

# PENILE ERECTION

Part of "42 - THE PENIS: SEXUAL FUNCTION AND DYSFUNCTION"

## *Hemodynamic Aspects*

Penile erection and detumescence are primarily controlled by hemodynamic events. Increased arterial inflow appears to be of primary importance; the contribution of increased venous resistance to the production of penile erection remains controversial. Furthermore, our understanding of precise anatomic details (including "shunts") and the neural control of vascular events is not complete.

More than half a century ago, Semans and Langworthy (315) demonstrated the importance of arterial inflow in the production and maintenance of a penile erection. They found in cats that aortic occlusion prevented the development of penile erection produced by sacral nerve root stimulation. After an erection had been produced by nerve stimulation, aortic occlusion resulted in detumescence. Similar animal studies were refined and again demonstrated the importance of increased arterial inflow in the production of erection. With pelvic nerve stimulation in the dog, Dorr and Brody (83) demonstrated that the dorsal artery perfusion pressure fell while venous pressure rose. Blood flow through both the dorsal artery and vein greatly increased. In addition, no venous pressure gradient with erection could be demonstrated when venous pressure was recorded at multiple sites from the erectile tissue distally to the internal pudendal vein proximally. These data are consistent with the hypothesis that the primary hemodynamic event leading to erection is increased arterial inflow and that increased venous resistance plays a minor, or insignificant, role.

Contradictory results have been reported in the canine model (209). With electrical stimulation of the cavernosal nerves, internal pudendal arterial flow was found to increase

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by 250% during the early phases of erection (Fig. 42.8). This was accompanied by a 20-mm Hg decrease in internal pudendal artery pressure. With erection, the flow rate gradually decreased to slightly above basal levels. A new equilibrium was established at full erection, with corporal pressure approximately 10 mm Hg below the systolic arterial pressure. At full erection, flow into and out of the corpus cavernosum, although present, was greatly reduced. Furthermore, with the aorta occluded and with saline solution infusing directly into the corpus cavernosum, an initial drop in intracorporal pressure and decreased venous flow during erection were demonstrated with cavernosal nerve stimulation. Thus these investigators have concluded that tumescence is the result not only of active arterial dilation and increased arterial flow but also of active relaxation of the corporal trabeculae and restriction of venous outflow. The decreased venous outflow is thought to be secondary to compression of venules located in the corpora cavernosa just beneath the tunica albuginea.

**FIGURE 42.8.** Changes in blood flow and pressure after cavernous nerve stimulation in the dog. (From Lue TF, Takamura T, Umraiya O, et al. Hemodynamics of canine corpora cavernosa during

erection. *Urology* 1984;24:347, with permission.)

In animals, other data exist that implicate obstruction of venous return as an important mechanism in the production of penile erection (138). Anesthesia of the ischiocavernosus muscles produced by lidocaine injection often prevents goats, bulls, and stallions from copulating because of the inability to attain an erection (21,277). The highest pressures in the corpus cavernosum in the dog penis occur during intromission and coincide with contractile activity of the ischiocavernosus muscles measured electromyographically (277). Presumably, blockade of venous return secondary to skeletal muscle contraction may promote the development of penile erection. To the contrary, in the human, erection can occur without electromyographically measurable increases in bulbocavernosus, urethral sphincter, or deep transverse perineal muscle activity (178).

Although “venous valve mechanisms” and sphincteric-like smooth muscle structures surrounding penile veins have been described anatomically and hypothesized to contribute to the development of penile erection (60), physiologic investigation in humans is necessary to resolve the controversy concerning the possible role of increased venous resistance. Xenon washout techniques would appear to be an ideal method to resolve this question. In the flaccid state, there is minimum blood flow through the corpora cavernosa. If  $^{133}\text{Xe}$  were placed into the corpora cavernosa and erection produced by visual stimulation, the rate of  $^{133}\text{Xe}$  “washout” during erection should give valuable information concerning the importance of venous resistance to flow. This study has been done in humans by two groups of investigators with markedly conflicting results. Shirai and Ishii (318) reported an increase of disappearance of  $^{133}\text{Xe}$  with erection and failed to show any significant increase in venous resistance. Wagner (355), however, described a decreased washout with erection, evidence that increased venous resistance and decreased venous flow occur with the development of an erection in humans. Primarily because of observations made by Lue and colleagues (209) and Aboseif and Lue (2), most investigators believe that penile erection is dependent not only on increased arterial inflow but also on relaxation of the corporal smooth muscle. Corporal smooth muscle relaxation and increased intracorporal pressure result in passive occlusion of corporal venous outflow.

