Erectile Dysfunction: Epidemiology, Physiology, Pathophysiology

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Key Points:

1. The prevalence of erectile dysfunction (ED) ranges from 6-64%, increases with age, and is found in higher rates in the United States than other parts of the world. It is poorly studied in men under the age of 40, however prevalence of ED in both young and older men seems to be increasing.
2. A complex coordination of the somatic and autonomic nervous systems, which is chemically mediated primarily by nitric oxide, allows for increased arteriolar inflow and decreased venous outflow.
3. Causes of ED can be divided into neurogenic, vascular, endocrine, medication-induced and psychogenic. There is also evolving research of the effect of the gut microbiome on different organ systems that may impact erectile function.

1. Introduction

A complex interplay of neural, vascular, hormonal, and psychological factors mediate the process of penile erection. Disruption in any or all of these pathways may lead to erectile dysfunction (ED). ED is defined as the consistent or recurrent inability to attain and/or maintain penile erection sufficient for sexual satisfaction. [1,2] An understanding of erectile physiology is essential to the practicing urologist.

2. Epidemiology of ED

Existing studies on the prevalence of ED rely on a variety of means for assessment including single item questionnaires and validated survey instruments. This variability complicates comparison between studies.

In the United States, the Massachusetts Male Aging Study (MMAS) was one of the first studies to prospectively study the epidemiology of ED in American men. [3] The overall prevalence of ED of any

severity in this population of 1,290 men aged 40-70 years was 52%; 35% of these men reported moderate to severe ED. Using the National Health and Social Life Survey, Laumann et al reported that 7% of men aged 18-29 reported difficulty attaining or maintaining erection; the prevalence of this complaint increased with age to 18% in men aged 50-59.[4] In the surveyed 1,244 men, prevalence for ED was less in Hispanics (5%) than Blacks (13%), other races/ethnic groups (12%), and Whites (10%).[5] The Boston Area Community Health survey reported ED in 10% of men aged 30-39 increasing to 59% of men aged 70-79.[6] Data from the 2005–2006 National Social Life, Health, and Aging Project estimated a 39% prevalence of ED in men aged 57-85 with prevalence greater with increasing age.

The Global Survey of Sexual Attitudes and Beliefs (conducted worldwide in men and women aged 40 to 80 years) reported some regional variation in the prevalence of ED; however, the general prevalence of ED of any severity for men globally ranged between 5 and 28%.[7] The European Male Aging Study, comprised of groups of men of similar age, reported a prevalence of ED ranging from 6-64% depending on different age subgroups. Prevalence of erectile dysfunction increased with age, with the average prevalence estimated at 30%. [8] The prevalence of ED in men younger than 40 is not as well-studied; however, however Maggi and colleagues found that out of 3,000 consultations for ED, 14% were men under 40 years of age.[9,] Few studies have evaluated the prevalence of ED worldwide, however almost all studies show a systematically higher prevalence of ED in the United States and southern/eastern Asian countries than in Europe and South America.[10] Especially when considering the rapidly aging populations worldwide, Ayta et al, using data from MMAS, predicted the prevalence of ED in 2025 to be 322 million men, more than the estimated 152 million men with ED in 1995,[11] underscoring the need for proper diagnosis and treatment in the future.

ED has clearly been associated with hypertension, diabetes mellitus (DM), and dyslipidemia. Accordingly, 38-42% of men with hypertension manifest some form of ED[12] while up to 42% of men with dyslipidemia also suffer from difficulty with erections.[13] Men with poor erections also have a roughly two-fold risk in elevated total cholesterol/high density lipoprotein cholesterol ratio compared to normal counterparts.[14] DM is possibly the most predictive of ED, with 52.5% of men with DM having ED and when compared to non-DM healthy controls, men with DM were at a 3.5 times increased risk of ED.[15] An increase in the relative risk of ED is associated with an increased duration of DM.[14] ED is also associated with certain behavioral risk factors, in particular smoking, alcohol and drug usage, while dietary intake, physical activity and intimacy are protective against ED.[16]

It is clear from existing data that ED is a common concern for men and their partners. ED profoundly impacts quality of life.[17,18] ED is also associated with anger, depression, and anxiety.[3,18,19]

