surgery
Neurologic conditions
<i>Idiopathic</i>

nocturnal, multiple and last for <3 h. The latter usually did not result in erectile dysfunction. Emond reported a 25% rate of erectile dysfunction in patients who have had priapism [6]. Though not commonly seen, priapism may also be seen in the sickle-cell trait (HbAS) or other combination genotypes, e.g. Hb Olmsted [6, 9]. Priapism may also be seen in thalassemia [10].

Thrombophilic states, as may be seen in patients with lupus, protein C deficiency, and polycythemia, have been associated with priapism [11–13]. Priapism may be seen paradoxically in

patients treated with the anticoagulants warfarin and heparin [14]. High concentration fat emulsion (20%) in total parenteral nutrition may precipitate priapism [15]. The etiology in this case may be due to a hypercoagulable state with fat emboli or direct cellular effects by the fat contents. Priapism may be seen in patients on hemodialysis treated with heparin and may represent a rebound phenomenon [16]. Fabry's disease is a genetic disorder of glycosphingolipid metabolism, presenting with renal insufficiency and priapism [17]. Other associated conditions include amyloidosis and glucose phosphate isomerase deficiency [18, 19].

Priapism is also seen in hematological malignancies such as leukemias, lymphomas, and multiple myeloma [20–22]. Asplenism and erythropoietin use has been associated with priapism [23, 24]. Priapism has also been associated with glucose-6-phosphate dehydrogenase deficiency [25].

Erectogenic Pharmacotherapy

With the introduction of intracavernosal treatment for erectile dysfunction, the incidence of priapism has increased. Nieminen and Tammala reported that the etiology of priapism in 21% of patients in their series was due to intracavernosal therapy for erectile dysfunction [26]. Intracavernosal papaverine, prostaglandin E1, and transurethral prostaglandin E1 have been associated with minor risks of priapism [27, 28]. Priapism resulting from the combination of alprostadil, papaverine, and phentolamine has been reported in 0.9% of users [29]. Several case reports have been published on the association of priapism with sildenafil use [30]. It is thought that younger patients with better baseline erectile function, patients with overt neurological disease, and patients without significant cardiovascular disease were more susceptible to priapism [31].

Non-erectogenic Pharmacotherapy

Priapism has been associated with several pharmaceuticals; however, the antihypertensives,

antipsychotics – conventional and atypical, and antidepressants are best quoted. Antihypertensives such as guanethidine, prazosin, and hydralazine have been implicated in causing priapism [32, 33]. Centrally acting agents such as trazodone, thioridazine, chlorpromazine, clozapine, quetiapine, haloperidol, and risperidone may cause priapism [34–38]. It is thought that the mechanism is via α -adrenergic antagonism.

Cocaine-induced priapism has been seen with topical and oral use [39]. Alcohol has been implicated in priapism [40].

There are also recent reports of the association of priapism and tamsulosin and alfuzosin [41, 42]. Tacrolimus (FK506) is said to be a risk factor for priapism [43]. Exogenous androgens may also be etiological [44]. Priapism has also been associated with scorpion toxin [45].

Neurological Disorders

Priapism has been seen in patients with lumbar disc disease, herniated disc, or cauda equina syndrome [46]. Decompression can potentially relieve symptoms. It may also be seen in patients with cerebrovascular disease, seizure disorders, syphilis, brain or spinal cord tumors, and brain and spinal cord trauma [47].

Regional and general anesthesia may also cause priapism [48].

Trauma

Blunt penile or perineal trauma may lead to an arterial-lacunar fistula, which bypasses the control of the helicine arteries [49, 50]. This typically leads to high-flow priapism. The venous system is unaffected and the condition is typically painless. This may also be seen in cases of traumatic needle insertion during intracavernosal therapy [51].

Solid Organ Malignancies

Penile, urethral, bladder, prostate, and testicular tumors may lead to priapism by malignant

infiltration of the corpora cavernosa and venous obstruction [52–54]. Metastatic rectosigmoid and renal carcinoma may also predispose to priapism [55, 56].

Idiopathic

Priapism for which there is no discernible cause may be seen in as much as 50% of presentations [57]. This can be quite frustrating.

Pathophysiology

There has been a dramatic shift in the theory of the pathophysiology of priapism moving from a solely vascular abnormality to the critical role of molecular dysfunction.

Significant contributions to the understanding of priapism must be credited to Frank Hinman Sr [47]. He classified priapism as mechanical or nervous. The former, he thought, was due to “thrombosis of the veins of the corpora.” Pelvic abscesses, penile tumors, perineal or genital injuries, and hematological dyscrasias were examples of this type. This type of priapism was said to account for 80% of cases. The nervous type could be seen in conditions such as syphilis, brain tumors, epilepsy, intoxication, and brain and spinal cord injury.

Continuing the theory of priapism and altered blood flow in the penis, Frank Hinman Jr hypothesized that the etiology of idiopathic priapism was vascular stasis and reduced venous outflow [49]. Hinman found dark, viscous deoxygenated blood after aspiration in patients with priapism. This theory was supported by similar findings in patients with sickle-cell disease, hemodialysis patients, trauma, or malignant infiltration of the corpora cavernosa. He theorized that the ischemia created a vicious cycle of combined deoxygenated blood (hypoxic and hypercarbic) associated with venous congestion, which increased the deformity of red cells.

Burt noted bright red blood after incision and irrigation of the corpora in a patient with priapism after traumatic coitus [50]. This increased

arterial inflow in priapism was later classified by Hauri as high flow priapism [58]. This non-ischemic priapism was recognized to be the result of a fistula between the cavernous artery and lacunar space. This allowed blood to bypass the high resistance in the helicine arteries.

Molecular Pathology

However, the rheologic changes previously theorized could not completely explain all types of priapism that were seen. This led to extensive research, which recognized that ischemic priapism was due to an imbalance of vasoconstrictive and vasodilatory forces in the corpora cavernosa. Vasoconstrictive factors included the RhoA/Rho kinase pathway, and the vasodilatory forces include the nitric oxide (NO) pathway [59, 60].

A normal erection requires an intact central nervous system, peripheral nervous system, penile arterial supply, and trabecular smooth muscle. Erection involves a delicate interplay of neuronal stimulation, smooth muscle relaxation, increased arterial inflow, and reduced venous outflow [60]. NO plays an important role in the regulation of normal erections. NO released from the endothelium (eNO) or nerve endings (nNO) diffuses to the smooth muscle and binds to guanylate cyclase. This leads to the conversion of

guanosine triphosphate (GTP) to 3,5 cyclic guanosine monophosphate (cGMP). Cyclic GMP acts as a second messenger and binds with a cGMP-dependent protein kinase which exerts itself on ion channels (see Fig. 18.2). Ultimately, smooth muscle intracellular calcium levels are lowered and this inhibits myosin light chain kinase, thus inhibiting the cross linking of actin and myosin. This leads to smooth muscle relaxation and vasodilatation. cGMP-dependent protein kinase also regulates smooth muscle contraction via the RhoA/Rho-kinase pathway. The RhoA/Rho kinase pathway is a calcium independent pathway, which is the predominant mechanism controlling corporal smooth muscle contraction [59]. RhoA is a member of the Ras low molecular weight of guanosine triphosphate-binding proteins, and mediates agonist-induced activation of Rho-kinase [60]. Rho-kinase phosphorylates and reduces the activity of myosin phosphatase, contributing to myosin light chain kinase phosphorylation. cGMP-dependent protein kinase also directly phosphorylates RhoA and downstream effectors of the RhoA/Rho kinase pathway [59]. The net effect is smooth muscle contraction. The activities of cGMP are kept under balance by its degradation by the enzyme phosphodiesterase type 5 (PDE5).

However, cGMP is produced in lower quantities after episodes of priapism, which destroy the endothelium and reduces the production of eNO.

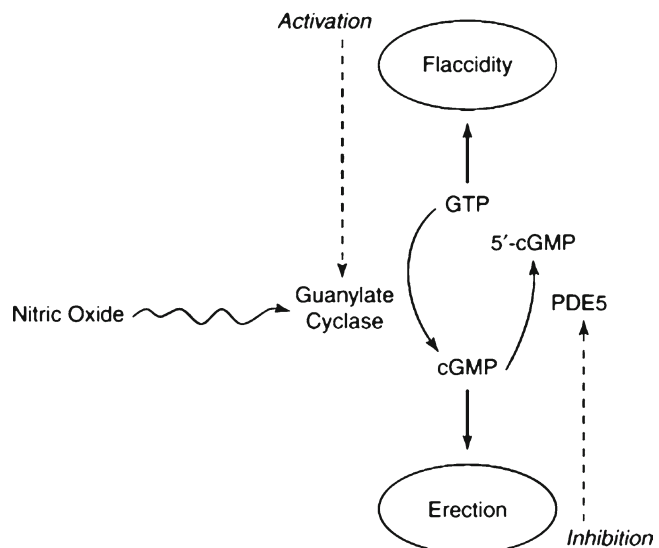


Fig. 18.2 Diagrammatic representation of the nitric oxide signaling pathway in the penis

This reduces the set point of PDE type 5 function. Therefore, with sexual stimulation or sleep-related erections, cGMP levels rise significantly due to insufficient production and activity of its metabolizing enzyme PDE5. Rho kinase activity is also reduced, which leads to less vasoconstrictor activity. The net result is unregulated vasodilatation and persistent erection. It has been demonstrated that transgenic sickle-cell mice have reductions in penile NO/cGMP signaling leading to deficient PDE5 and hence enhanced erectile responses [61]. There is reduced production of eNO, although there is increased sensitivity to nNO produced with sexual stimulation. This combined with downregulation of PDE5, leads to persistent erections in sickle-cell disease.