Although active arterial dilation, corporal smooth muscle relaxation, and passive venous occlusion are generally considered the mechanisms of penile erection, other theories have been proposed. Venous “sluices” were hypothesized by Deysach (80) to open and close and thereby produce erection by altering venous outflow. For years, the most widely accepted hypothesis to explain penile blood flow was the “polster” theory advocated by Conti (68). In an anatomic study performed on cadavers, Conti described “polsters,” that is, columns of smooth muscle cells within the intima of penile arteries and veins. Although such structures had been described anatomically by earlier investigators, Conti proposed that contraction and relaxation of these polsters could divert blood into and away from the cavernous spaces and thus induce erection and detumescence. Calcification and fibrosis of polsters have been cited as causes for impotence in elderly diabetic patients (298). No

data supporting a physiologic role for polsters, however, have been published, and the functional importance of these structures has been questioned. In addition, anatomic studies have demonstrated no innervation to polsters. Finally, evidence has been presented that suggests that polsters are actually atherosclerotic changes in penile blood vessels (27) (Fig. 42.9). Wagner and colleagues (354) proposed a mechanism of erection based on "shunt arteries." According to their hypothesis,

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the helicine arteries that supply the corpora cavernosa are constricted during detumescence, resulting in blood being diverted to the corpus spongiosum by means of shunt arteries. Erection results when the helicine arteries dilate and the shunt arteries constrict. To date, all of the theories of various "shunt" mechanisms resulting in penile erection remain physiologically unproved.

**FIGURE 42.9. A:** Atherosclerotic lesions from penile artery of 49-year-old man. **B:** Conti's drawing of penile polsters. (From Benson GS, McConnell JA, Schmidt WA. Penile "polsters": functional structures or atherosclerotic changes? *J Urol* 1981;125: 800 and Conti G. L'erection du penis humain et ses bases morphologico-vasculaires. *Acta Anat Basel* 1952;14:217, with permission.)

## Neurophysiology

The hemodynamic changes leading to penile erection and detumescence are clearly under neurologic control. One of the earliest investigations into the mechanisms controlling penile erection was Eckhard's demonstration that penile erection in the dog was produced by stimulation of the pelvic parasympathetic nerves, which he called the *nervi erigentes* (86). Eckhard was unable to produce an erection in the dog with stimulation of the hypogastric nerve, a sympathetic nerve. During the past century, investigators have attempted to understand and clarify Eckhard's findings.

In animals, the relative importance of the parasympathetic and sympathetic nervous systems in the control of erection was investigated by the classic studies of Muller (254) in the dog and Root and Bard (290) in the cat. In 1902, Muller observed that excision of the entire sacral and most of the lumbar spinal cord abolished reflex penile responses in the dog. Erection still developed, however, when the dog was placed with a bitch in heat. In addition, male dogs whose cords had been transected at a low thoracic level never exhibited erections in the presence of an estrous female; these animals, however, retained their ability to achieve full penile erection with penile stimulation. Forty-five years after Muller's study, Root and Bard performed similar, albeit refined, experiments in the cat. Excision of the sacral and lower lumbar spinal cord abolished erections normally produced by manipulation of the penis but did not alter the ability of the male cat to achieve an erection in the presence of an estrous female. The addition of spinal cord transection between T-13 and L-1 or T-11 and T-12 in cats that had previously undergone ablation of the lower spinal cord resulted in the cessation of erectile response to both tactile and psychic stimuli. Resection of the inferior mesenteric ganglion and hypogastric nerves also abolished erectile responses in animals whose lower spinal cord had been resected. Finally, resection of the sympathetic nerves (inferior mesenteric ganglion and hypogastric

nerves) had no effect on erection when the lumbosacral spinal cord was left intact. The results of the work of Muller and Root and Bard indicate that at least in the dog and cat, two peripheral neural pathways exist that control erection: (a) a sacral (parasympathetic) mechanism that responds to both tactile and psychic stimuli and (b) a lumbar (sympathetic) mechanism that responds to psychic stimuli.