3. Penile Anatomy

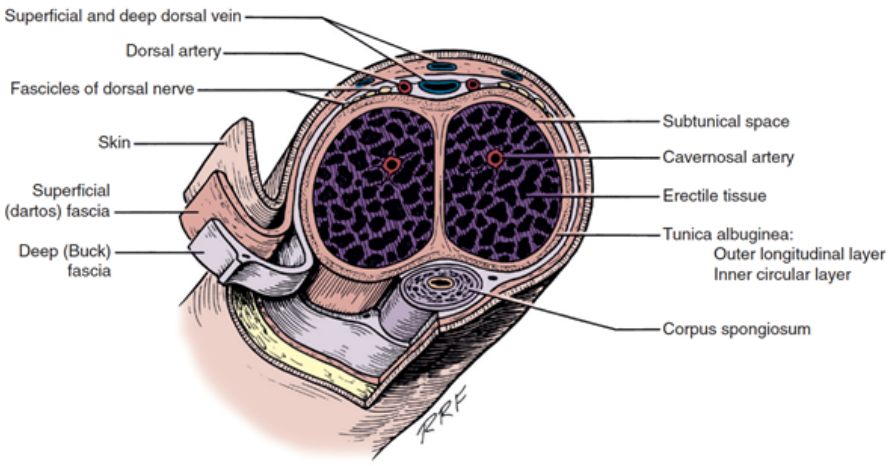

Figure 1: Schematic of the Corpus Cavernosum Cross-Sectional Anatomy

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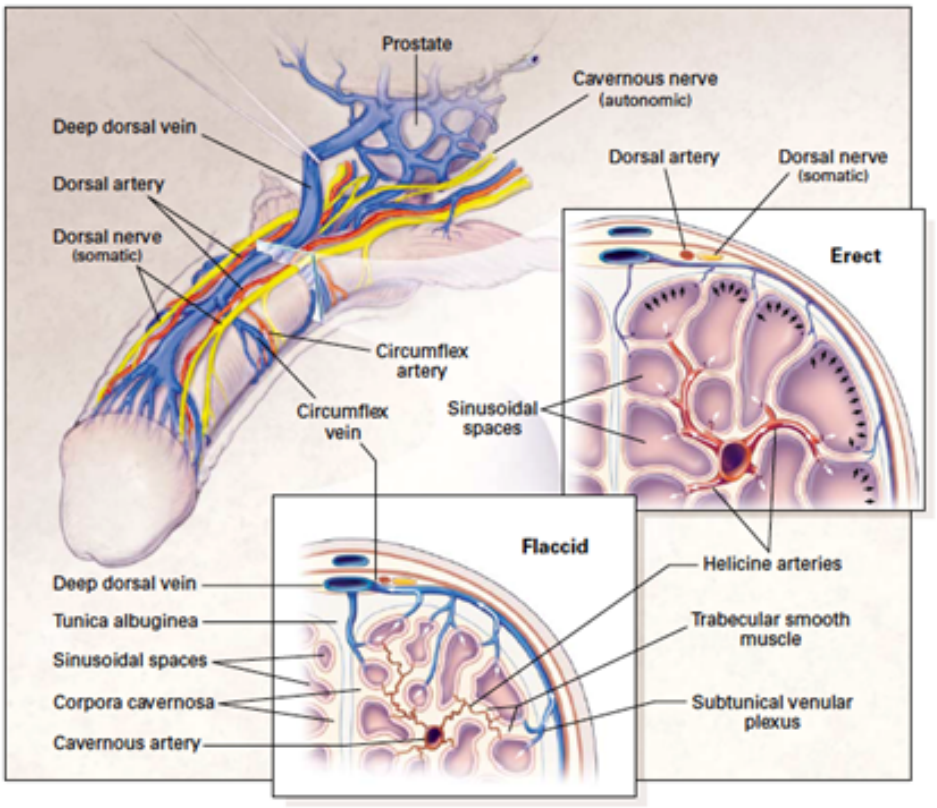

Figure 1. Anatomy and Mechanism of Penile Erection.

The cavernous nerves (autonomic), which travel posterolaterally to the prostate, enter the corpora cavernosa and corpus spongiosum to regulate penile blood flow during erection and detumescence. The dorsal nerves (somatic), which are branches of the pudendal nerves, are primarily responsible for penile sensation. The mechanisms of erection and flaccidity are shown in the upper and lower inserts, respectively. During erection, relaxation of the trabecular smooth muscle and vasodilatation of the arterioles results in a severalfold increase in blood flow, which expands the sinusoidal spaces to lengthen and enlarge the penis. The expansion of the sinusoids compresses the subtunical venular plexus against the tunica albuginea. In addition, stretching of the tunica compresses the emissary veins, thus reducing the outflow of blood to a minimum. In the flaccid state, inflow through the constricted and tortuous helicine arteries is minimal, and there is free outflow via the subtunical venular plexus.

Figure 2: Reprinted from Lue TF. “Erectile Dysfunction.” The New England Journal of Medicine 2000, 342: 1802-1813 with

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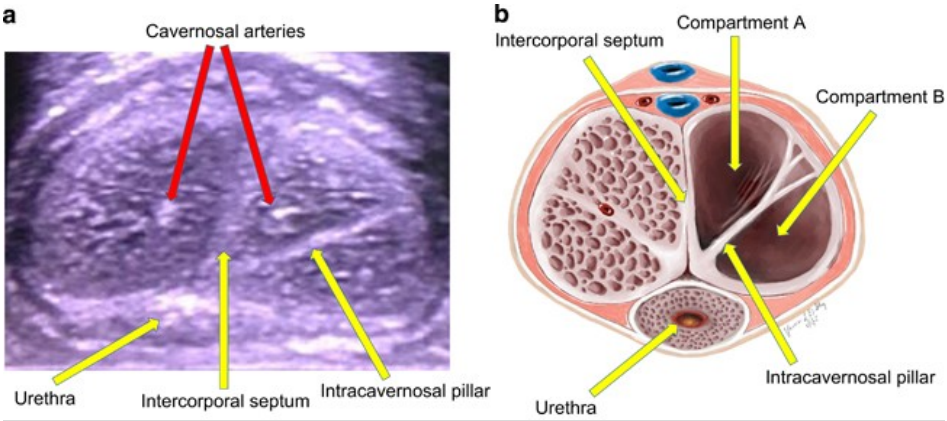

Figure 3: Reprinted from Pagano MJ, Weinberg AC, Deibert CM, Hernandez K, Alukal J, Zhao L, Wilson SK, Egydio PH, Valenzuela RJ. Penile intracavernosal pillars: lessons from anatomy and potential implications for penile prosthesis placement. Int J Impot Res. 2016 May;28(3):114-9

3.1 Corporal Bodies

The penis is composed of three cylindrical bodies. The paired and interconnected corpora cavernosa are located dorsally. The ventrally located corpus spongiosum contains the urethra and extends distally to fill the interior of the glans penis.[20] A simplified schematic of the penis is presented in **Figure 1**. Each corporal body is surrounded by a thick, fibrous sheath called the tunica albuginea; the tunica of the corpus spongiosum is thinner than that of the corpora cavernosa. The tunica albuginea is bilayered in structure (outer longitudinal and inner circular fibers) and composed of collagenous fibers and elastin fibers. This structure is relaxed in the flaccid state and stretched during tumescence. [21] The corporal bodies are composed of a meshwork of interconnected cavernosal spaces called sinusoids (or lacunae) in which blood accumulates during an erection. The sinusoids are lined with a single layer of vascular endothelium and are separated by trabeculae containing bundles of smooth muscle in a framework of collagen, elastin and fibroblasts.[20,22] It also has structures called intracavernosal struts (or pillars), which are thought to be important in keeping the erectile tissue in place (**Figure 3**).[23] All three corporal bodies are ensheathed by the deep (Buck's) and superficial (Dartos) fasciae of the penis.

