The Link Between Vasculogenic Erectile Dysfunction, Coronary Artery Disease, and Peripheral Artery Disease: Role of Metabolic Factors and Endovascular Therapy

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ABSTRACT: Erectile dysfunction (ED) is estimated to affect 150 million people worldwide and may indicate diffuse systemic macrovascular disease. Endothelial dysfunction represents the probable pathophysiological link between vasculogenic ED, coronary artery disease (CAD), and peripheral artery disease (PAD), and the artery size hypothesis along with evidence-based research support ED as the incident clinical event. Given that many common risk factors for atherosclerosis, including smoking, diabetes mellitus, hyperlipidemia, and obesity are prevalent and causative in patients with ED, it is likely that metabolic factors play a crucial role in the link between the two disorders. The interplay of these factors provides a unifying physiological, endocrinological, and behavioral model for the association between ED, CAD, and PAD. Current therapy is unlikely to reverse the natural history of ED. Percutaneous revascularization may improve ED symptoms, and thereby quality of life, in a select group of patients. Large prospective studies are needed to define male pelvic arterial anatomy and thus enhance the utilization of internal pudendal angiography and revascularization. In this review, we provide an overview of normal erectile anatomy and physiology, the pathophysiology of ED, currently accepted diagnostic imaging modalities and treatments for ED, and recently investigated endovascular therapies for ED.

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Erectile dysfunction (ED) is defined as the recurrent or persistent inability to achieve or maintain an erection in order for satisfactory intercourse to occur. Age-related decline in erectile function was first documented by Kinsey et al in 1948, though ED was thought primarily a psychogenic disorder until the late 20th century.[1] Only recently has ED been recognized as an organic and physiologic abnormality affecting the penile circulation as part of a more generalized vascular disorder. The contemporary prevalence of ED is approximately 52% in the general population between 40 and 70 years of age; both the prevalence and the severity of ED increase with age.[2] It is estimated that ED affects 150 million people worldwide and this number is expected to more than double by the year 2025.[3] In many patients, ED may be the first manifestation of a single clinical disease spectrum that will progress to include coronary artery disease (CAD) and peripheral artery disease (PAD) at a later stage. Indeed, in men with CAD, the prevalence of ED is as high as 75%.[4,5] In this review, we provide an overview of normal erectile anatomy and physiology, the pathophysiology of ED, currently accepted diagnostic imaging modalities and treatments for ED, and recently investigated endovascular therapies for ED.

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Erectile Anatomy and Physiology

The male penis consists of three erectile columns: paired corpora cavernosa and a single corpus spongiosum in which arteries, veins, nerves, smooth muscle, and endothelial cells comprising vascular sinuses make up the erectile tissue. The internal iliac artery, a branch of the common iliac, provides the arterial inflow to the penis via the internal pudendal artery and subsequently the common penile artery, which splits into the bulbourethral artery (supplies the bulb of the penis and the penile urethra), the dorsal penile artery, and the cavernosal arteries (each enters the corpus cavernosum at the crus and runs the length of the shaft, giving off the helicine resistance arteries, integral to penile rigidity) (Figure 1). Deep venous drainage is via the crural and cavernosal veins, which are consolidations of the emissary veins and drain into the internal pudendal vein.[6]

A complex balance between the central and peripheral nervous systems and the integrity of the penile vasculature determines whether the penis is in a flaccid or erectile state. The central nervous system's response to sexual stimulation is mediated by the hypothalamus, which when stimulated by dopamine, initiates erection. Dopaminergic neurons impinge on oxytocinergic cell bodies in the paraventricular nucleus, which then project to the hippocampus, ventral medulla, and spinal cord.[7] In addition, tactile stimulation of the penis sends an erectogenic stimulus directly to the sacral spinal cord, exciting sensory neurons in the S2-S4 region. Efferent neurons exit through the sacral neural foramina and synapse with postganglionic nonadrenergic, noncholinergic (NANC) fibers in the hypogastric plexus.[8]

NANC fibers run through the cavernous nerves to enter the cavernous bodies at the level of the crura. A central or reflexogenic impulse results in the release of nitrous oxide (NO) from nerve terminals of the cavernous nerves in the corpus cavernosum.[9]