Although these studies describe the contributions of the parasympathetic and sympathetic nervous systems in a straightforward manner, other animal data cast doubt on this relatively simplistic scheme. Sacral parasympathetic nerve or nerve root stimulation does produce erection in the dog, cat, and rabbit. Stimulation of sympathetic nerves, however, has achieved conflicting results, which may be explained at least in part by species variability. With hypogastric nerve stimulation, Eckhard observed erection in rabbits, but not in dogs. However, other reports have indicated that in the dog, hypogastric nerve stimulation results in a slight increase in penile volume (9). In cats, hypogastric nerve stimulation does not result in erection and, in addition, actually results in contraction

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of penile arteries and causes an erect penis to become flaccid (315).

Human data relating to the neurophysiology of erection are limited. Most of the information is retrospective and has been obtained by interview or questionnaire technique. In addition, the completeness of the neurologic lesion produced by spinal cord injury or neurosurgical ablative procedures is difficult to ascertain. A survey of sexual function in a large number of spinal cord-injured patients has been presented by Bors and Comarr (41). Patients with complete lower motor neuron lesions failed to achieve erection with genital stimulation. Of these patients, however, 24% reported erectile activity secondary to psychic stimuli. Most patients with upper motor neuron lesions (spinal cord lesions above the level of the sacral spinal cord) reported erections secondary to genital stimulation. The percentage of patients achieving erection with psychogenic stimulation depended on the level of the lesion: cervical (4%), thoracic T-1 to T-6 (0%), thoracic T-7 to T-12 (8%), and lumbar (57%). These human data are generally consistent with the feline data of Root and Bard and the canine data of Muller. Specifically, the development of penile erection secondary to genital stimulation appears to require an intact sacral reflex, whereas the sympathetic system appears capable of producing psychogenic erections through pathways that connect the cerebral cortex to the penis and its vasculature. Although patients who have undergone lumbar sympathectomy or extensive retroperitoneal lymph node dissection commonly develop symptoms consistent with sympathetic denervation (lack of seminal fluid emission or retrograde ejaculation), they do not report a disturbance in erectile function (166,179,291). Therefore, in humans, it would appear that the parasympathetic nervous system is of primary importance in penile erection and is probably capable of responding to both tactile and psychic stimulation. The sympathetic nervous system may be capable of producing erection secondary to psychic stimuli, but its role in sexual function is less clear and needs further definition.

Penile erection clearly is modified by supraspinal neurologic mechanisms. A better understanding of these mechanisms is necessary before we can rationally approach such problems as psychogenic impotence and the deleterious effects of drugs on erectile function. Animals have been studied to some extent with central nervous system (CNS)

stimulation and ablation experiments. Human data consist primarily of case reports dealing with patients with CNS diseases or after ablative surgical procedures.

Hypersexual behavior in monkeys that had undergone removal of both temporal lobes, including the uncus and part of the hippocampus, was reported by Kluver and Bucy in 1939 (177). These animals exhibited frequent penile erections even under nonstimulated conditions. Stereotaxic electrical stimulation of specific parts of the brain, particularly the limbic system, is known to result in penile erection (84,218,219,288). In humans, impotence has been associated with temporal lobe lesions and after bilateral pallidofugal section for myoclonus (148,241).

## **Neuropharmacology**

The neuropharmacology of penile erection has gained increasing attention in recent years, primarily because the introduction of intracorporal injection therapy, intraurethral therapy, and effective oral therapy has caused a resurgence of interest in the medical management of impotence. Numerous *in vitro* and *in vivo* animal and human experiments have been performed to study the responses of the penile vasculature and cavernosal tissue to pharmacologic stimulation. Because stimulation of the pelvic nerve produces erection and because the pelvic nerve has been classically thought to be made up primarily of a cholinergic nerve population, acetylcholine was previously thought to be the neurotransmitter responsible for penile erection.