The pelvic floor musculature is also relevant for the erectile response.[24,25] This musculature is separate from the penile erectile tissues. The principal pelvic muscles are the bulbospongiosus and ischiocavernosus muscles that surround the corporal bodies at the base of the penis within the pelvis.

3.2 Neuroanatomy of the Penis

Penile erection is a reflex mediated by the central nervous system. It may be triggered by tactile stimulation of the penis (reflexogenic erection mediated by stimulation of a parasympathetic sacral reflex arc) or mental/emotional arousal (psychogenic erection medicated by cortical suppression of

vasoconstrictive sympathetic tone).[26] The fundamental unifying factor in all penile erection is increased blood flow into the penis via vasodilation. The balance between contractile and relaxant stimuli modulates smooth muscle contraction in the cavernous artery and corpora cavernosa, which in turn modulates penile vasculature (see ***Section 2.3***).

The innervation of the human penis consists of autonomic and somatic (sensory and motor) input from the pelvic (parasympathetic), hypogastric (sympathetic) and pudendal (somatic) nerves. The pelvic ganglion (also known as the inferior hypogastric plexus) is the crossroads for genital autonomic nerves. These consist of non-cholinergic non-adrenergic (NANC, or nitrergic – nerve cells in which transmission is mediated by nitric oxide) parasympathetic fibers from the sacral nerve roots (S2-4) and noradrenergic sympathetic nerve fibers from the thoracolumbar sympathetic nerve roots (T11-L2). This important plexus is located along the posterolateral pelvic wall medial to the internal iliac artery.[27] Sympathetic and parasympathetic fibers within the pelvic plexus merge to form the cavernous nerve (CN), which provides innervation to the corporal tissues.

Neural impulses travel through the CN to effect the penile vascular changes that occur during erection and detumescence. Erection is driven primarily by parasympathetic neurons located in the pelvic ganglion, which projects to the corpora cavernosa via the CN.[28] Somatosensory neural pathways play an additional neuroregulatory role in penile erection. These pathways convey afferent sensory information that is involved in reflexive erections by stimulation of parasympathic sacral neurons in a reflex arc. Supplementary efferent outflow from sacral spinal cord levels via the pudendal nerve regulates the action of the pelvic floor musculature that subsequently promotes rigid erection.[29]

3.3 Vascular Anatomy of the Penis

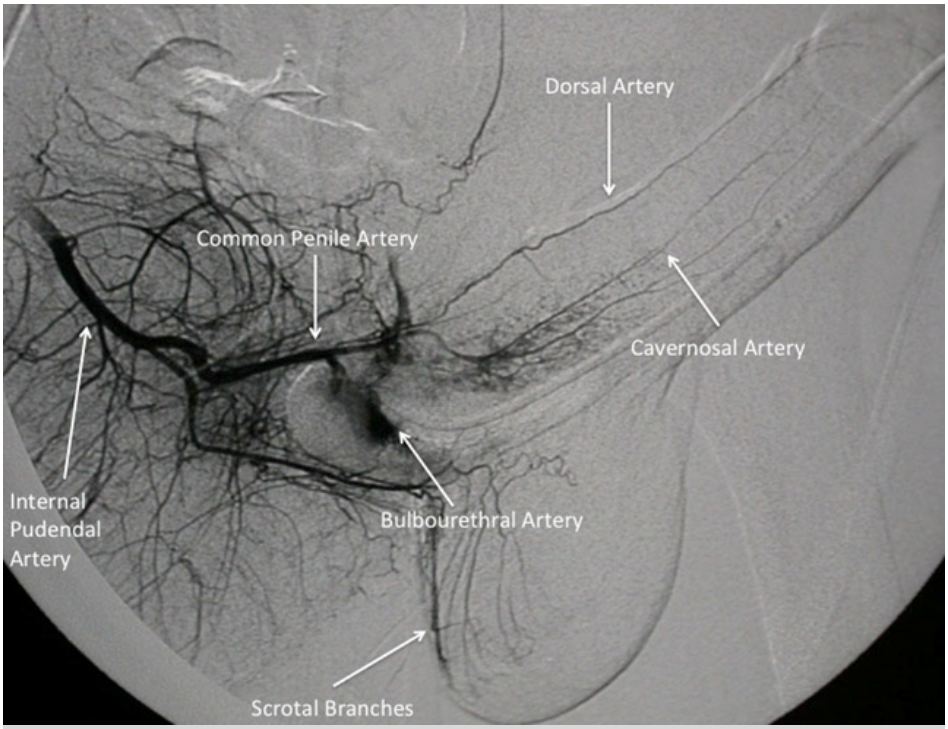

Figure 4: Vascular Anatomy of the Penis

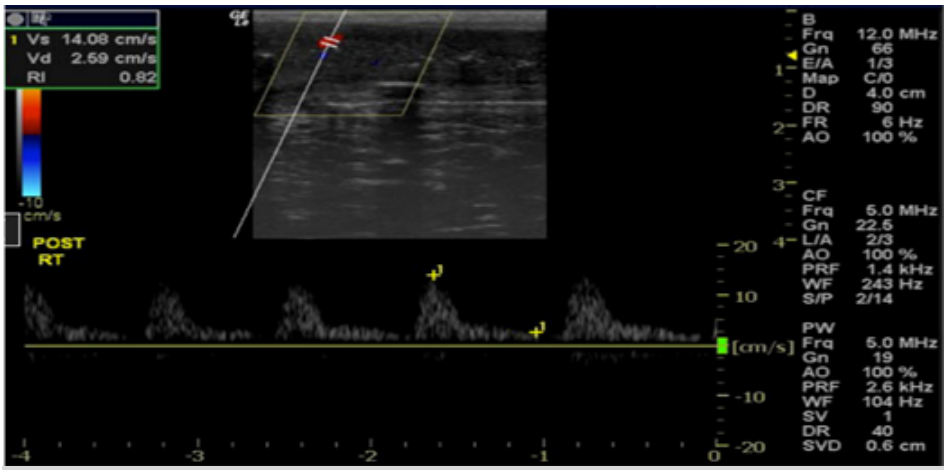

Figure 5: Doppler Ultrasound demonstrating Arterial Insufficiency: Erectile Dysfunction.