There is no clear answer as to what incites episodes of ischemic priapism; however, it is certainly known that there are molecular changes after repeated episodes. When corporal smooth muscle is exposed to hypoxia *in vitro*, apoptosis results and the tissue no longer responds to alpha adrenergic stimulation [62]. Experimental models have demonstrated an increase in reactive oxygen species in tissue after reperfusion after episodes of priapism. This may likely cause smooth muscle injury, which impairs adrenergic response and leads to persistent vasodilatation.

TGF- β which is responsible for the production of collagen normally is upregulated in the penis after priapism due to hypoxia [63]. This may explain the eventual fibrosis that is seen after prolonged episodes. Reperfusion after priapism leads to lipid peroxidation due to reactive oxygen metabolites. In addition, prostacyclin production, an inhibitor of platelet aggregation is reduced.

Certainly the molecular mechanisms responsible for sickle-cell disease associated priapism are becoming clearer. It is possible that there are more mechanisms in other etiological types of priapism, or potentially a combination of mechanisms. Hematological dyscrasias, including sickle-cell disease impair NO regulation, which affects corporal functioning. In addition, eNO levels are reduced by poor vascular function and endothelial damage. Further studies may be able to elucidate other mechanisms of the pathophysiology of priapism.

Pathology

Gross pathologic as well as microscopic and biochemical changes are evident after episodes of priapism. Quite obvious is the deformed megaphallic penis, typically seen in patients with sickle-cell disease after repeated episodes of priapism [64]. As described by Hinman, this grossly fibrotic penis prevents the normal compliance of the sinusoidal tissue and restricts inflow of blood during an erection.

Spycher and Hauri described ultrastructural changes in the penis after episodes of ischemic priapism [65]. After 12 h, there is trabecular interstitial edema. At 24 h, there is denudation of the sinusoidal endothelium with adherence of thrombocytes to the exposed basement membrane. After 48 h, thrombi form in the sinusoidal spaces and there is necrosis of smooth muscle cells and transformation of these cells to fibroblast-like cells.

As early as 4 h after an episode of ischemic priapism, aspirated corporal blood may demonstrate hypoxia, hypercarbia, and acidosis. Hypoxia, acidosis, and glucopenia impair corporal smooth muscle function. These effects lead to irreversible changes after 4 h of prolonged priapism.

Classification

Priapism may be broadly classified as ischemic or non-ischemic, with respect to haemodynamics and etiology (see Table 18.2). This classification allows for appropriate management and determining prognosis. There are several variants of priapism which deserve special mention, and these include stuttering, neurogenic, refractory, idiopathic, and drug-induced.

Ischemic Priapism

Ischemic priapism is also referred to as low-flow or veno-occlusive priapism. It is typified by poor

Table 18.2 Differentiating ischemic from non-ischemic priapism

Ischemic priapism	Non-ischemic priapism
Painful	Painless
Common	Less common
Surgical emergency	May be observed
Corporal tenderness	Non-tender corpora
Rigid corpora	Semi-rigid corpora
No history of trauma	History of perineal trauma
Abnormal cavernous blood gases	Normal cavernous blood gases
Reduced or absent cavernous blood flow	Normal or increased cavernous blood flow

or absent flow within the corpora cavernosa associated with poor venous outflow. Blood within the corpora is diagnostically hypoxic, hypercarbic, and acidotic. This represents a true compartment syndrome of the penis and constitutes a surgical emergency. Patients typically present with pain, and clinical examination reveals a tender rigid corpora. This appears to be the commonest type of priapism seen with numerous examples. Unfortunately, this type of priapism carries with it a high risk of corporal fibrosis and ultimately erectile dysfunction if not relieved quickly.

Non-ischemic Priapism

Non-ischemic or high flow priapism is less commonly seen. It is typically seen in cases of blunt penile or perineal trauma, but may also be seen after intracavernosal injections and Fabry's disease. Non-ischemic priapism is typified by high arterial inflow into the corpora cavernosa without obstructing venous outflow [50, 58]. Therefore, blood aspirated from the corpora does not demonstrate the extreme metabolic changes as observed in ischemic priapism. The corpora are usually non-tender and semi-rigid, and patients do not generally report pain. Emergency treatment is not required in these cases, and corporal fibrosis is not a complication.

Stuttering Priapism

Hinman described "acute transitory attacks" of priapism in 1914 [47]. These were brief episodes of ischemic priapism, usually nocturnal, lasting for 3 h or less. These episodes had a low risk of permanent erectile dysfunction. Patients with sickle-cell disease commonly report these episodes. Emond reported that 28% of patients with stuttering episodes subsequently experienced a major attack of priapism [6]. Since this type of priapism will not usually result in permanent erectile dysfunction, it may serve as an opportunity for prophylaxis for this group of patients.

Neurogenic Priapism

An intact central and peripheral nervous system is required for normal erections. Therefore, it is quite possible that neurological disorders can give rise to priapism. This category was first described by Hinman as nervous in aetiology [47]. However, it is seen in patients with spinal cord injury, cauda equina syndrome, and even after hanging. Interestingly, after hanging a regular practice by the executioner was to examine for priapism to determine if the act was complete.

Refractory Priapism

Refractory priapism is usually seen in patients with ischemic priapism who have incision or aspiration of the corpora. An immediately recurrent state of priapism occurs with rapid arterial refilling [49]. This has been corroborated by blood gas analyses of the aspirated blood and also via color Doppler studies. This has been demonstrated in patients with sickle-cell disease and Fabry's disease [17, 66].

Idiopathic Priapism

Up to 50% of cases of priapism have no documented cause [57]. Many of these episodes are

preceded by sleep or are erections that are sustained after sexual activity.

Drug-Induced Priapism

Many categories of medications can lead to priapism. They deserve a special category because of their importance.

Natural History

The natural history of priapism is that of permanent resolution or progression to recurrent episodes. Either of these may or may not be associated with permanent erectile dysfunction. Appropriate intervention is therefore required to prevent these sequelae.

Ischemic priapism may resolve spontaneously to a flaccid, non-painful state. In some cases, there may be an associated megalophallus due to repeated episodes of priapism. Also, persistent edema may lead to the appearance of a larger penis. The risk of long-term erectile dysfunction increases with increasing duration of the episode of priapism. A review of published cases of ischemic priapism managed with systemic therapy alone found that 35% of patients had erectile dysfunction. Pryor documented that 90% of men with ischemic priapism over 24 h had erectile dysfunction [67]. El-Bahnasawy documented preserved erectile function in only 43% of patients with a median duration of priapism of 48 h [68]. In patients with sickle-cell disease Emond reported partial and complete impotence in 20% and 16% respectively, of patients having priapism [6]. Similar results of a 29% incidence of erectile dysfunction were reported in patients with sickle-cell disease by Adeyoku et al. [69].

Non-ischemic priapism may also resolve spontaneously or persist unresolved for a long period of time. The former is more common and seen in as many as 62% of these cases [1]. At resolution, patients are pain-free and the

penis is flaccid. Unlike ischemic priapism, these episodes are not generally complicated by erectile dysfunction. However, there have been reports of erectile dysfunction in 20–33% of these cases [1].

Recurrent episodes of stuttering priapism usually resolve spontaneously. However, stuttering priapism may progress to major acute episodes. In sickle-cell disease, major episodes are preceded by prior episodes, single or more commonly, stuttering in 61% of cases [6]. These episodes are also usually spared of the complication of erectile dysfunction.

Diagnosis

Establishing the diagnosis of priapism is largely a clinical one and involves the history and physical examination of the patient [1]. However, a combination of these, and laboratory and radiological tests are important to help differentiate ischemic from non-ischemic priapism. This will allow for timely and emergency management of the former. In addition, the etiological or predisposing factors may be determined, which may allow for patient education and possible prophylaxis.

History

It is important to determine the duration of the history of priapism. The presence or absence of pain must be ascertained. Prior episodes of priapism and prior successful or unsuccessful medical, surgical, or radiological interventions must be sought. Baseline erectile function must be objectively evaluated. Presence of any established etiological factors such as sickle-cell disease or other hemoglobinopathies, solid tumors, hematological disorders, or medications must be determined. Use of any erectogenic drugs – oral or intracavernosal or illicit drugs must be asked. History of perineal or penile trauma must be ascertained.

Clinical Examination

Clinical examination should be general and focused. The general examination should look for supporting signs of any possible etiological factor, e.g. lymphadenopathy in solid organ malignancies or stigmata of sickle-cell disease. This should be brief and perhaps deferred until after relief of pain in the patient with ischemic priapism. The focused examination of the genitalia should document rigidity of the paired corpora cavernosa or the corpora spongiosum and glans penis, if present. The strength of the rigidity helps to differentiate ischemic from non-ischemic priapism. Scars from prior surgical interventions (aspirations or shunts) may also be seen. The abdominal, pelvic, and rectal exam may reveal underlying malignancies. The penis and perineum must also be examined for signs of trauma.

