CHAPTER

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Male erectile dysfunction

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Sexual dysfunction is a common, almost expected, consequence of autonomic dysfunction. Neurogenic sexual dysfunction may present with decreased erectile rigidity in the male, decreased clitoral and vaginal blood flow/lubrication in the female, or absent or delayed orgasm in either sex. Secondary rapid ejaculation may occur because of decreased erectile rigidity. This chapter focuses on decreased erectile rigidity.

Decreased erectile rigidity, often termed impotence in the past, is defined by inability to attain sufficient penile hardness for penetrative sex or inability to maintain erectile rigidity until ejaculation. Loss of erection after ejaculation is normal due to the burst of sympathetic stimulation during ejaculation causing markedly decreased penile corporal artery blood flow. Loss of erectile rigidity before ejaculation, however, often implies neurologic or endovascular dysfunction. Individuals with some types of autonomic dysfunction are markedly more prone to develop decreased erectile rigidity than those without autonomic dysfunction. Of men in the population at large, at age 40, approximately 5% never have penile rigidity sufficient for penetration. By age 70, at least 15% of men experience complete erectile dysfunction while approximately 50% have varying degrees of decreased erectile rigidity. Age and physical health are the most important predictors of the onset of erectile dysfunction. Smoking was the most important lifestyle variable. Erectile dysfunction does not correlate well with male hormone levels.

These figures contrast sharply with the prevalence of decreased erectile rigidity in the autonomic dysfunction population. Patients with Parkinson's disease and MSA (**multiple system atrophy**) both have a high rate of decreased erectile rigidity. Decreased rigidity is a common early finding in MSA, while Parkinson patients usually develop decreased rigidity and other urologic problems such as bladder overactivity later in their disease. Singer et al., in a population of older Parkinson patients, demonstrated that 60% of men were affected compared to 37.5% of age matched controls. Beck et al. evaluated 62 patients with MSA for impotence. Their data indicate that 96% of the men were impotent and that 37% appeared to have decreased rigidity as the initial symptom of autonomic dysfunction. Other studies have demonstrated similar results.

Mechanism of erection

Sexual thoughts originating in the cerebral cortex, visual or auditory stimulation, nocturnal cortical stimuli during REM sleep, and tactile sexual stimulation may trigger the pathway leading to penile erection. Nerve signals are carried through the pelvic plexus, a portion of which condenses into the cavernous nerves of the penile corpora cavernosa. It should be noted that while we are focusing on male neuroanatomy, the same structures are present in the female and control blood flow to the female corpora cavernosa.

Nerves course immediately below the aortic bifurcation into the pelvic plexus. Parasympathetic fibers originate in sacral spinal cord segments 2–4 and join the pelvic plexus. Discrete nerves carrying both sympathetic and parasympathetic fibers innervate the organs of the pelvis. Nonadrenergic noncholinergic (NANC) nerves also follow the pelvic plexus to join the cavernous smooth muscle and secrete nitric oxide (NO) into the corporal artery neuromuscular junction. In 1982 Walsh and Donker demonstrated that nerves coursing posterolateral to the seminal vesicles and prostate and immediately lateral to the membranous urethra continue on to innervate the corpora cavernosa. It is now known that branches of these NANC nerves are the principal innervation of the neuromuscular

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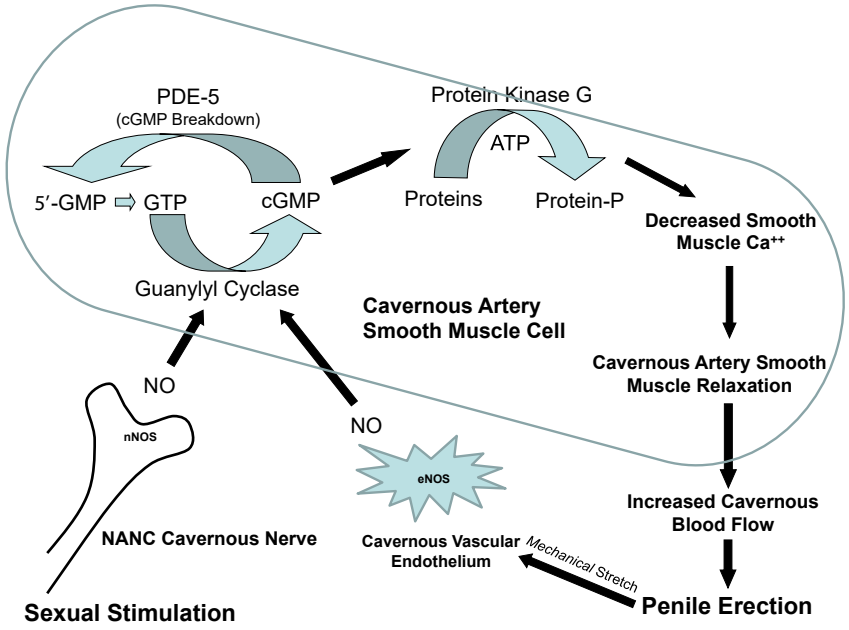

FIGURE 119.1 **Erectile pathway.** Erection is triggered by NO released by NANC nerves while NO produced by corporal trabecular endothelium plays an important role in maintenance of erection.

junction where corporal arterial smooth muscle controls penile blood flow.

