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ERECTILE DYSFUNCTION PHYSIOPATHOLOGY

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DEFINITION AND EPIDEMIOLOGY OF ERECTILE DYSFUNCTION

The Fourth International Consultation on Sexual Medicine has defined erectile dysfunction (ED) as the consistent or recurrent inability to attain and maintain penile erection sufficient for sexual satisfaction.[1] ED is classified as organic, psychological, or mixed (resulting from several simultaneous factors), which is the most common form. Even today, it is still problematic to obtain an accurate estimation of the impact and the incidence of ED because of social, ethical, cultural, and religious reasons leading to reduced and delayed seeking of medical advice. Aging is an independent risk factor for the development of erectile dysfunction, and thus many men are convinced that sexual impairment is an inevitable feature of late age.[2-4] The global mean ED prevalence ranges from 14% to 48%, with higher rates in the United States and Southeast Asia compared with European rates.[5,6] In the United States, at least 12 million men between 40 and 79 years of age have ED, whereas in Italy the reported prevalence of ED (complete and incomplete) is 12.8%, with a significant incidence of age-related ED (2% between 18 and 30 years and 48% over 70 years).[7] Based on the Massachusetts Male Aging Study (MMAS) data, for a population range between 40 and 70 years, ED increased with age from 5.1% to 15% and from

17% to 34 % for complete and moderate ED respectively; mild ED remained stable at around 17% over the years. Furthermore, the prevalence of ED worldwide is estimated to reach 322 million men by 2025,[8] but this percentage may be underestimated.

Performance anxiety and relationship issues are commonly recognized psychological causes of ED. However, its prevalence is also related to several age-independent comorbidities such as heart diseases, hypertension, other vascular disorders, psychiatric disorders (depression), endocrine disorders (diabetes, reduction of testosterone), neurological disorders, and other concomitant genitourinary disease related to surgery.[9] This chapter aims to give a fast and easy way to read an overview of ED physiopathology.

SUMMARY BOX

- Erectile dysfunction (ED), defined as the inability to obtain or maintain a penile erection, is a quite common condition among men and can be due to many factors.
- ED is classified as organic, psychological, or mixed (resulting from several simultaneous factors), which is the most common form.
- The global mean ED prevalence ranges from 14% to 48%. Based on the Massachusetts Male Aging Study (MMAS) data, the prevalence of ED worldwide is estimated to reach 322 million men by 2025.

ANATOMY OF AN ERECTION

ANATOMY, VASCULARIZATION, AND INNERVATION OF THE PENIS

An erection is a neurovascular event that consists of a vascular phase that is the consequence of the balance between arterial inflow and venous outflow. The penis is characterized by three cylindrical structures: the paired corpora cavernosa (which represent the dorsal and lateral portion) and the corpus spongiosum, including the urethra (which represents the ventral portion). A loose subcutaneous layer and skin cover all these structures. The tunica albuginea is a structure made up of bundles of collagen fibers; it is bilayered. The outer-layer bundles are oriented longitudinally from the glans penis to the proximal crura, while the inner-layer bundles are oriented circularly and house the corpora cavernosa. Oblique-oriented fibers connect these two main layers. Emissary veins are contained between these two layers and are compressed during erection by the outer one. The thickness of the albuginea varies among individuals and locations: it is higher at the ventrolateral level. On average, however, it measures between 2 mm and 3 mm when the penis is flaccid and reduces to 0.5 mm during erection, providing rigidity to the corpora cavernosa and participating in the veno-occlusive mechanism. Corpora cavernosa are a conglomeration of sinusoids – more abundant at the center and smaller near the periphery – in which the blood tends to circulate centrifugally from the central to the peripheral sinusoids (flaccid state). During an erection, the arterial blood rapidly flows

to both the central and the peripheral sinusoids, changing the intracavernous blood gas to the level of arterial blood.[10] The smooth muscle tone regulates the blood flow inside and outside the sinusoids. Even though the corpus spongiosum has a similar structure to the corpora cavernosa, it has no outer layer, a feature that guarantees a lower pressure during erection. The primary source of penile blood derives from the branch of the internal iliac artery: the internal pudendal artery. However, there may be accessory arteries (branches of the external iliac, obturator, vesical, femoral arteries), and in some men, they may represent the main or the only blood supply to the corpora cavernosa.[11] The internal pudendal artery ends in the common penile artery, which has three branches: dorsal, bulbourethral, and cavernous (Figure 1.1).