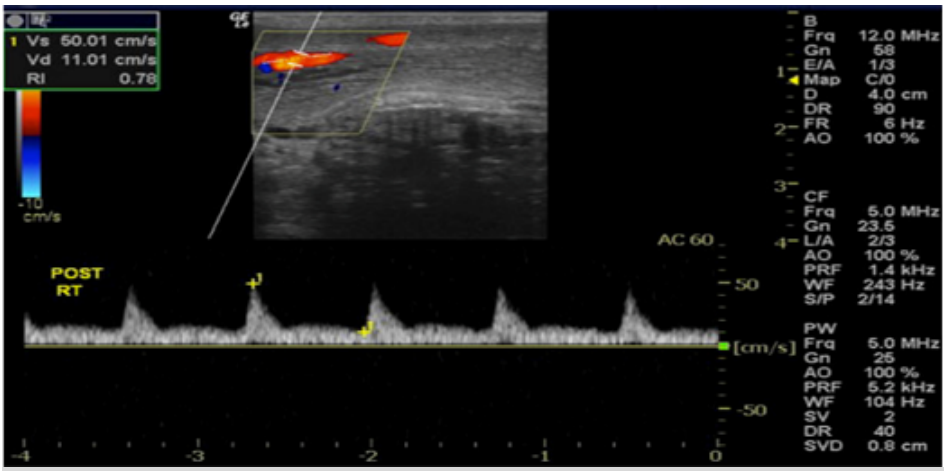

Figure 6: Doppler Ultrasound demonstrating Venous Leak leading to Erectile Dysfunction.

The arterial supply to the penis is derived from the internal pudendal artery, a branch of the internal iliac artery. The internal pudendal artery travels through Alcock's canal and splits into the bulbourethral, dorsal and cavernosal arteries[30] (**Figure 4**). The bulbourethral artery supplies the urethra and glans. The cavernosal arteries enter the corpora cavernosa and split into many branches, including the helicine arterioles that open directly into the cavernous sinusoids. The paired dorsal arteries supply superficial penile structures via circumflex arteries along the penile shaft and the corpora cavernosa through penetrating branches of the tunica albuginea into the corporal bodies. [30]

Venous drainage of the corporal bodies is accomplished via emissary veins located between the spongy corporal tissue and the tunica albuginea of the corpora cavernosa. These veins coalesce into the deep dorsal vein of the penis which drains to the prostatic venous plexus. The glans penis and parts of the corpora are also drained by the superficial dorsal vein of the penis. [30]

Erection is driven by the balance of blood inflow from the cavernosal arteries and blood outflow from penile veins. During erection, the sinusoids of the corpora cavernosa (and to a lesser extent the

corpus spongiosum) become filled with blood. In the absence of stimulation, the penile arterioles are partially constricted, restricting the blood flow into the sinusoids (flaccid state). During stimulation, parasympathetic nerve impulses travel from the spinal cord to the penile arterioles and cavernosal smooth muscle, causing smooth muscle relaxation and dilation of vessels and sinusoids. This allows more blood into the sinusoids, which puts pressure on the venous outflow from the corporal bodies. Restriction of venous outflow produces penile tumescence in what is known as the full erection phase. [31]

Veno-occlusion is a key feature for the mechanism whereby blood is maintained in the penis and intracorporal pressure is increased to produce penile erection.[32] The functional anatomy of the penis is critical for the function of this mechanism. Sub-tunical venules lie beneath the tunica while emissary veins traverse the tunica albuginea. The veno-occlusive mechanism works through compression of the sub-tunical venules and elongation and narrowing of the emissary veins as the cavernosal sinusoids expand. Thus, the normal composition and functional compliance of erectile tissues is critical to the mechanism of veno-occlusion during erection. [33] As smooth muscle content decreases (usually replaced by collagen), the pliability of erectile tissue drops and cannot expand as well with persistent patency of the venules with persistent venous outflow. This is colloquially termed ‘venous leak’.

Although penile erection is not dependent on the operation of pelvic floor musculature, contraction of the bulbospongiosus and ischiocavernosus muscles is triggered by the bulbocavernosus reflex during masturbation or sexual intercourse to produce the rigid erection phase. [34] Such muscle contraction is the reason erectile rigidity is usually greatest around the time of orgasm when these muscles contract maximally.