However, several experimental observations cast doubt on a purely cholinergic mechanism. Although the erection produced by pelvic nerve stimulation can be abolished by pretreating animals with hexamethonium (a ganglionic blocking agent), atropine does not completely block the response (83,144). Studies in humans also are consistent with the concept that erection is an atropine-resistant phenomenon (353). In addition, the infusion of acetylcholine into animals does not produce an erection (82,83). Finally, strips of corporal smooth muscle in an *in vitro* muscle bath respond minimally, if at all, to stimulation with acetylcholine (26). Although it has been argued that, in these experimental situations, acetylcholine and atropine do not reach the vascular and corporal receptors, an equally plausible explanation is that penile erection is not a cholinergically (or exclusively cholinergically) mediated event. Evidence has been presented that corporal smooth muscle relaxation caused by acetylcholine is mediated by nitric oxide (300,301).

Efforts have been directed toward ascertaining whether a catecholamine could be responsible for initiating and maintaining penile erection. The penile vasculature and smooth muscle of the corpora cavernosa are generously supplied with adrenergic nerves, and high norepinephrine levels have been detected in the corpora cavernosa (237). In humans, the corpora cavernosa possess a high  $\alpha$ -adrenergic receptor density determined by radioligand-binding studies (197). In the cat and rat, a portion of the sacral parasympathetic outflow is adrenergic (7,339), and these neurons conceivably could be responsible for the erection produced by pelvic nerve stimulation.

Strips of human corpora cavernosa relax when exposed to isoproterenol and salbutamol ( $\beta$ -adrenergic agonists) (4), and in the cat, erection has been produced by the intravenous infusion of salbutamol and phenoxybenzamine (an

$\alpha$ -adrenergic antagonist) (82). Other data, however, do not support the concept that an adrenergic mechanism is responsible for penile erection. The infusion of norepinephrine does not cause erection in the dog (83) or cat (82), and in fact, epinephrine causes constriction of canine penile arteries (92). Stimulation of human corporal strips *in vitro* with norepinephrine results in a marked contraction, which can be blocked by pretreating the strips with phenoxybenzamine (26). In humans, the oral administration of large doses of  $\alpha$ - and  $\beta$ -adrenergic blocking agents (phenoxybenzamine and propranolol) does not affect erections that result from mechanical or visual stimulation (353). The net effect of adrenergic stimulation therefore appears to promote penile detumescence (vascular constriction and corporal contraction) rather than erection.

It appears that the neuropharmacology of erection cannot be totally explained by classic cholinergic and adrenergic mechanisms (29). Numerous putative nonadrenergic, noncholinergic neurotransmitters have been investigated. Histamine, 5-hydroxytryptamine (serotonin), bradykinin, prostaglandins (PGE<sub>1</sub>, PGE<sub>2</sub>, and PGF<sub>2a</sub>), and amino acids do not appear to be responsible for the production of penile erection (175,176). Likewise, no convincing evidence has implicated adenosine triphosphate (a putative purinergic neurotransmitter) to be important in the production of penile erection.

The search for a nonadrenergic, noncholinergic mechanism to explain the neuropharmacology of penile erection has included the evaluation of possible peptidergic mechanisms. The polypeptide most investigated to date is VIP. The anatomic localization of VIP in the penis at both light and electron microscopic levels has been previously described. VIP is known to have a vasodilatory effect (302,344) and has been demonstrated to cause relaxation of strips of rabbit, cat, monkey, and human corpora cavernosa (132,190,332,372). In other work using nonhuman primates, however, VIP had little or no effect on the corpora cavernosa urethra of the rabbit, guinea pig, dog, and cat and no effect on penile vessels in the bull (322). In human corporal strips, VIP causes a weak relaxant effect in tissue that previously has been contracted with norepinephrine stimulation and also has been reported to cause detumescence of the erect penis obtained by cavernous nerve stimulation in the monkey (332).