SUMMARY BOX

- The penis comprises three cylindrical structures: the paired corpora cavernosa (which represent the dorsal and lateral portion) and the corpus spongiosum, including the urethra (which represents the ventral portion).
- Corpora cavernosa are a conglomeration of sinusoids in which the blood tends to circulate centrifugally.
- The primary source of penile blood derives from the branch of the internal iliac artery: the internal pudendal artery.
- The venous circulation starts from venules arising from the peripheral sinusoids, beneath the tunica albuginea, and form the subtunical venous plexus before ending in the emissary veins.
- The innervation of the penis is both autonomic and somatic.
- Triggering parasympathetic nerves leads to the erection, while detumescence is the consequence of sympathetic nerve stimulation.

The dorsal artery provides the engorgement of the glans, the bulbourethral artery vascularizes the bulb and corpus spongiosum, and the cavernous artery determines the tumescence of the corpora cavernosa during erection. The venous network starts from venules arising from the peripheral sinusoids, beneath the tunica albuginea. These venules run between the tunica and the peripheral sinusoids to form the subtunical venous plexus before ending in the emissary veins.

The innervation of the penis is both autonomic and somatic. Somatic innervation

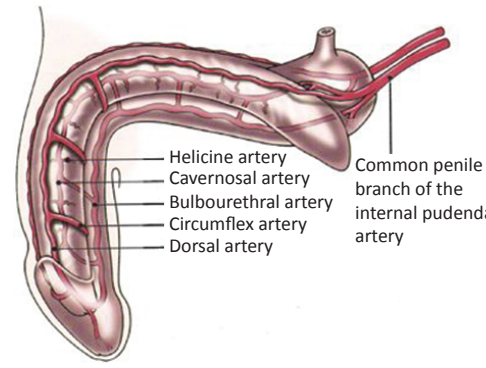

Figure 1.1. Penile vascular anatomy and arterial blood supply.[12]