Sexual stimulation causes release into the cavernous neuromuscular junction of a number of neurotransmitters from cholinergic parasympathetic and NANC fibers. From the standpoint of erectile rigidity, nitric oxide (NO) from NANC fibers appears to be the principle trigger (Fig. 119.1). The erectile pathway begins with an NO trigger from NANC nerves. Later steps in the pathway lead to corporal artery smooth muscle relaxation which increases corporal artery blood flow and begins erectile elongation. Adequate rigidity for penetrative sex also requires substantial NO production from vascular endothelium lining the trabecula of the corpora cavernosa. This produces the feedback loop shown in Fig. 119.1. NO activates guanylyl cyclase which converts guanosine-5′-triphosphate (GTP) into cyclic guanosine monophosphate (cGMP). Protein kinase G (PKG) is activated by cGMP and in turn activates several proteins which decrease intracellular calcium (Ca^{++}) concentration. Decreased smooth muscle Ca^{++} concentration causes muscular relaxation, cavernosal artery dilation, increased blood flow, and subsequent penile erection. The control of blood flow on the venous outflow side is less well understood.

Etiology of erectile dysfunction

The anatomic sites now felt to be the most common cause of decreased erectile rigidity in the general population are the neuromuscular junction where the NANC nerves meet the smooth muscle and the vascular endothelium of the corporal bodies. This is where nitric oxide and cGMP play a critical role in regulating penile blood flow. The typical erectile dysfunction (ED) patient releases less than the normal amount of NO into the neuromuscular junction. Neurologic disease can produce discrete lesions in central or peripheral nerves which cause erectile dysfunction by altering upstream nerve function, or can alter NO production at the neuromuscular junction and vascular endothelium. In particular, Parkinson disease, multiple system atrophy (MSA), multiple sclerosis, and processes affecting the spinal cord can produce decreased erectile rigidity, failure of emission, or retrograde ejaculation. Other causes of decreased erectile rigidity include drug-induced erectile dysfunction, endocrine disorders, vascular disease, and venogenic erectile dysfunction.

Neuromuscular junction disorders

Nitric oxide is released from cavernosal nerves causing activation of guanylyl cyclase within the corpus cavernosum. Fig. 119.1 illustrates several steps that, if not functioning properly, could impede erectile function. Generation of nitric oxide by the cavernous nerves and the vascular endothelium appears to be a critical trigger for the erectile mechanism. In particular, NANC nerves innervating cavernosal artery neuromuscular junctions appear to trigger penile engorgement and rigidity. Loss of NANC nerve function can markedly impact the patient's ability to achieve an erection.

NO production by corpora cavernosa endothelium appears to play a critical role in maintenance of erection. While further understanding of all the steps in the erectile pathway will likely implicate other biochemical reactions as causing ED, the fact that at least 50% of patients with decreased rigidity from all causes other than trauma or medical treatment respond to phosphodiesterase type-5 inhibition is strong evidence supporting the inference that biochemical dysfunction at the neuromuscular junction/vascular endothelium is the most common cause of decreased erectile rigidity.

Neurogenic erectile dysfunction

Pure neurogenic erectile dysfunction is a frequent cause of erectile failure. Interruption of either somatic or autonomic nerves or their end units may cause erectile dysfunction. These nerves control the flow of blood into and likely out of the corpora cavernosa. Afferent erotogenic somatic sensory signals are carried from the penis via the dorsal penile nerve to the pudendal nerve then to sacral segments 2–4. This information is routed both to the brain and to spinal cord autonomic centers. Parasympathetic autonomic nerves originate in the interomediolateral gray matter of sacral segments 2–4. These preganglionic fibers exit the anterior nerve roots to join with the sympathetic fibers of the hypogastric nerve to form the pelvic plexus and cavernosal nerves. The paired cavernosal nerves penetrate the corpora cavernosa and innervate the cavernous artery and veins. Parasympathetic ganglia are located distally near the end organ.

Sympathetic innervation also originates in the intermediolateral lateral gray matter but at thoracolumbar levels T10-L2. Sympathetic efferents course through the retroperitoneum and condense into the hypogastric plexus located anterior and slightly caudal to the aortic bifurcation. A concentration of postganglionic sympathetic fibers forms the hypogastric nerve which is joined by parasympathetic efferents. Adrenergic innervation plays an important role in detumescence as described previously. High concentrations of norepinephrine have been demonstrated in the tissue of the corpora cavernosa and tributary arterioles. Additionally, the alpha-adrenergic antagonist phentolamine is routinely utilized for intracorporal injection therapy to produce erection.