Laboratory Evaluation

The laboratory evaluation should include a complete blood count, reticulocyte count, sickle test or hemoglobin electrophoresis, blood film (peripheral blood smear), urine toxicology and drug screen, and penile aspirate blood gas analysis [1].

The complete blood count and blood film are invaluable in determining hemoglobinopathies and hematological malignancies. Specific attention must be paid to the differential and complete white cell count and platelet count. Abnormal or sickled cells may be seen on blood film. An elevated reticulocyte count is seen in hemoglobinopathies and indicates an increased bone marrow turnover. The sickle test and hemoglobin electrophoresis should be done in all patients and not excluded due to ethnicity. It is well documented that persons of African and Mediterranean ethnicity are at high risk for developing sickle-cell disease; however, the condition may also be seen in low risk groups. Due to the delay in obtaining results of the electrophoresis, this may be deferred in the acute setting and the sickle test done. Screening for psychoactive drugs such as

antipsychotic and antidepressants as well as for illicit drugs, e.g. cocaine should be done.

Cavernosal blood in ischemic priapism is dark and hypoxic as opposed to the bright red blood in non-ischemic priapism. The blood gas analysis is diagnostic for both. In ischemic priapism, the cavernosal blood gas analysis usually has a PO_2 of <30 mmHg, PCO_2 of >60 mmHg, and $pH <7.25$. The cavernosal blood gas analysis in non-ischemic priapism shows a PO_2 of >90 mmHg, a PCO_2 of <40 mmHg, and $pH 7.40$, consistent with normal arterial blood in room air. The flaccid penis has a cavernosal blood gas similar to normal mixed venous blood which has a PO_2 of 40 mmHg, PCO_2 of 50 mmHg, and $pH 7.35$ [1].

Radiological Evaluation

Color duplex ultrasonography is effective in distinguishing ischemic from non-ischemic priapism [1]. In ischemic priapism, color duplex ultrasonography identifies reduced or no cavernosal arterial blood flow. However, in non-ischemic priapism, there is increased penile cavernosal arterial velocity [70]. The study is performed in the frog-leg position. This enables the perineum as well as the penis to be scanned. This allows for identification of any arterial-lacunar fistula or pseudoaneurysm. Ultrasound may substitute for cavernosal blood gas analysis in the acute setting, if there is no delay in obtaining the investigation.

The use of penile arteriography has largely been supplanted by color duplex ultrasonography. Penile arteriography has value in patients with non-ischemic priapism who are scheduled for embolization.

Penile scintigraphy and cavernosography have been described, but are not used widespread.

Treatment

The aim of treatment of priapism is to relieve symptoms (pain and erection) in a timely fashion and potentially prevent long-term erectile

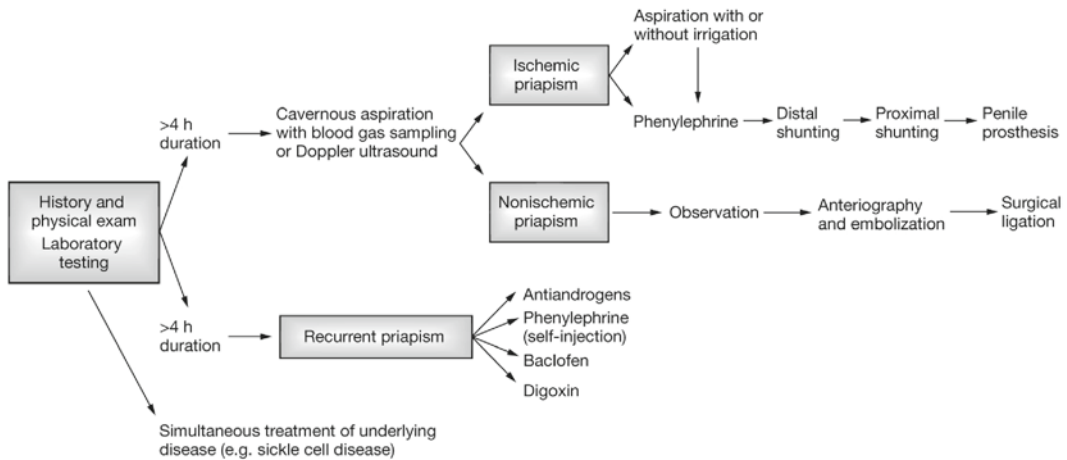


Fig. 18.3 Treatment algorithm for priapism. Management centers on the distinction between forms of priapism and the duration of priapism. Prompt and accurate diagnosis is, therefore essential

dysfunction. Treatment should also attempt to provide prophylactic measures for patients with recurrent episodes (see Fig. 18.3).

Treatment may therefore be subdivided as follows:

1. Ischemic
 - (a) Aspiration with/without irrigation
 - (b) Intracorporal sympathomimetic administration
 - (c) Penile shunts – distal; proximal
 - (d) Penile Prosthesis Surgery
2. Non-ischemic
 - (a) Observation
 - (b) Arterial embolization
 - (c) Surgical ligation
3. Treatment of systemic disease, e.g. sickle-cell disease
4. Prophylactic treatment
5. Miscellaneous therapies

Ischemic Priapism

Ischemic priapism is a surgical emergency and should be treated as such. Initial assessment should begin with inserting a 19- to 21-gage butterfly needle into the corpora and aspirating blood. The appearance and blood gas analysis confirms the diagnosis. Treatment should be in a stepwise approach as outlined below, beginning with intracavernosal

aspiration and progressing to surgical shunting only if other methods fail [1]. Patients should always be advised before attempting treatment about their diagnosis and the potential for erectile dysfunction with and without treatment.

Aspiration With/Without Irrigation

Aspiration is achieved by inserting a needle into the corpora cavernosa with an aim of reducing intracorporal pressures. Before attempting intracavernosal therapy, anesthesia may be achieved locally via a dorsal nerve block or penile block. Under aseptic techniques, aspiration may be done transglanularly or perpendicularly into the penile shaft (using a 16- or 18- gage angiocatheter). The former is more favorable as there is minimal hematoma post procedure and the tract between the glans and corpora may remain patent for some time after the needle is removed. Aspiration may be attempted with irrigation of the corpora with normal saline. This may be done through the initial angiocatheter [1]. Alternatively, Chung et al. described placing two 18-gage needles into the corpora in the perineum and another in the glans to achieve maximum irrigation [71]. Saline is instilled proximally and removed distally. The efficacy of aspiration with or without irrigation ranges from 24–36% [1].

Intracorporal Sympathomimetic Administration

Intracorporal sympathomimetics work by causing α mediated vasoconstriction within the corpora. Several agents are potentially available and include epinephrine, norepinephrine, phenylephrine, ephedrine, and metaraminol. Sympathomimetics have side effects if released into the systemic circulation. These are chiefly α and β mediated effects. Some may also stimulate endogenous norepinephrine release. Phenylephrine is an α selective adrenergic agonist. It is the most widely used intracorporal agent as it has less adverse effects and a quoted efficacy of 65% [1]. The drug is diluted in normal saline to 100–500 $\mu\text{g}/\text{ml}$ and 100–200 μg is given in repeated doses every 5–10 min intracavernosally to a maximum of 1,000 μg . The patient's pulse, blood pressure, oxygen saturation, and electrocardiogram should always be monitored during this administration. Subjective response should be assessed during the procedure by observing the patient's complaint of pain and level of detumescence. Resolution rates range from 43–81% [1]. Potential side effects include pain, injection site hematoma, and fibrosis. Cardiovascular effects include acute hypertension, headache, reflex bradycardia, tachycardia, palpitations, and cardiac arrhythmias. Sympathomimetics are less effective in conditions of prolonged ischemia and acidosis as smooth muscle cells respond poorly. Therefore, they tend to be poorly effective in episodes of priapism lasting for greater than 48 h.

Oral sympathomimetics are not supported for the treatment of priapism [1].

Penile Shunts – Distal and Proximal Corporoglanular (Cavernoglanular)

Shunts are used in ischemic priapism to bypass the occlusive venous outflow. They facilitate drainage of the high pressure corpora. Shunts should only be attempted after aspiration and sympathomimetics fail. Distal shunts are associated with erectile dysfunction in 25% of cases and proximal, in 50%

of cases [1]. Erectile dysfunction should only occur with shunts if they fail to close [72]. It is unknown if the erectile dysfunction is due to the shunt procedure itself or merely the prolonged episode of priapism [73]. Nevertheless, due to the invasive nature and potential complications of shunts, shunts should always be a last resort. Ideally, one should commence with a distal shunt and progress to a proximal one (see Fig. 18.4).

The Winter's shunt is a distal glandularcavernous shunt that was classically performed using a Tru-cut biopsy needle placed percutaneously through the glans. Alternatively, a blade may be used in the Ebbehøj shunt. The Al-Ghorab shunt is performed by making an incision in the glans and excising a portion of tunica albuginea at the tip of the corpus cavernosum. This appears to be the most effective.