4. Physiology of Erection

Table 1: Major Molecular Mediators of Penile Erection

Relaxant Factors		Contractile Factors	
Molecule	**Proposed Mechanism of Action**	**Molecule**	**Proposed Mechanism of Action**
Nitric Oxide (NO)	activation of soluble guanyl cyclase (sGC)	**Norepinephrine**	Produces Inositol Triphosphate (IP3) and Diacylglycerol
sGC	Cleaves GTP to cyclic GMP (cGMP)	IP3	Binds to release Ca2+ ions from the sarcoplasmic reticulum
cGMP	activation of Protein Kinase G (PKG)	Calmodulin	Binds with calcium ion to activate myosin light chain kinase (MLCK)
PKG	Phosphorylates gap junctions, K & Ca channels, RhoA†	MLCK	Phosphorylates myosin light chain leading to contraction
K+ Channels	Increased potassium influx (hyperpolarization)	Diacylglerol	Possible binding to protein kinase C and muscle contraction
Ca^{2+} Channels	Reduced calcium influx and calmodulin dissociation		

Phosphodiesterase 5	Breaks down cGMP		
Prostaglandin E_I (PgE1)	activation of adenyl cyclase		
Adenyl Cyclase	Cleaves ATP to cyclic AMP (cAMP)	**Endothelin-1**	Binds to membrane receptor to activate RhoA
cAMP	activation of adenyl cyclase	RhoA	Binds and activates Rho Kinase (ROCK)
PKA	Phosphorylates gap junctions, K & Ca channels, RhoA†	ROCK	Phosphorylates (inactivates) myosin light chain phosphatase (MLCP)
K+ Channels	Increased potassium influx (hyperpolarization)	MLCP	Dephosphorylates (inactivates) myosin light chain‡
Ca^{2+} Channels	Reduced calcium influx and calmodulin dissociation		
Angiotensin II	Binds to membrane receptor to activate RhoA		
Natriuretic Peptide	activation of particulate guanyl cyclase (pGC)	RhoA	Binds and activates Rho Kinase (ROCK)

pGC	Cleaves GTP to cyclic GMP (cGMP)	ROCK	Phosphorylates (inactivates) myosin light chain phosphatase (MLCP)
cGMP	activation of Protein Kinase A (PKA)	MLCP	Dephosphorylates (inactivates) myosin light chain‡
PKG	Phosphorylates gap junctions, K and Ca channels		
K+ Channels	Increased potassium influx (hyperpolarization)		
Ca^{2+} Channels	Reduced calcium influx and calmodulin dissociation		
Hydrogen Sulfide (HS)	Inhibition of PDE, activation of membrane K+ channels		

† Phosphorylation of RhoA by PKG leads to inhibition of the RhoA-ROCK pathway

‡ The net effect of Rho/ROCK activation is inhibition of the inactivation of the myosin-actin crossbridge; this has the net effect of favoring vasoconstriction

Adapted from: Lin et al Asian J Androl 2008;10:433-440 Qiu et al J Androl 2012 Jul-Aug;33:529-535

4.1 Molecular Regulation of Erectile Function

Molecular regulation of penile erection is quite complex. A number of chemical mediators are involved in the process (**Table 1**) It is important to note that the cavernosal smooth muscle is functionally a syncytium due to the presence of ion channels and gap junctions. These cellular features facilitate rapid transmission of molecular signals and subsequent unified activity of corporal smooth muscle cells. [35]

At the molecular level, diverse neurotransmitters, hormones, and other regulatory substances that may be locally released in erectile tissue serve as effectors of the erectile response.[36,37,38,39] Nitric oxide (NO) is the predominant mediator of penile erection and is synthesized by NO synthase (NOS) in neurons (nNOS, NOS-I), endothelium (e-NOS, NOS-III) and in response to immunological stimulation, inducible NOS (iNOS, NOS-II). [40,41,42] Additional regulation of NOS occurs through post-translational phosphorylation of activator and repressor sites on NOS-I and NOS-III. The phosphorylation state of NOS is altered in aging, diabetic and sickle cell ED models; this is thought to contribute to ED in these clinical states. [43]

nNOS is present in NANC neurons innervating the penis; NO from NANC neurons is thought to be one of the prime factors in initiating penile erection.[40,41,42,44] NO is also produced by eNOS, which is present in cavernosal endothelial cells. Cavernosal endothelial cells are stimulated to produce NO by action of cholinergic neuronal fibers of the parasympathetic nervous system and also by shear forces in the vascular lumen. [26]

NO stimulates guanylate cyclase in the penis, which in turn cleaves Guanosine Triphosphate (GTP) into cyclic guanosine monophosphate (cGMP). Increased cGMP promotes protein-kinase-G dependent smooth muscle relaxation via a number of downstream effectors that modulate calcium homeostasis and other cellular processes.[45] The net result of smooth muscle relaxation is penile erection. Relaxant prostanoids and cyclic adenosine monophosphate (cAMP) derived from parasympathetic activation of adenylate cyclase also contribute to smooth muscle relaxation and erection in the penis. [26,35] A host of other molecules including vasoactive intestinal polypeptide, carbon monoxide,[46] monoamines, amino acids, neuropeptides and gaseous molecules have also been linked to erection by action in spinal and supraspinal centers.[26,28] The role of these mediators in penile erection has not been completely defined.

Baseline flaccidity of the penis is maintained by the sympathetic division of the autonomic nervous system, which operates under the influence of the conventional adrenergic neurotransmitter norepinephrine.[47] A variety of extracellular (endothelin, angiotensin-II) and intracellular (inositol-triphosphate) effectors also contribute to corporal smooth muscle contraction and penile flaccidity. [35,48]

Phosphodiesterase type 5 (PDE5) is the enzyme primarily responsible for degradation of cGMP in the penis. Hence, PDE5 is primarily responsible for reducing tumescence by opposing the NO pathway in the penis.[49] Selective PDE5 inhibitors (PDE5i) are the mainstay of modern oral

erectogenic therapies.