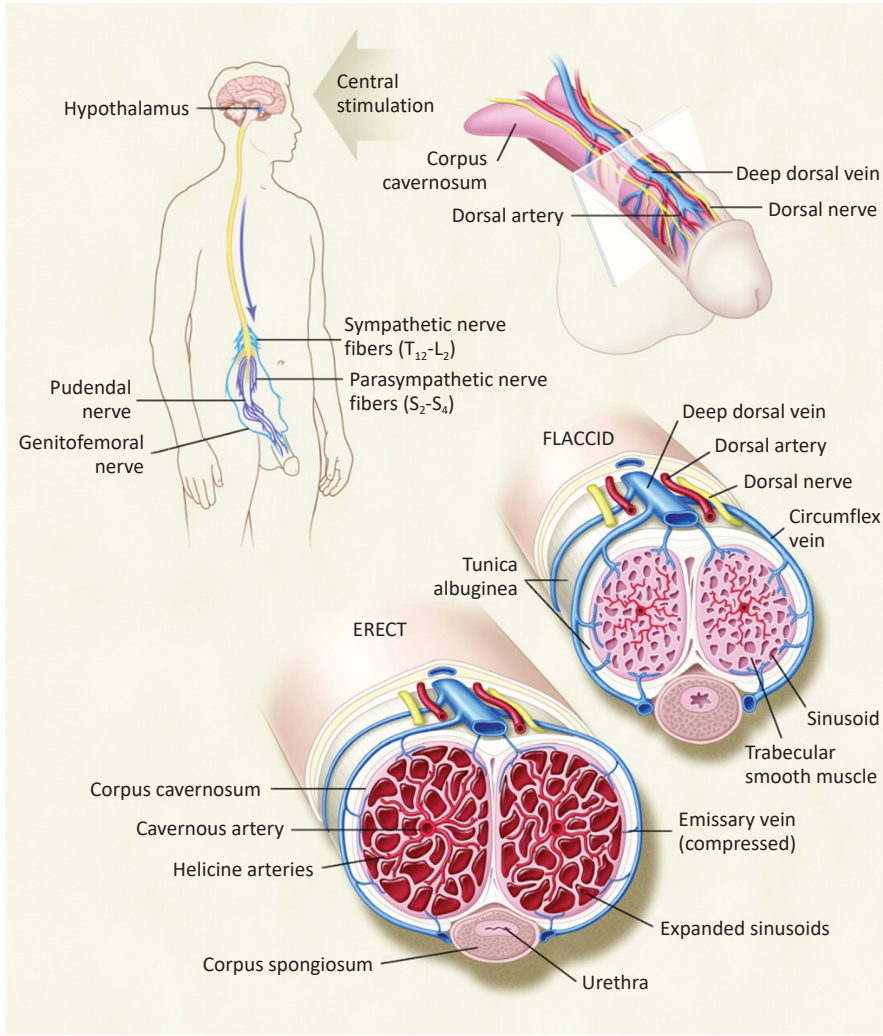

Figure 1.2. Nerve pathway for penile mechanism of erection; the trigger can be a direct genital stimulation and a central stimulus.[13]

(responsible for sensation and muscle contraction) arises from the second to fourth sacral spinal cord segments. These nerves travel into the pudendal nerve to innervate the ischiocavernosus and the bulbocavernosus muscles, which are responsible, respectively, for the rigid erection phase and the semen expulsion. Sympathetic nerves originating from the eleventh thoracic to the second lumbar spinal segments are responsible for the autonomic innervation represented by sympathetic chain ganglia and parasympathetic nerves that arise from the second, third, and fourth sacral spinal cord segments (pelvic

nerves). Some of the sympathetic fibers run through the lumbar splanchnic nerves to the superior hypogastric and the inferior mesenteric plexuses, from which fibers end in the hypogastric nerves to the pelvic plexus. The pelvic nerves of the parasympathetic fibers pass into the pelvic plexus, where they merge with the sympathetic nerves arising from the superior hypogastric plexus. Finally, the cavernous nerves, branches of the pelvic plexus, are responsible for penile innervation. Triggering the pelvic plexus and the cavernous nerves leads to an erection, while detumescence is the consequence of sympathetic nerve stimulation (Figure 1.2).

VASCULAR MECHANISMS OF AN ERECTION

EXPLANATION OF THE PRIMARY VASCULAR PATHWAYS AT THE BASE OF AN ERECTION

An erection is a combination of sinusoid relaxation, arterial dilation, and venous compression. The cavernous smooth musculature and the smooth muscles of the arteriolar and arterial walls play a fundamental role in the erectile process: In the flaccid state, these smooth muscles are tonically contracted, a state that prevents blood from properly flowing into the corpora. α-adrenergic nerve fibers – α1, α2, and their receptors – are located in the cavernous trabeculae and cavernous arteries. Post-junctional α1-adrenergic receptors trigger contraction, whereas prejunctional α2-adrenergic receptor activation downregulates the release of neurotransmitters (norepinephrine and nitrile oxide [NO]).[14,15] Norepinephrine is the principal neurotransmitter involved in the flaccid state. Adrenergic nerves release norepinephrine to stimulate adrenergic system; when bound with its receptor, it produces a contraction that involves Ca^{2+} entry through calcium channels and the activation of protein kinase C, tyrosine kinases, and Rho-associated protein kinase.[14,15] Endothelin-1 is synthesized by the endothelium and acts as a potent vasoconstrictor, more than epinephrine: It induces long-lasting smooth muscle contractions, enhances catecholamine-mediated constrictor effects on trabecular smooth muscle, and is considered a mediator for detumescence.[16,17]

When arousal occurs, parasympathetic activity from the sacral segments of the spinal cord triggers the cavernous nerve terminals to release neurotransmitters. Sexual function is related to numerous neurotransmitters and neuropeptides; the main ones are dopamine, oxytocin, NO, norepinephrine, serotonin (5-hydroxytryptamine), and prolactin. Acetylcholine is no longer considered to be the primary neurotransmitter: By presynaptic inhibition of adrenergic neurons and release of NO by endothelial cells, it contributes indirectly to penile erection.[18] NO released from noncholinergic neurotransmission and the endothelium is currently considered to be the predominant neurotransmitter responsible for penile erection. NO spreads at the cellular level and activates the guanylate cyclase (Figure 1.3), increasing the production of cyclic guanosine monophosphate (cGMP), which relaxes the cavernous smooth muscle.[14]