Modifications of distal shunts have recently been described in patients with severely prolonged episodes of ischemic priapism. The recently described T shunt, by Lue involves, under local anesthesia, inserting a blade through the glans and turning laterally to create the T shunt [74]. This may be combined with the insertion of a straight female sound into the corpora. The "snake" maneuver described by Burnett is a modification of the Al-Ghorab shunt [75]. This involves inserting a Hegar dilator into the corpora after tunical incision. These shunts aim to improve drainage of thick and congested corporal blood, which may be difficult to release in the originally described procedures.

Proximal shunts include the Quackels and Grayhack. The Quackels shunt is a proximal corporospongiosal shunt. The Grayhack shunt is a proximal shunt anastomosing the saphenous vein to the corpora cavernosa. Proximal shunts have been associated with urethral fistulae, cavernositis following the Quackels shunt and pulmonary embolism following the Grayhack shunt.

Penile Prosthesis Insertion

Patients with prolonged episodes of priapism that do not respond to intracavernosal therapy of surgical shunting may benefit from early insertion of

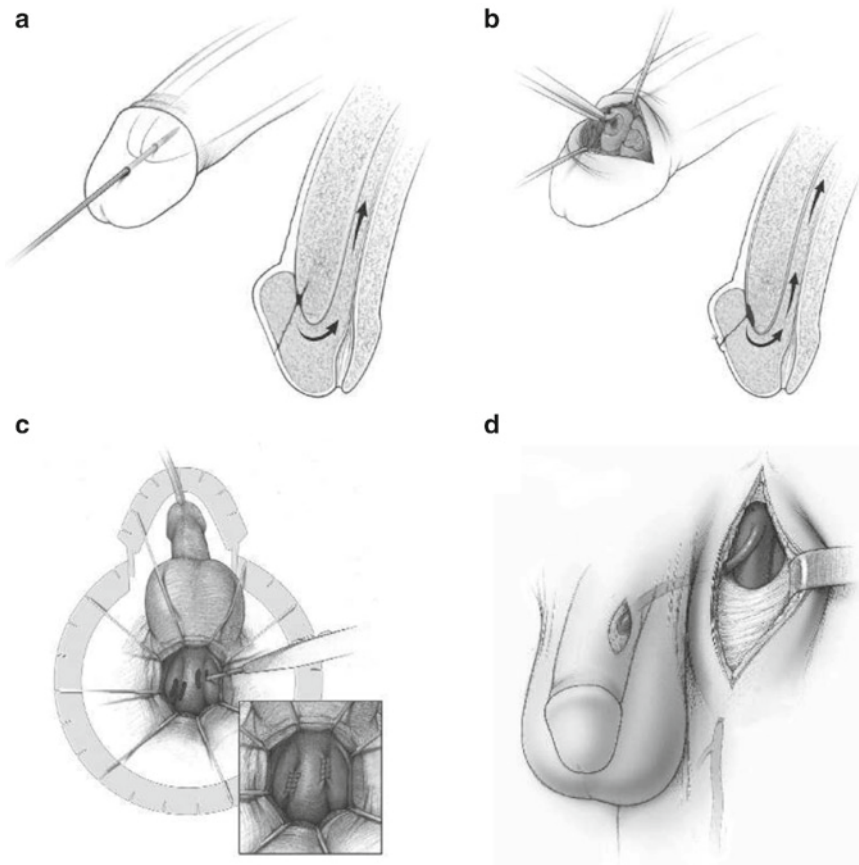


Fig. 18.4 Surgical shunts for treatment of priapism. (a) Winter, (b) Al-Ghorab shunt procedures, (c) Quackels/Sacher and (d) Grayhack shunt procedures

a penile prosthesis. Persistent priapism leads to cavernosal fibrosis, penile induration and shortening. This makes insertion of a penile prosthesis difficult. However, early insertion is easier. Rees demonstrated this in eight patients with priapism present for a mean duration of 91 h [76].

Non-ischemic Priapism

Observation

Since non-ischemic priapism resolves spontaneously in over 60% of cases with no attendant morbidity of erectile dysfunction, patients should be treated primarily with observation [1]. As opposed to ischemic priapism, this entity is not a surgical emergency.

Arterial Embolization

Arterial embolization should only be offered to patients who request this intervention while aware of the natural history of non-ischemic priapism. Patients should be made aware of the natural spontaneous resolution of non-ischemic priapism, regardless of the timing with no deleterious effects and minimal risk of erectile dysfunction. The procedure may be performed with absorbable or non-absorbable material. Absorbable material, e.g. clot, gelatin sponge is preferred as it is efficacious, with a resolution rate of 74% and a rate of erectile dysfunction of 5%. This is as opposed to non-absorbable tissue, such as ethanol, coils, polyvinyl alcohol particles, and acrylic glue which are permanent. They have a resolution rate of 78% and an erectile dysfunction rate of 39% [1]. Perineal abscess has been reported after embolization [77].

Surgical Ligation

Surgical ligation is again usually only offered upon patient request and after knowledge of the natural history of this type of priapism. It is usually preceded intraoperatively by color duplex ultrasonography, which identifies the fistula or pseudoaneurysm. The penis is next explored and the pudendal artery ligated. This procedure is effective in 63% of cases, but with an erectile dysfunction rate of 50% [1].

Treatment of Systemic Diseases, e.g. Sickle-Cell Disease

Patients with systemic diseases should have their disease appropriately treated. However, this should not substitute for or delay intracavernosal treatment. Patients with systemic disease, who only treat the systemic illness, have a 35% risk of erectile dysfunction. Patients with sickle-cell disease should also be managed with analgesia, hydration, oxygenation, alkalization, and possible exchange transfusion [1].

Prophylactic Treatment

Prophylactic treatment may be instituted in patients who have stuttering priapism. These may be seen in idiopathic cases, but is quite common in patients with sickle-cell disease. The episodes are quite distinct from major episodes or rapid recurrences. They are brief and do not have a significant risk of erectile dysfunction. However, it is known that these episodes of stuttering recurrences may evolve in time to major episodes of priapism, carrying risks of erectile dysfunction [6]. There are many potential prophylactic treatments mentioned in the literature. However, these have not been subjected to controlled clinical trials. These include oral systemic therapies and intracavernosal treatment.

The *oral systemic therapies* may be classified as oral adrenergic agents, hormonal agents, phosphodiesterase inhibitors, and miscellaneous

agents. Oral terbutaline has been used in cases of intermittent idiopathic priapism [78]. However, there is no strong evidence to suggest its successful use in stuttering priapism. Oral etilefrine use has also been reported [79]. Hormonal agents include diethylstilboestrol, antiandrogens (e.g. flutamide, bicalutamide, nilutamide, cyproterone acetate), and leutenizing hormone releasing hormone [80–82]. Diethylstilboestrol use should be cautioned because of the risk of venous thromboembolism and gynaecomastia. Antiandrogens and leutenizing hormone releasing hormones may reduce libido, but in case reports, patients have been able to maintain potency. Hormonal agents should be cautioned in children due to their ability of promoting fusion of the epiphyseal plate and also the effect on sexual maturation. These agents are contraindicated in children who have not completed sexual maturation and growth or in patients who are attempting to conceive [1]. The use of phosphodiesterase type 5 inhibitors as prophylaxis has been recognized as a result of extensive work into the molecular pathophysiology of priapism, especially in patients with sickle-cell disease [83]. The use of this agent may seem counterintuitive. Early reports suggested the mechanism of phosphodiesterase type 5 inhibitors may be via selective vasodilatation in the corpora. Downregulation of phosphodiesterase type 5 expression has been seen in cavernosal tissue in cases of recurrent priapism. In young adult rats chronically treated with sildenafil, phosphodiesterase type 5 expression is increased. So the use of phosphodiesterase type 5 inhibitors increases levels of cGMP which leads to increased phosphodiesterase type 5 promoter activity and hence transcription and production of the enzyme. This enzyme metabolizes cGMP and controls the excessive cGMP signaling in priapic tissue. Burnett et al. reported on four cases of stuttering priapism, three of who had sickle-cell disease and were treated with phosphodiesterase type 5 inhibitors [83]. The agents were able to reduce the episodes of stuttering priapism and preserve potency. The drug should ideally be taken in the morning to avoid high concentrations at night during sleep related erections. Only one episode of major priapism has occurred with use and this was taken in the

evening preceding sexual stimulation. Phosphodiesterase type 5 inhibitors are generally well tolerated, but may cause headache, facial flushing, rhinitis, and dyspepsia. There may be transient effects on the blood pressure and heart rate as these drugs are vasodilators. They are contraindicated with the use of nitrates.

Adrenergic agents may be administered as self intracorporeal injections in patients who fail or refuse systemic oral therapy for stuttering priapism [1]. McDonald et al. documented success with home self injections of metaraminol in a patient with sickle-cell trait with stuttering priapism [84]. These patients should be taught about the injection site, dosing and systemic adverse effects. It must be emphasized that this is not true prophylaxis, as episodes of priapism are being treated rather than prevented. In addition, there is the potential for adverse systemic effects if drugs are injected inadvertently systemically. Alpha agonists are contraindicated in patients with uncontrolled hypertension, coronary insufficiency, and arrhythmia [84]. There have also been case reports of success with use of intracorporeal injections of epinephrine and etilefrine [79, 82]. Nevertheless, this form of treatment is not preferred over oral systemic prophylaxis.