4.2 Penile Tumescence and Detumescence

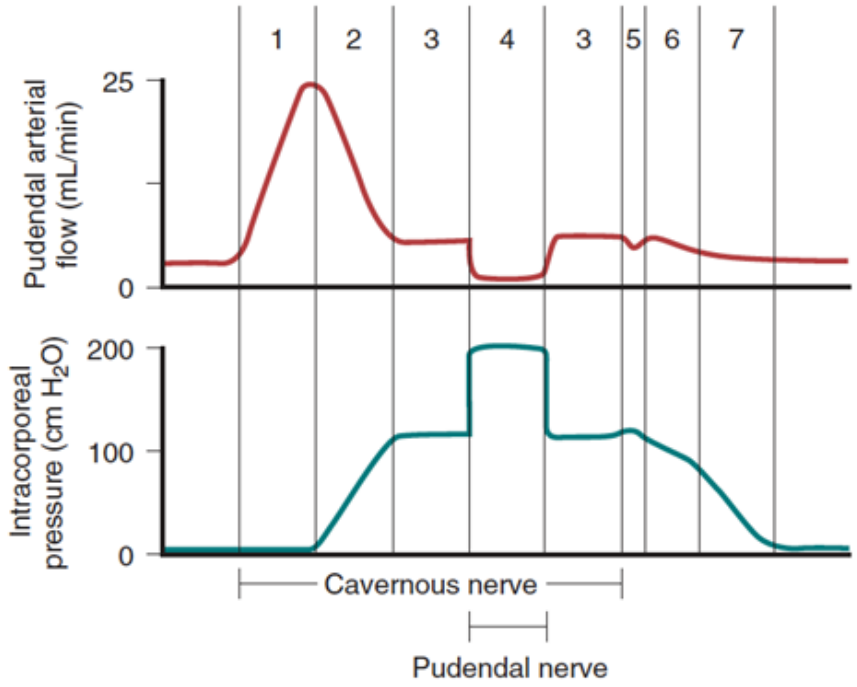

Figure 23–6. Blood flow and intracavernous pressure changes during the seven phases of penile erection and detumescence: 0, flaccid; 1, latent; 2, tumescence; 3, full erection; 4, rigid erection; 5, initial detumescence; 6, slow detumescence; 7, fast detumescence.

Figure 7:

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Penile erection is a spinal reflex that can be initiated by stimuli from the periphery and/or from the central nervous system.[27] The balance between contractile and relaxant factors controls the degree of contraction of the smooth muscle of the corpora cavernosa and determines the functional state of the penis by regulating blood flow into the erectile tissue. Thus, erection is a balance of blood inflow from the cavernosal arteries and blood outflow through penile veins.

Erection is divided into a series of four phases:[28]

1. Flaccid Phase: Corresponds to the baseline state of the penis. During this phase, arterial flow is low and corporal resistance is high due to contraction of smooth muscle in the corporal arteries [31] the partial pressure of oxygen in the penis during this phase is low at around 35 mmHg.
2. Filling Phase: Corresponds to increasing firmness of the penis from increased blood flow.
3. Full Erection Phase: Corresponds to erection of the penis to a non-dependent position. During

full erection, the partial pressure of oxygen increases to approximately 90 mmHg and intracavernous pressure may increase to greater than 80 mmHg. Penetration may be accomplished during this phase.[31] Maximal tumescence occurs during the rigid erection phase.
4. Rigid Erection Phase: Engorgement of the corpus spongiosum occurs as blood is forced into the penis by contraction of the pelvic floor musculature; intra-penile pressure may exceed systolic blood pressure (into the hundreds of mmHg) during the rigid erection phase.[31]

Penile detumescence follows a predictable sequence:

1. During the first phase, there is a slight rise in intracorporal pressure related to constriction of the cavernous arteries against the engorged spongy tissues of corpora cavernosa.
2. The second phase is a slow process of detumescence as partial venous drainage resumes.
3. The third and final phase of detumescence is rapid and associated with complete restoration of venous drainage.[29]

5. Erectile Dysfunction

ED is defined as the consistent or recurrent inability to attain and/or maintain penile erection sufficient for sexual satisfaction.[2] ED is classified as organic, psychogenic, or mixed. Organic ED is due to physical defects and may be further classified into vasculogenic, neurogenic, hormonal, and cavernosal smooth muscle abnormalities.[19] Psychogenic ED refers to ED that is caused by a host of factors including but not limited to anxiety, guilt, lack of confidence, depression and/or conflict about sexual issues. Psychogenic ED does have a biological underpinning; it is thought that stress response associated with psychological disturbance may lead to inhibition of the tumescence mechanism via increased activity of the sympathetic nervous system. It is likely that most men with a primary organic etiology have some secondary psychogenic component to their ED.

6. Pathophysiology of ED

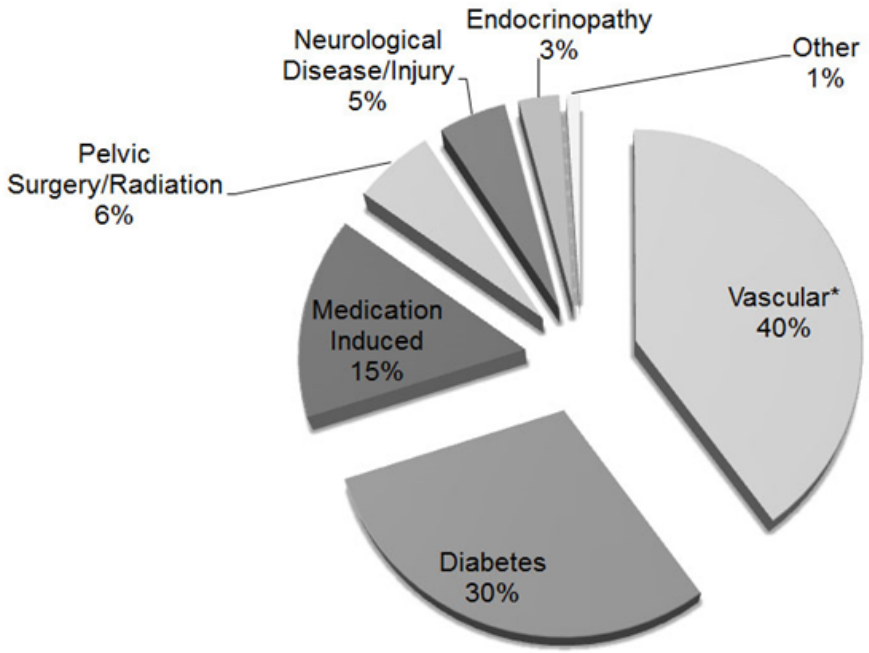

Figure 8: Primary Etiologies of Organic ED

Known independent risk factors for organic ED include age, coronary artery disease, smoking, hypertension, dyslipidemia, atherosclerosis, peripheral vascular disease, higher body mass index, DM, spinal cord injury, medications, neurodegenerative conditions (e.g. multiple sclerosis, Alzheiner's Disease, etc.), renal insufficiency, and prostate cancer treatment including prostatectomy and radiation therapy. [19,31,50,51,52,53]

The primary etiologies of organic ED are presented in **Figure 8**.