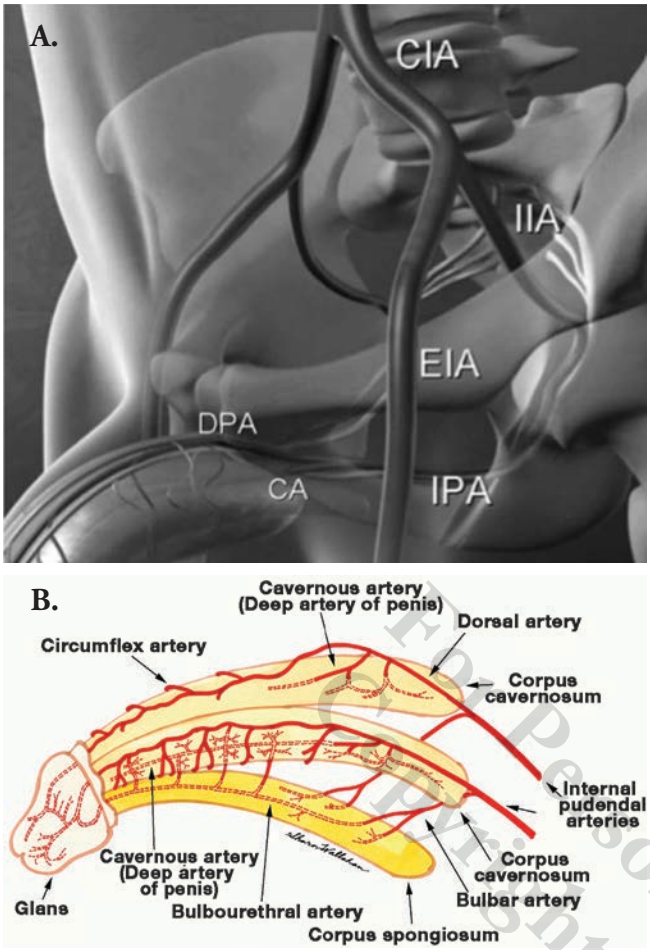

Figure 1. *Illustration of penile arterial anatomy.* **(A)** *Penile inflow anatomy. CIA = common iliac artery; IIA = internal iliac; IPA = internal pudendal; EIA = external iliac artery; DPA = dorsal penile; CA = cavernosal. Adapted with permission from Rogers JH, et al. Catheter Cardiovasc Interv. 2010;76(6):882-887.* **(B)** *Penile arterial anatomy. Adapted with permission from Terlecki RP, et al. Phimosis, adult circumcision, and buried penis. Medscape: 2011, Aug 15.*

NO is also released from the vascular endothelium in response to parasympathetic stimulation and the release of acetylcholine, and shear stress due to increased blood in the cavernosal sinusoids.[8] NO in turn activates guanylate cyclase in the cavernosal smooth muscle cells, increasing the conversion of guanosine triphosphate into cyclic guanosine monophosphate (cGMP). Through a protein kinase cascade, hyperpolarization, and intracellular calcium sequestration, cavernosal smooth muscle relaxation and arteriolar vasodilation occur.[10] Simultaneously, sinusoidal engorgement compresses the subtunical venular plexuses, resulting in venous outflow occlusion and completion of the erectile cascade.[11] Phosphodiesterase type 5 (PDE-5) mediates return to flaccidity via hydrolysis of cGMP.[6]

The parasympathetic pro-erectogenic mechanism described is counterbalanced by sympathetic adrenergic nerve fibers, which also run in the cavernous nerves. The tonic release of norepinephrine by sympathetic neurons triggers detumescence and maintains flaccidity via stimulation of α1-G protein coupled receptors on the cavernosal smooth muscle. This activates a cascade initiated by phospholipase C, ultimately resulting in increased cytoplasmic calcium and smooth muscle contraction.[8,12]

Etiology of Erectile Dysfunction

Proper interplay of the psychological, neurological, hormonal, and vascular systems is required for normal sexual function. Correct determination of the cause of ED is pertinent to fast and complete treatment and identification of more severe comorbidities.

Psychogenic. Psychogenic ED may be attributed to relationship stress, performance anxiety, or overt psychological disorders, such as depression or schizophrenia.[10] Multiple predisposing and precipitating factors likely contribute to a loss of libido and ultimately sexual dysfunction, including traumatic or abusive experiences, inadequate sex education, social pressures, and major life events, such as loss of a job.[13]

Neurogenic. Central nervous system disorders and spinal cord injury can impede initiation and maintenance of an erection. Sensory impairment of the genitalia may also inhibit reflexogenic erection. Neurologic conditions frequently associated with ED include Parkinson's disease, stroke, Alzheimer's dementia, multiple sclerosis, diabetes mellitus, and spinal cord injury. Neurogenic ED can also be caused by cavernous nerve injury during radical pelvic surgery. The degree of ED depends on the nature, location, and extent of the neurological lesion.[10,13]

Hormonal. Androgen deficiency is a recognized cause for decreased libido, and erectile and ejaculatory function. Testosterone regulates the expression of NO synthase and phosphodiesterase-5, and maintains the integrity of the vascular smooth muscle and endothelium.[10,13] Low testosterone is not only associated with ED but also with cardiovascular morbidity and mortality.[14] Testicular disorders, such as orchitis and cryptorchidism, hypothalamic-pituitary disregulation, as found in pituitary tumors and hemochromatosis, and generalized chronic diseases are common causes of androgen deficiency.[10] Hyperprolactinemia, often due to antidopaminergic pharmacotherapy, inhibits the release of gonadotropin-releasing hormone and causes hypogonadotropic hypogonadism.[10]

Drug-induced. Many medications used to treat systemic illnesses can lead to ED, including antipsychotic, antidepressant, and antihypertensive drugs. Risperidone, olanzapine, and serotonin reuptake inhibitors have the highest likelihood of causing sexual dysfunction. Thiazides, spironolactone, and β-blockers can also cause ED, the latter via potentiation of α1-adrenergic activity in the penis.[10] Statins have also been implicated.[13] Clinicians should take a thorough sexual history prior to prescribing these drugs and be aware of their potential sexual side effects when treating ED.