Miscellaneous Therapies

Miscellaneous agents include baclofen, gabapentin, hydralazine, digoxin, and hydroxyurea [85–89]. There are case reports of the use of these agents; however, none can be recommended for routine use due to lack of evidence basis.

Methylene blue is a guanylate cyclase inhibitor and inhibits the production of cGMP. It thereby blocks smooth muscle relaxation. It has been used by several groups and has the advantage of no significant adverse effects. However, it does cause a temporary blue discoloration of the tissues, pain, and is ineffective in cases of corporal fibrosis [90]. A case report of the use of tissue plasminogen activator use in recalcitrant priapism has also been documented [91]. There is limited data to recommend these treatment options currently.

Risk Management

There is the potential for medicolegal issues in priapism management due to the unfortunate complication of erectile dysfunction. This complication may be due to improper diagnosis, delayed intervention or complication of intervention. However, it may also be due to the result of the prolonged priapism episode. It is therefore important to discuss with patients on initial assessment the nature of the disease and these risks before embarking on any treatment. Consent should be obtained for all interventions. Patients should be made aware of the critical irreversible time period and urged to present early. Medical personnel should be expeditious in management and follow the advised stepwise evaluation process. Patients who have stuttering episodes may be offered prophylaxis. Patients with erectile dysfunction may be offered therapy.

Summary

Key Points

- Priapism is a persistent penile erection that continues beyond, or is unrelated to, sexual stimulation.
- Priapism is a urological emergency.
- Aetiological factors include hematological dyscrasias, erectogenic pharmacotherapy, non-erectogenic pharmacotherapy, neurological disorders, trauma, solid organ neoplasms, and idiopathic disorders.
- Patients with sickle-cell disease are at high risk for priapism.
- Priapism may be classified as ischemic (low-flow) or non-ischemic (high-flow).
- Traditional teaching suggests that priapism is due to altered blood flow in the penis.
- Molecular dysfunction, involving the corporal nitric oxide/cGMP pathway may explain recurrent episodes of priapism in patients with sickle-cell disease.

- Diagnosis of priapism is clinical and must be expedited.
- Delay in treatment may lead to erectile dysfunction.
- Ischemic priapism must be treated as an emergency; whereas non-ischemic priapism may be observed.
- Treatment of ischemic priapism must be in a step-wise fashion progressing from intracavernosal aspiration to penile shunting.
- There are modifications of distal shunts to augment egress of blood in prolonged episodes of priapism.
- Brief, recurrent episodes of priapism are called stuttering priapism.
- Recent research suggests that phosphodiesterase type 5 inhibitors may reduce and prevent the frequency of stuttering episodes in patients with sickle-cell disease.

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Chapter 19

Ejaculatory Disorders

Robert E. Brannigan

Abstract Ejaculation is a highly integrated process that involves both the sympathetic and parasympathetic neural pathways. Numerous studies reveal that ejaculatory dysfunction is a common disorder and the source of significant bother for many of those affected. Ejaculatory dysfunction is comprised of several different, more specific abnormalities including: premature ejaculation, inhibited ejaculation (consisting of delayed and absent ejaculation), and painful ejaculation. The evaluation of affected patients should include a comprehensive medical history, physical examination, and laboratory testing. Numerous therapeutic options are available to treat ejaculatory disorders, with many of these leading to marked improvement in patients' symptoms and associated bother.

Keywords Desire • Arousal • Orgasm • Resolution • Emission • Expulsion • Premature ejaculation • Inhibited ejaculation • Painful ejaculation • Anejaculation

Introduction

The normal male sexual cycle consists of four stages: desire, arousal, orgasm, and resolution. As Masters and Johnson originally reported, each of these stages is associated with distinct

physiological changes in the male [1]. Ejaculation, which normally occurs during the orgasm phase, is a highly complex, integrated process essential for the normal delivery of semen into the female reproductive tract during intercourse. Ejaculation disorders can lead to impaired reproductive potential in men and may necessitate the use of a variety of advanced diagnostic and therapeutic maneuvers. The impact of ejaculatory dysfunction is not confined to detrimental effects on men trying to achieve a pregnancy, as a recent study by Rosen et al. showed [2]. In a survey of 12,815 US and European men aged 50 years or older, the authors found that ejaculatory disorders are common, affecting 30.1% of men between 50 and 59 years of age. A majority (50.2%) of these affected men reported bother due to their ejaculatory problems. The authors noted that despite the pervasive focus among many clinicians on erectile dysfunction when assessing a patient's sexual health, ejaculatory problems are almost as common and should also be considered. For these reasons, physicians should be capable of identifying and treating the broad spectrum of ejaculatory disorders; this is essential in order to effectively care for the large numbers of affected men.

The Physiology of Ejaculation

Ejaculation in human men occurs simultaneously with orgasm. The concurrent timing of ejaculation with the rewarding sensory experience of orgasm, from an evolutionary perspective,

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serves to facilitate sexual behavior and human reproduction [3]. Despite the close temporal link between orgasm and ejaculation, these are two distinct and unique physiologic events. Orgasm is largely a central nervous system process that can be generated by cerebral stimulation without any accompanying genital input [4]. Thus, it is possible for men to experience orgasm in the absence of ejaculation. Clinically, this is illustrated in men who have undergone radical retro-pubic prostatectomy, with surgical extraction of their ampullary vas deferens, seminal vesicles, and prostate gland. Despite the absence of these accessory sex glands that play a central role in ejaculation, patients who have undergone radical prostatectomy are typically capable of achieving orgasm postoperatively [5].

Ejaculation consists of two phases: emission and expulsion. Each phase is coordinated by anatomical structures functioning together in a highly integrated fashion and is separately discussed below.

Emission Phase

The anatomical structures involved in emission include the epididymis, vas deferens, seminal vesicles, prostate gland, prostatic portion of the urethra, and bladder neck. These structures have both sympathetic and parasympathetic innervation with nerve fibers that arise predominately from the pelvic plexus. These nerve fibers are located in the retroperitoneum, traveling alongside the rectum and also lying posterolateral to the seminal vesicles [6]. Pelvic plexus nerve fibers come superiorly from the hypogastric and pelvic nerves, and inferiorly from the caudal paravertebral sympathetic chain [7]. Emission is initiated when afferent stimulatory input, primarily arising from sensory fibers within the glans penis, is integrated at the level of the spinal cord [8]. Sympathetic nerves (T10-L2) mediate the release of several neurotransmitters, including norepinephrine, causing epithelial cell secretion and smooth muscle cell contraction throughout the excurrent ductal system [9]. As a result, accessory gland secretions

are admixed with spermatozoa and ejected into the posterior urethra.

Expulsion Phase

The anatomical structures involved in seminal expulsion include the bladder neck, urethra, and striated pelvic muscles. Expulsion is a spinal cord reflex triggered once inevitability, or “the point of no return” is reached during sexual activity. During expulsion, the bladder neck smooth muscle fibers, under sympathetic fiber stimulation, forcibly contract to prevent retrograde ejaculation. Next, the striated pelvic floor muscles, in particular the ischiocavernosus and bulbocavernosus muscles, contract in an intermittent, rhythmic fashion, and the external urethral sphincter relaxes. While these muscles are innervated solely by the somatic nervous system (S2–4), the expulsion phase of ejaculation does not appear to have any component of volitional control. In the setting of tight bladder neck contraction, the series of striated pelvic muscular contractions leads to antegrade propulsion of semen through the prostatic, bulbar, and penile urethra and out the urethral meatus. To date, the specific trigger for the expulsion phase has not been clearly elucidated. Early work in a rat model suggested that the presence of semen in the bulbous urethra is the predominant factor that triggers seminal expulsion [10]. Subsequent manuscripts describe the presence of a spinal ejaculatory generator that leads to the expulsion of seminal fluid once a critical level of spinal activation has been achieved [11]. The spinal ejaculatory center is believed to integrate stimuli from peripheral and central sites, with efferent output through both parasympathetic and somatic pathways [12]. In 2002, Truitt and Coolen reported that neurons having a role in generating ejaculation are located within lamina X and the medial portion of lamina VII of lumbar segments 3 and 4. These neurons receive descending input from the nucleus paragigantocellularis, the medial preoptic area, and the paraventricular nucleus of the hypothalamus, each providing

supraspinal modulatory effects on the spinal ejaculatory generator [13]. While descending cortical input may influence ejaculation, it is not essential for ejaculation to occur. Men with complete spinal cord transection superior to the tenth thoracic segmental level (superior to the location of the spinal ejaculatory generator) exemplify this point; in these men, the ejaculatory reflex is typically still feasible. Penile vibratory stimulation is routinely used in such patients to induce the ejaculatory response for reproductive purposes, in order to collect sperm for assisted reproductive techniques, such as intrauterine insemination or in vitro fertilization. The intact function of the spinal ejaculatory generator neurons is essential for normal ejaculatory function, as their ablation leads to the complete loss of ejaculatory function [12].