Afferent signals capable of initiating erection can either originate within the brain, as is the case with psychogenic erections and visual sexual stimulation, or result from tactile stimulation. Patients with spinal cord injury often respond to tactile sensation, but usually require medical therapy to maintain the erection through intercourse. There is no discreet center for psychogenic erections. The temporal lobe appears to be important, however, other locations such as the gyrus rectus, the cingulate gyrus, the hypothalamus, and the mammillary bodies also appear to be important.

Multiple sclerosis (MS) is often associated with erectile dysfunction. Studies have shown the degree of ED to follow the extent and progression of neurologic impact. Winder et al. demonstrated that 45% of patients with insular multiple sclerosis lesions show decreasing International Index of Erectile Function-5 (IIEF-5) score over a 3-month study period. Prevalence of erectile dysfunction, and for that matter sexual dysfunction in both sexes, is high. Zorzon et al. have shown that 50%–90% of MS patients experience both ED and sexual dysfunction in general.

Parkinson's disease is often more problematic for erectile and sexual function than MS. The cerebral dopamine system and pathways are known to be critically important for sexual desire. Loss of desire and ED has been identified as an early autonomic symptom in patients who will later develop Parkinson's. Yang et al. longitudinally followed a cohort of 3153 newly diagnosed ED patients for at least 5 years. Regression analysis revealed the risk of PD was 1.52 times higher in the ED patients versus non ED controls. Similar numbers resulted from the Olmstead County study where a history of ED resulted in 1.5 fold increased odds of a later α-synucleinopathy diagnosis of any type. Overall, Sakakibara et al. reported the prevalence of sexual symptoms in patients with PD ranging from 37% to 65% while the prevalence of ED was 79%.

Men with MSA are probably the group with the highest rate of ED. Mendoza-Velásquez et al. note that erectile dysfunction is present in 97% of men diagnosed with MSA. Additionally, ED was the initial autonomic symptom in 48% with onset of ED predating MSA diagnosis for as long as a decade. Treatment of ED in the MSA population is especially problematic due to often marked orthostasis upon PDE-5 administration.

Endocrine disorders

Testosterone plays a permissive role in erectile function. However, the amount of androgen necessary for normal erectile function is relatively low. Androgen replacement (testosterone cipionate 200 mg q2–3 weeks or daily topical testosterone preparations) is expected to induce return of erectile function in patients with very low (<200 ng/mL) or undetectable serum total testosterone concentration due to true primary or secondary hypogonadism. These patients are relatively uncommon, however. More commonly, the patient with decreased erectile rigidity will have normal or mildly decreased free or total testosterone levels often

diagnosed as adult-onset hypogonadism. Testosterone replacement rarely restores erectile function in those with mildly decreased serum testosterone levels (225–300 ng/mL) and should not be routinely given for that indication. Testosterone supplementation is never indicated for patients with normal circulating androgen levels.

The most common endocrine disorder affecting erectile ability is diabetes mellitus. The most important effect diabetes has on erectile ability appears to relate to loss of function of long autonomic nerves. Erection is partially mediated by efferent parasympathetic cholinergic neural stimuli. Loss of long cholinergic neurons results in interruption of the efferent side of the erectile reflex arc. Diabetes also appears to produce dysfunction of the neuromuscular junction at the level of arterial smooth muscle in the penile corpora cavernosa. Studies have indicated markedly decreased acetylcholine and nitric oxide concentrations in the trabeculae of the corpora cavernosa in diabetics. These findings probably represent a combination of neural loss and neuromuscular junction dysfunction.

Medical and surgical treatment

Effective oral medical therapy has changed the work-up and treatment of ED. Diagnostic tests such as serum testosterone are often deferred unless the patient fails medical therapy if they present with normal libido, no gynecomastia, and testes of normal size and consistency. Guidelines of the American Urological Association recommend a stepwise algorithm beginning with history, physical exam, and quickly progressing to a phosphodiesterase type-5 (PDE-5) inhibitor.

Current medical therapy is based on inhibition of phosphodiesterase type-5 (PDE-5). Fig. 119.1 illustrates that cGMP is broken down to inactive 5′-GMP by PDE-5. Sildenafil, vardenafil, avanafil, and tadalafil competitively inhibit PDE-5 breakdown of cGMP by binding to the catalytic domain of PDE-5 and thereby increasing cGMP concentration. Use of a PDE-5 inhibitor results in improved erectile rigidity even in patients with decreased nitric oxide production or cGMP synthesis. Generally, 60% of patients overall and 80% with ED due to spinal cord injury respond to PDE-5 inhibition.