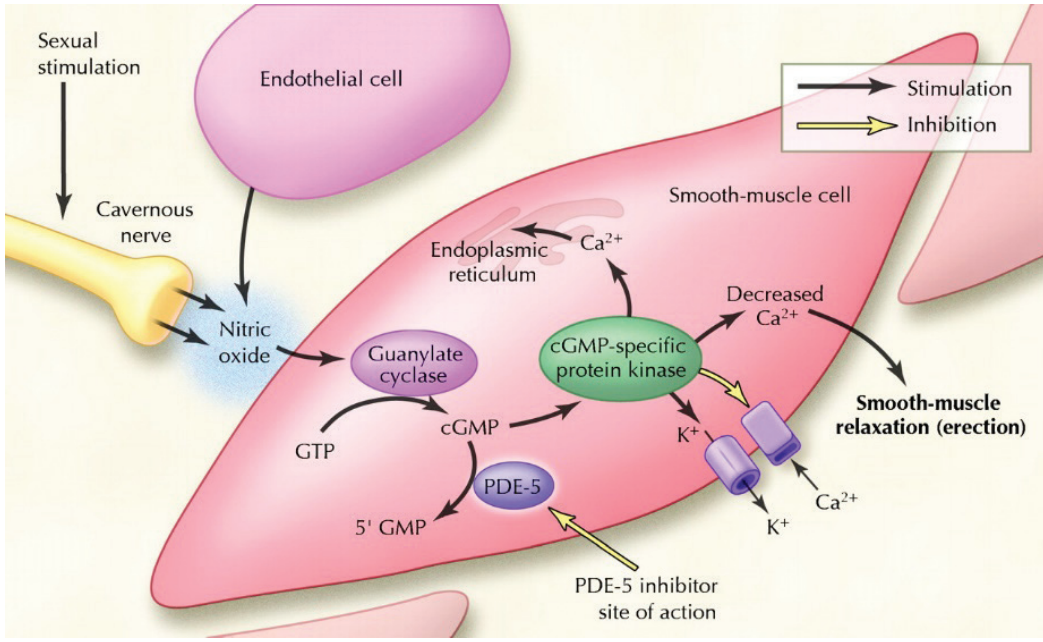

Figure 1.3. The molecular pathway of penile erection, including the central role of nitric oxide (NO). NO is released from nerve endings to increase the intracellular level of cyclic guanosine monophosphate (cGMP), which in turn induces a cascade reaction that leads to smooth-muscle relaxation through a reduction of the intracellular calcium level.[13]

NO-induced smooth muscle relaxation allows a series of events to occur:

1. dilation of the arterioles, increasing the blood inflow;
2. dilation of sinusoids, entrapping the incoming blood;
3. reduced venous outflow by the compression of the subtunical venous plexuses;
4. elongation and shrinking of the tunica, contraction of the ischiocavernosus muscle, which occludes the emissary veins, and an increase in the intra-cavernous pressure to a level higher than systolic pressure (the full erection phase).

During sexual stimulation, reflex contractions of the ischiocavernosus muscles (rigid-erection phase) can lead to an additional pressure increase. The corpus spongiosum and glans penis act distinctly from corpora cavernosa: The spongiosum and glans mostly work as a large arteriovenous shunt during the erection phase. In this phase, the arterial flow increases in a similar way; however, the flow pressure in the corpus spongiosum and glans represent only 30-50% of all corpora cavernosa. This is due to the tunica albuginea (thin at the corpus spongiosum and practically absent on the glans), which facilitates weaker venous occlusion. In the full-erection phase, partial compression of the deep dorsal and circumflex veins contributes to glans tumescence. In the rigid-erection phase, the ischiocavernosus and bulbocavernosus muscles compress the

spongiosum and penile veins. These actions contribute to additional engorgement and increased pressure in the glans and spongiosum. After ejaculation, the smooth muscles contract to gradually reduce intra-cavernous pressure, leading to venous relaxation and, consequently, blood outflow, supported by the breakdown of cGMP by phosphodiesterases (PDEs), the cessation of NO release, and sympathetic discharge (responsible for ejaculation).

SUMMARY BOX

- When arousal occurs, parasympathetic activity from the sacral segments of the spinal cord triggers the cavernous nerve terminals to release neurotransmitters, among which nitric oxide (NO) is predominant.
- NO-induced smooth muscle relaxation allows a series of events to occur:
  - dilation of the arterioles, increasing the blood inflow;
  - dilation of sinusoids, entrapping the incoming blood;
  - reduced venous outflow by the compression of the subtunical venous plexuses; and
  - elongation and shrinking of the tunica, contraction of the ischiocavernosus muscle occluding the emissary veins, and an increase in the intracavernous pressure to a level higher than systolic pressure (the full erection phase).