Premature Ejaculation

Premature ejaculation (PE) is a highly prevalent condition; based on data from the National Health and Social Life Survey, this condition affects 21% of men between 18 and 59 years of age [14] in the USA. This disorder is classified into two categories: primary PE, which is present from the time a male first becomes sexually active and secondary PE, which is acquired later in life.

Etiology

The specific cause of PE is not known. A number of etiologies have been proposed, including a variety of psychological and organic causes. Dunn and colleagues performed a cross-sectional population survey in 1999 and found that anxiety was strongly associated with the presence of PE. While the authors acknowledge that the direction of this and other associations from their study need to be clarified, their results suggest that psychological factors such as anxiety could possibly

have a causative role in sexual problems such as PE [15]. In contrast to psychosexual causes, organic causes have also been postulated to cause PE. Waldinger et al. proposed that PE is a neurobiological disorder due to serotonergic hypoactivity.

Studies of male rats have shown that serotonin (5-hydroxytryptamine or 5-HT), and various serotonin receptors, play a role in the process of ejaculation [3]. Activation of 5-HT_{1B} and 5-HT_{2c} receptors delays ejaculation, while activation of 5-HT_{1a} receptors facilitates ejaculation. Some authors have related decreased central serotonergic activity (increased 5-HT_{1a} sensitivity or decreased 5-HT_{2c} sensitivity) to PE.

Diagnosis

One of the first definitions for PE was offered by Masters and Johnson, who described it as the inability of the male partner to delay ejaculation long enough for the female partner to achieve orgasm 50% of the time [16]. The Diagnostic and Statistical Manual of Mental Disorders, revised version 4 (DSM-IV-TR) highlights the individual and interpersonal distress caused by male climax earlier than desired by the male. Key aspects of the DSM-IV-TR definition include:

1. Reduced control over ejaculation;
2. A decrease in the patient's and/or partner's satisfaction with sexual intercourse;
3. Distress or bother in the patient and/or partner regarding the PE.

This DSM-IV-TR definition has been widely utilized clinically, and the Premature Ejaculation Diagnostic Tool (PEDT) is a five-item questionnaire developed specifically to apply the DSM-IV-TR criteria for PE. In 2006, Waldinger and Schweitzer reported on the limitations of the DSM-IV criteria for PE diagnosis, noting that it resulted in a low, positive predictive value [17]. Symonds et al. subsequently published a manuscript arguing the opposite, stating the PEDT is a reliable and valid PE diagnostic tool [18].

Many investigators favor the use of intravaginal ejaculation latency time (IELT) to diagnose

PE. IELT is defined as the time from vaginal intromission to the onset of ejaculation [19]. Advantages include that IELT is, at least in theory, a reproducible, objective measure. However, a 2005 manuscript by Patrick et al. highlighted some of the limitations of IELT [20]. The authors assessed 207 men with PE and 1,380 men without PE. At the time of the first study visit, subjects were asked to estimate their own IELT. After this visit, the patient and his partner were provided with a stopwatch and journal in which to document each episode of sexual intercourse. The IELT was measured and recorded by the female partner. For men with PE, the median measured IELT was 1.8 min, while the mean estimated value was 2.0 min. For men without PE, the median measured IELT was 7.3 min, while the mean estimated IELT was 9.0 min. This study highlights the fact that men with and without PE tend to overestimate their IELT, and it also sheds light on the time of ejaculation in both normal men and men diagnosed with PE [20]. While no firm IELT defining PE has been determined, some authors consider an IELT < 2 min as characteristic of PE [21].

Normative IELT data has been provided by a recent multinational, community-based, age-ranging study using IELT assessed by stopwatch [22]. The authors found that IELT decreased with age and varied among countries. The distribution of IELT was positively skewed, with a median value of 5.4 min (0.55–44.1 min). Waldinger et al. suggested that men with an IELT < 1 min (0.5 percentile of subjects) have “definite” PE, while men with IELT’s 1–1.5 min (0.5–2.5 percentile of subjects) have “probable” PE [22].

The Sexual Assessment Monitor is a new device developed by Dinsmore and colleagues to measure the time from the start of vibration to ejaculation. This device has been shown as safe and effective, and has been validated to collect IELT data in both healthy volunteers and men with PE [23].

In 2003, the Second International Consultation on Sexual Dysfunction (ICSD) met to develop evidence-based guidelines for a variety of disor-

ders of sexual function. At this meeting, PE was defined based on three criteria:

1. Brief ejaculatory latency;
2. Loss of control over ejaculation;
3. Psychological distress to the patient and/or his partner [24].

The specific definition of PE generated at this meeting was, “ejaculation with minimal stimulation and earlier than desired, before or soon after penetration, which causes bother and distress and over which the sufferer has little or no voluntary control [25].” While the ICSD noted that men with IELT < 2 min qualify as having PE, they stipulated that diagnostic criteria required all three components: decreased IELT, inability to delay/control ejaculation, and marked associated distress over their condition.

In 2004, the American Urological Association published “AUA Guideline on the Pharmacologic Management of Premature Ejaculation [26].” The panel members conducted a literature review and found a lack of standardization in PE studies, with a wide variety of PE definitions, study criteria, and physiological measurements. The panel determined that a meta-analysis was thus inappropriate, particularly in consideration of the variety of PE outcomes measures and populations studied. The panel’s recommendations were thus developed based on consensus combined with a review of the limited evidence available.

The guidelines’ first recommendation states, “The diagnosis of PE is based on sexual history alone. A detailed sexual history should be obtained from all patients with ejaculatory complaints.” The authors highlighted the importance of eliciting a number of clinical factors from the patient, including the frequency and duration of PE, the degree of stimulation resulting in PE, the impact of PE on sexual activity, factors that exacerbate or alleviate PE, and the frequency and nature of sexual activity. The guidelines stipulate that special laboratory or physiological testing is *not* indicated unless the history or physical exam reveals the presence of other complicating medical factors in need of additional investigation.

Treatment

Therapies for PE include psychological, behavioral, and pharmacological approaches. In general, men with lifelong PE likely have lower ejaculatory thresholds compared to unaffected men, and thus may benefit most from medical therapies [27, 28]. In contrast, men with a history or acquired PE are more likely to be better treated with cognitive or behavioral therapy [29]. Among the psychological approaches, psychotherapy has been reported as a primary therapy, but there is a lack of well-designed clinical trials assessing the efficacy of this intervention.

Behavioral Techniques

Behavioral techniques include the “stop and start technique” and the “squeeze technique.” With the “stop and start technique,” patients are instructed to manually stimulate themselves in a controlled fashion and involve their partner in the manual stimulation once controlled arousal has been achieved. The couple then proceeds onto intercourse [16]. The “squeeze technique” is very similar to the “stop and start technique,” except the penis is manually squeezed during the times when stimulation is stopped [30]. The obvious advantage of behavioral techniques is that they are nonpharmacologic and thus avoid possible side effects associated with medical therapies. While some authors report success with behavioral approaches, these treatment modalities are overall poorly studied and lack long-term efficacy [31].

Pharmacological Therapies

A number of pharmacological therapies have been utilized to lengthen IELT for men with PE. These therapies include both topical and oral agents, and dosing varies from on-demand to daily schedules.

The ICSD recognized three pharmacologic treatment options for PE:

1. Topical anesthetics (lidocaine or prilocaine);
2. Daily treatment with serotonergic antidepressants (paroxetine 20–40 mg, sertraline 50–100 mg, fluoxetine 20–40 mg, or clomipramine 10–50 mg);
3. On-demand treatment with antidepressants.

The ICSD Guidelines state that none of the above drugs have been approved for the treatment of PE by regulatory agencies, and the majority of studies to assess their efficacy are limited by inadequate design.

Topical Therapies

Topical therapies address the issue of “penile hypersensitivity.” Local anesthetic medications are available in topical gel, cream, or spray forms. Busato et al. conducted a double-blind, randomized, placebo-controlled study assessing topical lidocaine–prilocaine; they reported a significant increase in IELT from 1.49 to 8.45 min in the treatment group versus 1.67–1.95 min in the placebo group [32]. In this particular study, no systemic side effects were reported. Possible side effects do include skin irritation or numbness and erectile dysfunction [33]. Additionally, transfer of these topical medications from the treated male to his partner is another possible bothersome side effect potentially limiting the use of this mode of therapy. Hence, the ICSD noted that while topical therapy is moderately effective, penile hypoesthesia is a significant adverse side effect in the male. In the female, transvaginal absorption with possible vaginal numbness and female anorgasmia may limit efficacy for the couple if a condom is not used.

Oral Therapies

A number of oral therapies are used to treat PE. This includes the phosphodiesterase type 5 (PDE-5) inhibitors, as well as the selective serotonin

reuptake inhibitors (SSRI) agents. Neither of these classes of drug was developed specifically for the treatment of PE, and the use of these medications for patients with PE is thus done in an off-label fashion. However, the AUA Guideline on the Management of Ejaculatory Dysfunction recommends, "In patients with concomitant PE and ED, the ED should be treated first." The rationale for this approach is that PE sometimes improves concomitantly with improvement in the ED. The authors note that in this setting the intense stimulation needed to achieve and maintain an erection, or the anxiety associated with ED, may cause secondary PE.