6.1 Neurological Causes of ED

Neurogenic ED results when there is loss of innervation to the corpora cavernosa. This can result from injury to the peripheral nervous system including the pelvic ganglia and CN (lower motor neuron lesions), or at the central nervous system level including the spinal cord and brain (upper motor neuron lesions). Loss of innervation results in the inability of the cavernosal smooth muscle to relax and allow blood flow into the penis. Denervation also causes irreversible morphological remodeling of the corpora cavernosa, including smooth muscle apoptosis[54] and fibrosis,[55] which make the tissue less compliant and incapable of responding to normal signaling mechanisms, and as a result leads to veno-occlusive dysfunction.[56]

Any factor that interferes with spinal root (S2-4) or cavernous nerve integrity or function can lead to ED. The common causes of this pelvic surgery, DM and spinal cord injury and aging. The most common pelvic surgery that causes ED is radical prostatectomy (RP). Rates of ED following RP are wide-ranging, there are very few randomized controlled trials that analyze ED rates following RP using different approaches. [57,58] One landmark study from Sweden by Sooriakumaran and colleagues assessed 2545 Swedish men with prostate cancer that underwent either robotic-assisted or open RP

at 14 different centers by 50 experienced surgeons from 2008-2011. Interestingly, in a well-balanced study, the investigators demonstrated robot-assisted patients to have earlier recovery of erections and better erections at 24 months. This observation was predominantly noted in D'Amico low and intermediate risk cohorts, and overall rate of erectile function recovery did not exceed 51% in either open or robotic approaches.

Autonomic neuropathy is a leading cause of ED in diabetic patients.[59] DM leads to neurogenic ED by progressive demyelination of peripheral nerves, including the CN. Diabetic men are at least three times more likely than healthy men to develop ED and the reported prevalence of ED in diabetic men is as high as 75%. Diabetic men are also prone to development of ED at an earlier age.[60] It is likely that the vascular effects of DM also contribute to the high rate of ED in diabetic men.

Spinal cord injury results in defects in erectile function, ejaculation and male reproductive potential.[61] Spinal cord injury leading to ED can occur through several mechanisms including direct trauma, compression by bone fragments, hematoma, tumor or disc material and ischemia from damage or impingement on the spinal arteries.[61]

The physiological link between the brain and ED is incompletely understood. Regions of the brain that are involved in regulation of erectile function include the anterior cingulate, insula, amygdala, hypothalamus, and secondary somatosensory cortices.[30,62,63] Research on brain centers essential in erectile function is a fertile ground of current and ongoing investigation.

6.2 Vascular Causes of ED

Erection and the flaccid state are regulated by relaxation and contraction of arterial and trabecular smooth muscle. Any condition that results in an imbalance between contractile and relaxant factors in the corpora cavernosa, penile arteries and veins will lead to ED development. Hypertension (blood pressure greater than 130/85), hypertriglyceridemia (> 150 mg/dL), low high-density lipoprotein < 40 mg/dL), diabetes (fasting blood sugar > 110 mg/dL), obesity (body mass index > 30 and waist circumference greater than 40 inches), tobacco use, and lack of exercise (< 3 metabolic equivalents per week) have all been independently associated with risk of ED. [50,51,52,53,64] While occlusive disease of the internal iliac-internal pudendal arterial pathway is a major cause of arterial insufficiency and vasculogenic ED, it is likely that reduced availability of endothelial NO contributes to early vasculogenic ED. [65]

The metabolic syndrome (MetS, also known as syndrome X or insulin resistance syndrome) is a constellation of disorders that are associated with markedly higher risk of vascular disease. While a variety of definitions have been advanced, the unifying characteristics of MetS include truncal obesity (waist circumference greater than 201 cm), high density lipoprotein (HDL) less than 40 mg/dL, hypertriglyceridemia (greater than 150 mg/dL), hypertension > 130/85 mmHg, and fasting blood glucose > 110 mgdL.[66] The various components of MetS are individually associated with risk of ED; interestingly, the diagnosis of MetS is also a risk factor for ED independent of its component diagnoses. [67,68] Treatment of MetS with lifestyle change (dietary modification, exercise, weight loss) has been shown to significantly improve penile erection in a randomized controlled trial.[69]

ED is widely acknowledged as an early warning sign for cardiovascular disease, with a lead-time of 2-3 years between moderate ED diagnosis and presentation with clinically significant systemic vascular disease.[70,71] Data from the MMAS indicate that men with substantial difficulty obtaining erections at baseline have a 52% increase in relative risk for developing MetS over 15 years of follow up. Interestingly, the rate of MetS was more than double in non-obese men (body mass index less than 25) with ED at baseline over the same follow up period.[72] More concerningly, ED has been established as an independent predictor of all cause (hazard ratio 1.26) and cardiovascular (hazard ratio 1.43) mortality.[73]

With the recent COVID-19 pandemic, a new risk factor for ED has been described. A histopathological study on penile tissue showed that COVID-19 viral particles can be found near penile vascular endothelial cells long after resolution of infection. In these COVID+ specimens, eNOS expression was significantly lower when compared to COVID negative controls, thus providing a mechanism for ED caused by COVID-19. [74] These mechanistic findings are further supported by a survey study which demonstrated COVID positive patients to have significantly higher rates of ED (28% v. 9%) than COVID negative controls.[75] The link between COVID-19 and ED still needs to be investigated further, however the current limited evidence does suggest a link between the virus and ED.