ED ETIOPATHOGENESIS AND RISK FACTORS

CLASSIFICATION OF ED AND MAIN RISK FACTORS

ED can be classified as psychogenic or organic,[19] even though it is believed that it is the result of a complex interaction between psychogenic and organic factors (mixed ED). Primary ED refers to a lifelong condition, beginning with the first sexual encounter. Although most cases are due to psychological factors, a few afflicted men have a physical cause resulting from maldevelopment of the penis or the blood and nerve supply.

PSYCHOGENIC FACTORS

Primary psychological dysfunction is usually related to anxiety. In younger men, it is more likely that psychogenic factors are involved, whereas in men older than 50 years, an organic origin is acknowledged in more than 50% of cases. Psychogenic ED was previously considered to be the most common,[20] and this view led to the belief that ED is usually a mixed condition. In psychogenic impotence, emotional factors play a key role in the onset of the symptoms. It can be determined by neurosis or more frequently by socio-environmental situations, which tend to reoccur over time. Psychogenic ED can be explained by direct inhibition of the spinal erection center by the brain, causing an excessive sympathetic nerve activity or elevated serum levels of catecholamines, preventing the relaxation of smooth

muscle.[21] Levels of peripheral norepinephrine have been reported as higher in patients with psychogenic ED compared with healthy controls.[22] It has been proven that male sexual response is a balance between excitatory and inhibitory impulses within the central nervous system (CNS).[23] For example, ED has higher rates in men with psychiatric disorders (schizophrenia, bipolar affective disorder, recurrent depressive disorder, or substance use disorder), and in patients attending psychiatric clinics, the prevalence of ED was 83%.[24]

ARTERIOGENIC FACTORS

Hemodynamic changes in vascular ED could be responsible for lower arterial inflow or impaired venous outflow. In the first case, atherosclerotic or traumatic arterial occlusion of the hypogastric-cavernous-helicine arterial tree (Leriche syndrome) can result in decreased arterial flow to the sinusoids, with a slow loss of penis rigidity and increased latency time to the full erection phase. Oxygen tension in corpus cavernosum blood is lower in arteriogenic ED[25] and may cause alterations in cavernous smooth muscle, leading to a venous leakage.[26,27] Common risk factors associated with arteriogenic ED are hyperlipidemia, diabetes mellitus, cigarette smoking, hypertension, pelvic irradiation, or pelvic trauma. These risk factors are, for the most part, similar to those for cardiovascular disease.[9,28] In ED patients with atherosclerosis, diffuse arterial disease of the principal pelvic arteries responsible for penile vascularization (internal pudendal, common penile, and cavernous) has been demonstrated.[29] ED may be indicative of ischemic disorder in other districts. Given that ED and cardiovascular disease share the same risk factors, many studies have underlined the association of ED with cardiovascular pathologies. The finding of sexual dysfunction in men with cerebral, peripheral, and coronary arterial disease is higher.[30] Men with coronary arteriopathy showed an increased prevalence of ED proportional to the severity of coronary lesions.[31] The interaction between chronic inflammation, androgens, and cardiovascular risk factors determines endothelial dysfunction and, consequently, atherosclerosis, which affects both penile and coronary arteries. Moreover, penile arteries have a smaller size compared with coronary arteries: hence, for the same level of arteriopathy, a more significant blood flow reduction will occur in erectile tissue compared with coronary circulation. Ninety-three percent of patients with chronic coronary disease and ED had an earlier onset of sexual dysfunction compared to coronary artery disease onset.[31]

Hypertension is an independent risk factor for ED.[9] The potential factors determining ED in men suffering from hypertension include longer duration of disease, older age, greater disease severity, and the use of antihypertensive agents.[32] Arterial hypertension is a chronic condition in which the vascular tone is altered by increased contractility, resulting in higher levels of blood pressure. However, the increased blood pressure itself does not affect sexual function. In essence, the interaction of biochemical and structural changes in the arterial walls (such as proliferation, migration of vascular smooth muscle cells, and increased levels of inflammation) is thought to be the cause.[33] Obesity and hyperlipidemia have been related to erectile impotence: High body weight, body mass index (BMI), and total body fat percentage are independent factors for the onset of moderate to