PDE-5 Inhibitors. The use of PDE-5 inhibitors has been found to provide limited efficacy for the treatment of PE in men without concurrent ED. Nitric oxide (NO), which is augmented by the use of PDE-5 inhibitors, exerts both central and peripheral effects on emission. Hull et al. reported that systemic administration of a nitric oxide synthase inhibitor (N-nitro-L-arginine-methyl ester) led to a decrease in latency to the first emission and increased the overall number of emissions [34].

These same authors reported that NO causes a decrease in peripheral smooth muscle activity, likely mediated by a decrease in sympathetic nervous system activity, thus leading to inhibited seminal emission. They concluded, based on their collective findings, that NO may help prevent PE.

The PDE-5 inhibitors have been evaluated clinically in numerous studies for the treatment of PE, both as monotherapy and also in combination with SSRI agents. In 2005, McMahon et al. reported the results of an 8-week, double-blind, placebo-controlled, parallel group study of sildenafil citrate in men aged 18–65 years with PE [35]. The authors reported that while IELT was not significantly improved, subjects on sildenafil did report increased confidence, increased the perception of ejaculatory control, increased overall sexual satisfaction, and decreased refractory time to achieve a second erection. The authors suggested that the lack of a significant increase in IELT suggests a lack of direct central or peripheral effect of sildenafil on ejaculation function. They also noted that the

perceived improvement in ejaculatory control and confidence may have been related to the improved erectile functioning and reduced performance anxiety.

McMahon et al. subsequently published a systematic review of the efficacy of PDE-5 inhibitors in the treatment of PE in 2006. They found that 13 of the 14 published studies did not fulfill evidence-based medicine criteria for ideal PE drug trial design (double-blind, placebo-controlled study, differentiation of lifelong and acquired PE subgroups, exclusion or categorization as a separate subgroup men with concurrent ED or other sexual disorders, and consistent and objective physiological measurements or use of sensitive, validated outcome assessment instruments as study endpoints). The one study that did fulfill these ideal design criteria reported that the treatment with sildenafil failed to increase baseline IELT in men with PE. The authors concluded that there is no convincing evidence to support any role for the use of PDE-5 inhibitors in men with lifelong PE and normal erectile function. They did, however, acknowledge that there is limited evidence for the role of PDE-5 inhibitors either alone or in combination with on-demand or daily SSRI agents for men with PE *and* concurrent ED. They proposed that the mechanisms of action in these men include: the ability to maintain an erection after ejaculation, reduction of the erectile refractory period with reliance on a second, subsequent erection which may be better controlled, reduction in performance anxiety with resultant better erections, and/or a decrease in erectile threshold to a diminished level of arousal, facilitating a relatively greater level of arousal to achieve ejaculation threshold.

Selective Serotonin Reuptake Inhibitor (SSRI) Agents. The SSRI class of medications has been used widely to treat PE. Serotonin is active in the nerve synapse, and low levels are known to cause depression. The tricyclic antidepressant (TCA) and SSRI agents were developed for the treatment of depression. While the TCA agents prevent the reuptake of both serotonin and norepinephrine, the SSRI agents are more specific and work by inhibiting the reuptake of serotonin into the presynaptic nerve terminal. These agents thus

prolong or promote serotonin's effects. Therefore, it is not surprising that many patients who were administered SSRI agents, which were developed for the treatment of depression, complained of increased time to reach ejaculation on this therapy.

The ICSD reported that daily paroxetine provides the most robust delay in ejaculation, and delay with daily use of any of these agents is noted by the second week of therapy. Regarding efficacy of on-demand therapy with antidepressants, the ICSD was unable to provide conclusions due to the limited number of studies, insufficient number of patients, and inadequate study designs.

At the time of the publication of the AUA Guideline on the Pharmacological Management of PE document, as well as at this time, there is no pharmacological agent approved by the US Food and Drug Administration (FDA) for the treatment of PE. As is stated in the AUA Guideline, PE can be treated successfully with several different SSRI agents. The off-label use of the SSRI agents, fluoxetine, paroxetine, sertraline, and the TCA agent clomipramine, were noted in the Guideline to have demonstrated enhanced benefit over placebo in the treatment of PE. Other agents, such as nefazodone, citalopram, and fluvoxamine, were reported to be ineffective in treating PE.

The AUA panel charged with developing the Guideline could not conclude whether daily dosing or on-demand dosing was superior. The authors also noted that medical therapy only provides symptomatic relief, and not cure of PE. Adverse events are a potential concern when using antidepressant pharmacological agents. While adverse event profiles have not been widely studied in the setting of PE therapy, those associated with the use of SSRIs and TCA agents in patients with depression include: dry mouth, drowsiness, nausea, and decreased libido. The most concerning adverse event is called "serotonergic syndrome." In mild cases, patients experience headache, dizziness, sweating, and nausea, while in severe cases patients may experience delirium, hyperthermia, and rigidity. Generally, the dosages of these medications used in treating men with PE are lower than dosages used to treat depression; nonetheless, these potential adverse

events remain a concern and should be discussed with patients prior to initiating therapy.

Special mention should be made of dapoxetine hydrochloride, another SSRI agent. Dapoxetine hydrochloride, a short acting SSRI that is being studied for the specific indication for PE. In 2006, Pryor et al. published a manuscript in *Lancet* summarizing the efficacy of dapoxetine in two identically designed 12-week, randomized, double-blind, placebo-controlled Phase III clinical trials [36]. Both studies evaluated men with moderate to severe PE who received placebo, dapoxetine 30 mg, or dapoxetine 60 mg as needed one to 3 h prior to intercourse. Both dosages of dapoxetine resulted in prolonged IELT when compared to placebo (p , 0.0001), and both dosages were associated with only mild side effects [36]. Safarinejad published the results of a double-blind, placebo-controlled, fixed-dose, randomized study of dapoxetine in the treatment of PE in 2007 [37]. He reported that daily dapoxetine has moderately better results in terms of IELT and intercourse satisfaction when compared to placebo. Dapoxetine did not provide men with long-term benefit after withdrawn. In November 2005, the FDA denied the application of dapoxetine in the treatment of PE, and the application for dapoxetine is still pending before the European Medicines Agency [38]. A recent manuscript by Waldinger et al. in the *Journal of Sexual Medicine* questioned what the authors termed the "statistically significant but clinically small ejaculation-delaying effects of dapoxetine [38]." The authors also questioned several aspects of the methodology of the Phase III clinical trials, including the importance of patient reported outcomes of perceived control over ejaculation and satisfaction with sexual intercourse, over more objective measures such as IELT. At this time, the manufacturer notes that the clinical development program is still ongoing and consists of five Phase III placebo-controlled trials.

In summary, both the AUA and ICSD guidelines recommend specific antidepressants and topical anesthetics for the pharmacologic management of PE. Only the ICSD, however, highlights the benefits of psychological and behavioral interventions.

Miscellaneous Approaches

In closing, some investigators have reported efforts to block nerve receptors for penile tactile stimuli via selective dorsal penile nerve division and hyaluronic acid gel injection. Both of these approaches have been reported to prolong IELT, but clearly need further investigation given their very limited evaluation to date [39].

Inhibited Ejaculation (Delayed Ejaculation and Anejaculation)

Etiology

Inhibited ejaculation (IE) consists of delayed ejaculation (DE) and anejaculation (AE), two conditions along the same clinical spectrum. Inhibited ejaculation refers to persistent or recurrent difficulty, delay in, or the inability to achieve ejaculation despite sufficient sexual stimulation. Delayed ejaculation and AE may be lifelong or acquired, constant or situational, and patients with DE and AE may or may not experience concurrent orgasm.

Delayed ejaculation and AE can be caused by a number of factors, including medical conditions, surgical procedures, and psychological issues. Any factors affecting the central control of ejaculation, the afferent and/or efferent nerve supply to the vas deferens, bladder neck, penis, and pelvic floor, can potentially lead to DE or AE. Aging is a leading risk factor for IE [40]. Aging-related changes suggested by some authors that lead to IE include: progressive loss of the fast conducting peripheral sensory axons, collagen infiltration of myelin, and atrophy of the dermis, which collectively can lead to an aging-related hypoanesthesia of the penis [41]. Spinal cord injury can also lead to IE. In contrast to erectile function, a man's ability to ejaculate increases as the level of his spinal cord injury descends, and less than 5% of men with complete upper motor neuron lesions have intact ejaculatory capability [41, 42]. Sometimes, surgical

procedures can result in IE. Such procedures include aortic bypass surgery, repair of aortic aneurysms, or other operations involving the periaortic region or pelvis. A particular example of this type of surgery that is familiar to urologists is retroperitoneal lymph node dissection. Retroperitoneal lymph node dissection is often used in treating testicular cancer and may involve the removal of the postganglionic sympathetic nerves emanating from the sympathetic chain and hypogastric plexus. The result of this intervention is ablation of the efferent stimulation for seminal emission and bladder neck closure, essential components of successful ejaculation [43]. Nerve-sparing techniques using modified templates to preserve the essential sympathetic nerves are now commonly employed and result in a high degree of retained ejaculatory function. Even with a nerve-sparing approach, other factors such as large retroperitoneal tumor mass or preoperative chemotherapy increase the risk of postoperative ejaculatory dysfunction.