One study examined the response to sildenafil in patients with Parkinson disease and MSA. Parkinson disease patients experienced improved erectile rigidity similar to patients with idiopathic ED. They did not experience significant orthostatic hypotension. One hour after medication, the standing mean blood pressure dropped 9 mm Hg, compared to 6 mm Hg in normal volunteers. Such was not the case for MSA patients, however. Six patients had been enrolled before the study was halted due to profound orthostatic hypotension. Three patients who had stable blood pressures at study entry experienced standing blood pressure drops of 128/85–65/55, 104/60–56/32, and 115/70–55/39 one hour after taking medication. PDE-5 inhibitors should be used very cautiously in patients with MSA.

Autonomic dysfunction may progress to a point where NANC nerves produce little or no NO. At that point PDE-5 inhibitors are no longer effective. Other therapeutic interventions may be used including pharmacologic injection of prostaglandin E-1 or other agents into the penile corporal body, intraurethral delivery of prostaglandin E-1, vacuum erection devices, and inflatable penile implants. Patients who have good performance status should be offered urologic referral if initial medical therapy fails to achieve adequate penile rigidity.

Further reading

[1] Feldman HA, Goldstein I, Hatzichristou DG, et al. Impotence and its medical and psychosocial correlates: results of the Massachusetts male aging study. J Urol 1994;151:54–61.
[2] Singer C, Weiner WJ, Sanchez-Ramos JR, et al. Sexual dysfunction in men with Parkinson's disease. J Neurol Rehab 1989;3:199–204.
[3] Beck RO, Betts CD, Fowler CJ. Genitourinary dysfunction in multisystem atrophy: clinical features and treatment in 62 cases. J Urol 1994;151:1336–41.
[4] Wenning G, Shlomo Y, Magalhaes M, et al. Clinical features and natural history of multisystem atrophy. Brain 1994;117:835–45.
[5] Walsh PC, Donker PJ. Impotence following radical prostatectomy: insight into etiology and prevention. J Urol 1982;128:492.
[6] Kim N, Azadzoi KM, Goldstein I, et al. A nitric oxide-like factor mediates nonadrenergic, noncholinergic neurogenic relaxation of penile corpus cavernosum smooth muscle. J Clin Invest 1991;88:112.
[7] Winder K, Linker R, Seifert F, Deutsch M, Engelhorn T, Dörfler A, Lee D, Hösl K, Hilz M. Insular multiple sclerosis lesions are associated with erectile dysfunction. J Neurol 2018;265:783–92.
[8] Zorzon M, Zivadinov R, Monti Bragadin L, et al. Sexual dysfunction in multiple sclerosis: a 2-year follow-up study. J Neurol Sci 2001;187(1-2):1–5.
[9] Zorzon M, Zivadinov R, Bosco A, et al. Sexual dysfunction in multiple sclerosis: a case-control study. I. Frequency and comparison of groups. Mult Scler 1999;5(6):418–27.
[10] Yang Y, Liuc H, Linc T, Kuoc Y, Hsieh T. Relationship between erectile dysfunction, comorbidity, and Parkinson's disease: evidence from a population-based longitudinal study. J Clin Neurol 2017;13(3):250–8.
[11] Hasan S, Mielke M, Ahlskog JE, Bower J, Turcano P, Savica R. Erectile dysfunction preceding clinically diagnosed α-synucleinopathies: a case-control study in Olmsted County. Parkinson's Dis 2019:6. Article ID 6303945.
[12] Sakakibara R, Uchiyama T, Yamanishi T, Kishi M. Genitourinary dysfunction in Parkinson's disease. Mov Disord 2010;25(1):2–12.
[13] Mendoza-Velásquez JJ, Flores-Vázquez JF, Barrón-Velázquez E, Sosa-Ortiz AL, Illigens BW, Siepmann T. Autonomic dysfunction in a-synucleinopathies. Front Neurol April 2019;10. Article 363.

[14] Blanco R, Saenz de Tejada I, Goldstein I, Krave RJ, Wotiz HH, Cohen RH. Dysfunctional penile cholinergic nerves in diabetic impotent men. J Urol 1990;44:278–80.
[15] Burnett AL, Nehra A, Breau RH, et al. Erectile dysfunction: AUA guideline. J Urol 2018;200:633.
[16] Turko IV, Ballard SA, Francis SH, Corbin JD. Inhibition of cyclic GMP-binding cyclic GMP-specific phosphodiesterase (type 5) by sildenafil and related compounds. Mol Pharmacol 1999;56: 124–30.
[17] Hussain IF, Brady CM, Swinn MJ, Mathias CJ, Fowler CJ. Treatment of erectile dysfunction with sildenafil citrate (Viagra) in parkinsonism due to Parkinson's disease or multiple system atrophy with observations on orthostatic hypotension. J Neurol Neurosurg Psychiatr 2001;71:371–4.