In the feline submandibular gland, VIP has been shown to be responsible for the atropine-resistant vasodilation seen with nerve stimulation (215). In this tissue, VIP and acetylcholine are present in the same neuron, and both are released with nerve stimulation. It is possible that a similar situation occurs in the penis and that VIP is responsible for some of the pharmacologic findings, such as atropine resistance, which at present are not well understood. It is equally possible that VIP and other polypeptides may act as neuromodulators to control the rate of release of acetylcholine at nerve terminals.

The recognition of the importance of nitric oxide in the physiology of vascular smooth muscle relaxation has led to new insights into the mechanisms responsible for penile erection. Nitric oxide is synthesized in many types of mammalian cells and is a modulator of several biologic activities, including endothelium-dependent dilation of blood vessels, inhibition of platelet aggregation, and macrophage cytotoxic activity (170,249). Nitric oxide synthase, located in nerves and endothelium, synthesizes nitric oxide and the amino acid citrulline from arginine and molecular oxygen (248). Nitric oxide does not interact with a

receptor on the cell membrane, but it crosses the cell membrane and interacts with the enzyme guanylate cyclase. Activated guanylate cyclase catalyzes the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). The accumulation of cGMP induces a series of intracellular events that leads to smooth muscle relaxation. Phosphodiesterase type 5 inactivates cGMP. In strips of corporal smooth muscle from rabbits and humans, nitric oxide causes relaxation, which mimics electrical field stimulation. This relaxation occurs in the presence of guanethidine and atropine in the bathing media and is therefore thought to be mediated by nonadrenergic, noncholinergic neurons (52). Acetylcholine also is capable of causing endothelium-dependent relaxation by mechanisms that involve nitric oxide (301). Relaxant responses to nitric oxide are enhanced by pretreating the smooth muscle strips with a cGMP phosphodiesterase inhibitor. These observations support the hypothesis that stimulation of nonadrenergic, noncholinergic neurons in the corpus cavernosum cause corporal smooth muscle relaxation mediated by nitric oxide. In addition to cGMP, cyclic adenosine monophosphate (cAMP) may also be important in causing corporal smooth muscle relaxation. Both VIP and PGE<sub>1</sub> induce the formation of cAMP and cause corporal smooth muscle relaxation. In addition, VIP and neuronal nitric oxide synthase have been reported to be colocalized in the same nerves within the corpus cavernosum (88).

Valuable information concerning the neuropharmacology of erection has been obtained from the technique of intracorporal injection. Brindley's observation that the intracorporal injection of phenoxybenzamine (an  $\alpha$ -adrenergic blocking agent) resulted in penile erection clarified to a large extent our understanding of the physiology of human corporal smooth muscle (42). Norepinephrine causes contraction of corporal smooth muscle, and this drug effect is blocked by phenoxybenzamine. Therefore relaxation of the corporal smooth muscle appears to be an important component in the development of penile erection. The intracorporal injection of the smooth muscle relaxant papaverine, an agent that does not act through neuroreceptors but rather directly on the smooth muscle cell, as well as the injection of multiple other agents also cause penile tumescence (43,350). The use of these drugs not only has created a new research approach to the understanding

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of erection but also has been a valuable addition to the clinical diagnosis and therapy of impotence (320,385).

The neuropharmacology of the CNS as it relates to penile erection is less well understood than our understanding of peripheral mechanisms. In the rat, serotonin inhibits and dopamine activates male sexual behavior (123). Some of these animal data may be applicable to humans. Levodopa, for example, is known to cause heightened sexual activity (15,154). In addition, trazodone, a widely used antidepressant, affects the actions of serotonin, and priapism is a known side effect of this agent (235).

### ***Hormonal Factors***

Although most physicians agree that a relationship between male hormones and penile erectile activity exists, the nature of this relationship and the mechanisms responsible for hormonal control of sexual activity remain unclear. The difficulties encountered in separating libido from erectile ability in clinical studies are well known. In addition, neither

the mechanism of action nor the primary site of action (penis, spinal cord, or brain) of androgens in promoting penile erection is understood.

Clinical studies on the effects of castration and studies using testosterone replacement in hypogonadal men have been conducted. In a study of patients with carcinoma of the prostate undergoing either orchiectomy, estrogen therapy, or both, Ellis and Grayhack (93) found that a number of patients retained their potency after castration. Castration plus estrogen therapy appeared to more adversely affect sexual function in this small group of patients than did castration alone. Although an argument can be made that these patients did not undergo objective posttreatment evaluation, retained sexual potency after bilateral orchiectomy has been reported by others (141,231,289).