6.3 Metabolic Syndrome and ED

Certain endocrinopathies contribute to ED.[72,76] Several endocrine conditions are particularly relevant in this regard: hypogonadism (testosterone deficiency syndrome), hyperprolactinemia (suppression of LH secretion), hypothyroidism (suppression of LH secretion), hyperthyroidism (associated with hyper-estrogenism), and DM. Hyperprolactinemia, which may be associated with a prolactin-secreting adenoma or medications that result in prolactin level increases, may contribute to erectile dysfunction via disruption of testosterone production and/or suppression of libido. [77,78]

6.4 Medication-induced ED

Medication use has been associated with erectile dysfunction in up to 25% of clinical presentations (**Table 2**).[79] The most commonly implicated classes of drug include antihypertensive drugs (thiazide diuretics, beta-adrenoceptor antagonists) and psychotherapeutic drugs, particularly selective serotonin reuptake inhibitor (SSRI) antidepressants. Other broad classes of drugs affecting erectile function include antipsychotics, anti-androgens, antiulcer drugs, cytotoxic agents, opiates, 5 alpha-reductase inhibitors and digoxin. It is important to note that virtually every medication has been associated with sexual dysfunction on at least an anecdotal level, so a thorough medication history (including over-the-counter supplements and herbals) is essential when evaluating ED.

It is often difficult to determine whether the medication or the underlying disease state (hypertension, depression, BPH) is driving the ED complaint. It is also important to recognize that medications may affect various components of the male sexual response cycle including sexual desire, arousal and orgasm; disruption of these other issues may exert secondary effects on erectile function.

Table 2: Medications Associated with ED
5-Alpha Reductase Inhibitors
Anti-androgens
LH-RH agonists/antagonists
• Beta Blockers • Thiazide Diuretics • Angiotensin Converting Enzyme Inhibitors • Spironolactone
H2 Blockers
Psychiatric Drugs
• Selective Serotonin Reuptake Inhibitors • Tricyclic Antidepressants • Benzodiazepines • Antipsychotics • Phenytoin
Miscellaneous
Digoxin

6.5 Lower Urinary Tract Symptoms and ED

Lower urinary tract symptoms (LUTS) are common in older men, the demographic group that is also at greatest risk of ED.[6,80] A prospective study indicated a 40% increase in risk of incident ED in men with LUTS.[81] Several experts have hypothesized that there may be pathogenic mechanisms linking ED and LUTS; proposed unifying explanations include alteration of NO metabolism, increased tone of pelvic alpha receptors, and vascular disease.[80] Evidence indicates that men under treatment for ED with daily dose PDE5 inhibitors have improvement in LUTS compared to men treated with placebo;[82,83] daily dose tadalafil has been approved by the United States Food and Drug Administration as an option for both ED and LUTS related to prostate enlargement.[84] Interestingly, these improvements in symptoms were not associated with any clear change in objective parameters of urinary function (post-void residual urine, flow rate, etc).[82,85] As an exact mechanism beneficially impacting erections has yet to be delineated, recent investigations have demonstrated additive benefit of combination alpha blocker therapy with PDE5Is.[86] In addition, newer evidence would suggest that there is a distinct **α**1A receptor subtype in erectile tissue, **α**1AL or **α**1L, further strengthening the connection between BPH and its treatment and erectile dysfunction.[87]

6.6 Psychological ED

Psychological factors that impair erectile function include a host of psychological and interpersonal dynamics factors.[3,4] The presence and interactions of mental health problems, emotional stressors, and interpersonal relationship difficulties, both past and present, may be relevant negative influences on erectile function. It is very likely that psychological issues contribute in at least some fashion to all cases of ED, either primarily or secondarily. Since the inception of the internet, and specifically widespread availability of pornography, a new psychogenic cause of psychogenic ED has emerged – Pornography Induced Erectile Dysfunction (PIED). In their survey on sexual function and pornography, Christman and colleagues found increased use of pornography to be associated with higher rates of erectile dysfunction.[88] Consideration should be given to mental health/psychosocial referral as sex therapy is seldom if ever harmful and may yield substantial benefit.

6.7 ED and the Gut Microbiome

Human health and sexual function are determined by numerous factors, one of which is the gut microbiome. The gut microbiome has been researched in various disorders including hypertension, cardiovascular disease, chronic kidney disease, and diabetes mellitus. More recently, investigators have looked at the gut microbiome and its association with ED. In animal models, the gut microbiome has been found to regulate the endocrine system and affect androgen levels.[89,90] Based on this data, it stands to reason that the microbiome can positively and negatively regulate sex hormone levels based on host physiology, bacterial strains, and concomitant risk factors. In 2021, Geng and colleagues reported on the correlation between the gut microbiome diversity and psychogenic erectile dysfunction.[91] In this study of 30 patients with mild-to-moderate ED (IIEF ≥ 11 and ≤ 20) and 30 healthy controls, men with greater intestinal microbial diversity had a lower risk of ED. Similarly, a

2020 study from Japan revealed that increased levels of certain GI bacteria (*Alistipes*) were independent risk factors for a higher IIEF-5 score and decreased IIEF-5 scores for other bacteria (*Clostridium XVIII*). The authors hypothesized that pro-inflammatory microbes such as *Clostridium XVIII* create micro-inflammation and vascular endothelial dysfunction while *Alistipes*, a sulfonolipid producing bacteria, may inhibit tumor necrosis factor alpha (TNF-α).

In summary, the gut microbiome works through several different pathways and is a promising area of investigation for future strategies to prevent and treat erectile dysfunction.

Presentations

Erectile Dysfunction Physiology, Pathophysiology Presentation 1

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