Medical conditions can also lead to IE. While much has been written recently about the negative effects of diabetes mellitus (DM) on erectile function, the issues of ejaculatory dysfunction associated with DM are less well studied. Diabetes mellitus-related ejaculatory problems typically parallel the overall progression of autonomic neuropathy and have a course characterized by a slow decline in ejaculatory function. The initial changes may be hallmarked by a decline in ejaculate volume and even complete loss of antegrade ejaculate, with cloudy postejaculate urine representative of retrograde ejaculation. Over time, these changes can progress to loss of emission all together, with no antegrade ejaculate and no evidence of semen in the postejaculate urine [44].

Patients may also suffer from a variety of neurological problems that can lead to impaired ejaculation. These include readily evident congenital problems, such as spina bifida, or more occult spinal cord dysplasias, such as tethered spinal cord. These conditions can all lead to IE and are typically found in men with a history of lifelong IE. Acquired neurological conditions can also lead to ejaculatory dysfunction. These

include transverse myelitis, multiple sclerosis, and vascular spinal cord injuries [45].

A number of medications can also lead to IE. Among these, the TCA agents and SSRI agents, as discussed above in the section on PE, are well documented to lead to delayed and possibly completely IE. Alpha blocking agents can potentially lead to either retrograde ejaculation or inhibition of seminal emission.

Inhibited ejaculation can also be related to religious beliefs, cultural background, and a variety of psychological factors. Sometimes, termed “idiopathic anejaculation/anorgasmia,” these patients typically have no demonstrable pathophysiologic cause for their inability to achieve climax and ejaculation. Many of these individuals report a history of strict religious upbringing [46]. On medical history, these patients are often capable of orgasm and ejaculation with masturbation, but not during intercourse. They may also report periodic nocturnal emissions [47]. The intact functioning of nocturnal emission but the absence of awake ejaculation suggests a psychogenic etiology, much as in the case of psychogenic erectile dysfunction [45].

Special mention should be made of anejaculation. Anejaculation most commonly arises from a variety of neurogenic causes. Spinal cord injury is the most common cause of anejaculation. While men with a history of spinal cord injury often have the ability to obtain reflex erections and possibly engage in sexual intercourse, they often suffer from the loss of ability to ejaculate.

Diagnosis

The diagnosis of IE is based largely on history obtained from the patient. A thorough review of the patient’s medical history is essential. The onset of ejaculatory dysfunction and any temporal associations with medical, surgical, or psychosocial issues should be assessed. Physicians must be sensitive to the fact that patients often have difficulty differentiating erectile dysfunction, ejaculatory dysfunction, and orgasmic dysfunction. Careful questioning regarding each of these

components of male sexual health is essential. Distinguishing “pre-ejaculate” from true antegrade ejaculation is also important in delineating the patient’s underlying function [45]. Prior medical problems, surgeries, and medications should be discussed. In particular, the use of antidepressants and alpha-antagonists should be assessed. During the physical examination, testicular volume and consistency, as well as vasal and epididymal presence or absence, should be assessed. Serum testosterone levels should be checked because the accessory sexual glands (prostate, seminal vesicles, and bulbourethral glands) are androgen-dependent structures, and secretory function may be impaired by markedly diminished serum testosterone levels. Urinalysis testing should be performed because the presence of elevated urine glucose levels may signify the presence of DM. If the patient is able to provide an antegrade semen sample, semen analysis should be performed. For patients with no antegrade ejaculate or low ejaculate volumes <1.0 mL, postejaculate urinalysis should be performed immediately after ejaculation to assess for the presence of sperm in the urine.

Treatment

For men with IE thought to be due to medications, the suspected agents can be withheld and change in ejaculatory function then assessed. Alpha agonist administration is potentially beneficial in some patients with IE, particularly those with autonomic dysfunction [48, 49]. While the goal of this therapy is to optimize seminal emission and bladder neck closure, the severity of the underlying autonomic dysfunction is often so profound that this therapeutic maneuver is unsuccessful [45]. Alpha agonists can cause numerous adverse side effects, including hypertension, tachycardia, dry mouth, and urinary retention, and these must be closely considered before dosing. Alpha agonists should be administered with care, particularly in patients with DM, as these individuals are at increased risk of cardiovascular disease.

Numerous reports of psychological and behavioral therapies for IE have been published, but the overall efficacy of such approaches is unclear. Most studies are case report format and lack controls, hampering the assessment of the effectiveness of this treatment modality [50–55]. While psychological and behavioral therapies are certainly a reasonable option and should be considered for men with a suspected psychogenic cause of ejaculatory dysfunction, additional work is needed to better characterize this therapeutic approach.

Vibratory stimulation devices can also be employed, with the enhanced stimulatory input providing benefit for some affected patients. The best vibratory stimulation devices allow both frequency and amplitude modulation, although some patients may benefit from less expensive and more accessible commercially available vibratory devices.

Painful Ejaculation

Etiology

Painful ejaculation is perhaps the least well-studied and characterized of the ejaculatory disorders discussed in this chapter. This condition can have a dramatically negative impact on relationships, leading to the avoidance of sexual intimacy with one's partner, sexual distress, sexual dissatisfaction, and ultimately, marital problems [56, 57]. A variety of causes have been cited, but the underlying etiology is not well understood. Some authors suggest spasm of the bladder neck or dystonia of the pelvic floor musculature during orgasm [58], and others note that ejaculatory duct obstruction may be the underlying cause [26, 59]. This obstruction could arise from ejaculatory duct calculi, intrinsic stenosis, or external compression by a prostatic cyst leading to ejaculatory duct compression and blockage. Antolak et al. have suggested that pudendal nerve compression and neuropathy may be the cause of ejaculatory pain in some men [60]. Finally, some

authors have suggested that antidepressant medications may induce painful ejaculation as a side effect [61–65].

The true incidence of painful ejaculation is unclear. Most studies assessing this condition employ retrospective questionnaires, and are thus subject to some form of bias. In 2003, Rosen et al. reported that 6.7% of men participating in a large multinational survey of aging males noted pain or discomfort on ejaculation [2]. Roberts et al. found that 1.5% of the 2,115 respondents from Olmsed County, Minnesota experienced ejaculatory pain [66]. Another US study reported that 9.7% of respondents (age 20- to 74-years-old) noted perineal pain or discomfort with ejaculation [67]. Finally, the authors who developed the National Institutes of Health Chronic Prostatitis Symptom Index found that ejaculatory pain was present in 58% of men with prostatitis, 17% of men with BPH, and 4% of controls [68].

Diagnosis

The diagnosis of ejaculatory pain is largely based on subjective complaints; objective diagnostic information can be gathered in some instances. For example, in men with ejaculatory duct obstruction, transrectal ultrasound imaging can be utilized to visualize ejaculatory duct anatomical abnormalities (such as calculi or compressing cyst) and/or seminal vesicle dilation (a possible sign of distal ejaculatory duct obstruction). Antidepressant medication-related symptoms may be clarified by converting to another medication or ceasing this therapy (in conjunction with the prescribing physician). In patients with suspected pudendal neuropathy, neurophysiological tests may help delineate pudendal neuropathy associated with perineal pressure [69]. Most of the purported causes of ejaculatory pain, however, are more challenging to diagnose and not associated with clear physical findings or alterations in laboratory values. This fact can make pursuit of a clear therapeutic plan challenging for both the patient and the treating physician.

Treatment

The treatment of painful ejaculation should be based on objective findings from the examination and laboratory workup. Prostatitis and urinary tract infections should be treated. Patients with ejaculatory duct obstruction should be considered for transurethral resection of the ejaculatory duct. Patients with seminal vesicle anomalies (i.e., seminal vesicle stone) suspected of being the root cause of the pain should be informed of the option of laparoscopic seminal vesicle excision, as this has been reported as providing durable relief in the setting of ejaculatory pain [70]. Finally, consideration should be given for enlisting the assistance of physical therapists specializing in pelvic floor physical therapy. Anderson et al. reported encouraging results with trigger point release and paradoxical relaxation training in 133 men with refractory chronic pelvic pain syndrome and sexual dysfunction (ejaculatory pain [56%], decreased libido [66%], erectile and ejaculatory dysfunction [31%]) [71]. The authors noted significant improvement in the above categories of sexual dysfunction, with 70% of patients reporting markedly or moderately improved symptoms after trigger point release/paradoxical relaxation training. Thus, physical therapists can help elicit and treat underlying musculoskeletal anomalies, which may be the root cause of many patients' complaints of ejaculatory pain.

Conclusions

The physiology of ejaculation is highly integrated and relies on both the sympathetic and parasympathetic neural pathways. Ejaculatory dysfunction is fairly common and is a source of significant bother for many of those affected. Ejaculatory dysfunction can entail a wide array of anomalies, including premature ejaculation, inhibited ejaculation (consisting of delayed and absent ejaculation), and painful ejaculation. Patients should be evaluated through a thorough medical history, physical

examination, and laboratory testing to help ensure proper diagnosis. Finally, with directed therapy, many disorders of ejaculation can be successfully treated.

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