Androgen replacement in hypogonadal men has been analyzed in placebo-controlled clinical evaluations (74,214,323). In this group of patients, androgen increases sexual activity and interest. The relationship between androgen and penile erection, however, is less clear. Hypogonadal men demonstrate decreased erectile activity during nocturnal penile tumescence testing and report fewer spontaneous daytime erections. These abnormalities are corrected with testosterone replacement (72,189). Laboratory-tested erectile responses to erotic films and fantasy are not abnormal, however, in hypogonadal men. These observations are consistent with the hypothesis that the major effect of androgens on male sexual function is to enhance libido and not to directly control penile erection in a sexual setting. Nocturnal erection appears to be testosterone dependent (189). Therefore certain types of stimuli that promote erection appear to be androgen sensitive, and others do not (14).

There are no current data to suggest that serum testosterone levels in the normal laboratory range are correlated with sexual behavior in humans (74). Although a "threshold" serum level of testosterone for sexual activity probably exists, changes in circulating testosterone concentration do not correlate with sexual activity or interest. Furthermore, testosterone is no more effective than placebo in restoring sexual potency to impotent men without androgen deficiency. In a controlled study involving these patients, more than half of the men reported marked improvement in sexual potency, regardless of whether they received androgen or placebo (23).

Animal models have been used to study the effects of androgens on sexual function. In the rat, castration results in a rapid disappearance of circulating testosterone. Castrated animals exhibit diminished ejaculatory behavior, decreased number of intromissions, and finally, loss of mounting behavior. The administration of testosterone restores normal sexual activity (74). Although testosterone is known to affect spinal reflex activity (139), the primary site of testosterone action in controlling sexual function is probably the brain. The implantation of small amounts of testosterone into the hypothalamic preoptic area, but not into other parts of the brain, restores normal sexual behavior in castrated rats (74).

Hormones other than androgens also are proposed to be important in controlling sexual function. In addition to a loss of libido, most men with hyperprolactinemia are impotent (271). Although a small number of patients with hyperprolactinemia and a normal serum testosterone level have been reported, most patients, and in some series, all of the patients, with hyperprolactinemia have markedly depressed serum testosterone levels (58).

The mechanism responsible for depressed testosterone levels in hyperprolactinemic states is unknown. Increased prolactin may inhibit the action of luteinizing hormone (LH) on Leydig cell function or decrease the secretion of LH either by inhibiting the response of the pituitary to LH-releasing hormone or decreasing the secretion of the latter from the hypothalamus (58). However, impotence associated with this syndrome is not solely related to low testosterone levels. Testosterone replacement does not correct the erectile dysfunction. The fact that sexual function improves when prolactin levels are lowered by bromocriptine therapy has led to speculation that hyperprolactinemia per se may be related to impotence (58). Evidence also exists that supports the concept that the primary effect of hyperprolactinemia is one of diminished libido and that the impotence is secondary or psychogenic (13,311).

## **Summary**

The realization of the importance of the smooth muscle of the corpora cavernosum in the physiology of penile erection has led not only to a better understanding of the erectile process but also to innovative approaches, including oral therapy, to the patient with erectile dysfunction. Penile erection is produced by three interrelated

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processes: (a) relaxation of the smooth muscle of the corpora cavernosa, (b) arteriolar dilation, and (c) decreased venous outflow (probably from passive compression of venules just beneath the tunica albuginea). The sympathetic nervous system (acting through  $\alpha$ -adrenergic receptors) causes contraction of corporal smooth muscles and arterioles and therefore promotes detumescence. Stimulation of parasympathetic nerves produces erection. The neurotransmitters that cause corporal smooth muscle relaxation appear not to be related to classic adrenergic, cholinergic mechanisms, and nitric oxide is an important mediator of this process. Major unanswered questions include the specific events leading to corporal smooth muscle relaxation, the influence of hormones on penile erection, and CNS control of the erectile process.

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