Lifestyle factors and systemic disorders. Cigarette smoking contributes to ED both indirectly though its atherogenic effects and endothelial injury and directly through the effects on cavernosal smooth muscle. While a small amount of alcohol intake improves libido and erection, larger amounts trigger central sedation and transient ED, and chronic alcoholism can cause hypogonadism and penile neuropathy.[10] In addition, diabetes mellitus, chronic kidney, liver, and pulmonary disease, as well as a sedentary lifestyle and sleep disorders may cause ED.[13]

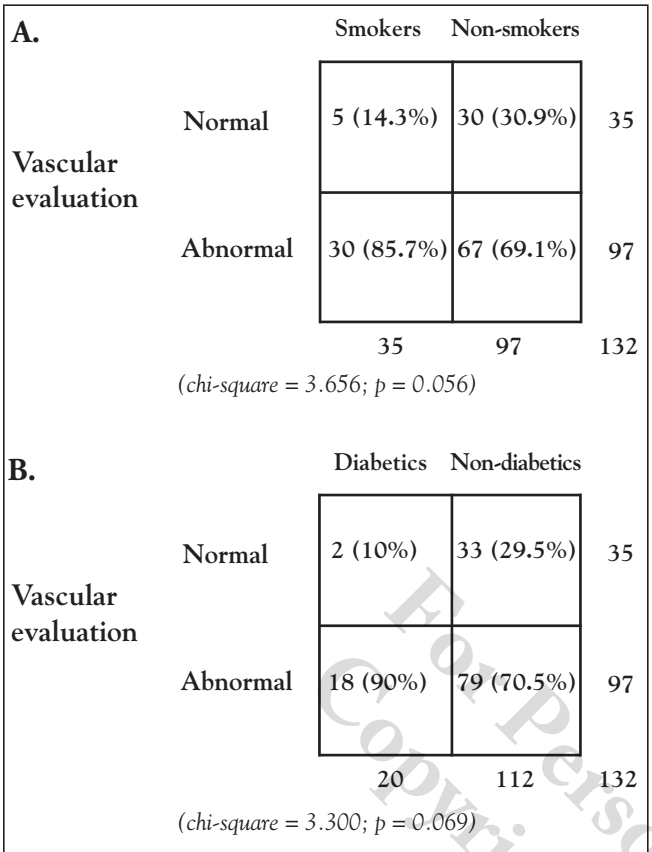

Figure 2. *Penile vascular dysfunction by duplex ultrasound utilizing penile papaverine injection for vasodilation. In smokers* **(A)** *and diabetics* **(B).** *Adapted with permission from Shabsigh R, et al. Urology. 1991;38(3):227-231.*

Vasculogenic. Proper functioning of the penile vasculature requires a complex interplay of multiple components. Veno-occlusive disease, blunt trauma, and cavernosal fibrosis contribute to less-common forms of vasculogenic ED, all of which are difficult to treat by currently accepted therapies. Radiation therapy, priapism, trauma, or surgery can cause an increase in extracellular matrix and fibrosis of the cavernosal smooth muscle and endothelial cells.[10,15] Structural alterations in the corporal smooth muscle, trabecular framework, or tunica albuginea may cause veno-occlusive failure due to excessive outflow of lacunar blood through the subtunical venules. This can occur due to aging, hypercholesterolemia, and atherosclerosis, and results in inadequate penile rigidity and erection duration. Chronic hypoxemia appears to be an independent factor associated with ED and is frequently the result of obstructive sleep apnea and chronic lung disease. Hypoxia profoundly affects blood vessel tone and induces the production of vascular growth factors, inhibiting endothelial-mediated relaxation, ultimately leading to vasoconstriction. Oxygen may also regulate NO synthesis in the corpus cavernosum.[15]

Hypercholesterolemia, hypertension, cigarette smoking, and other common atherosclerotic risk factors all promote occlusive disease in various arterial beds and ultimately lead to one form of vasculogenic ED, on which the remainder of this review will focus. Impaired arterial inflow to the penis due to occlusion or narrowing of the common iliac arteries, internal iliac arteries, and the internal pudendal arteries and their downstream branches may cause decreased penile rigidity during erection as well as prolongation of the time to peak erection. Arterial insufficiency can also cause impaired cavernosal smooth muscle relaxation via diminished neuronal or endothelial NO and chronic tissue ischemia.

Endothelial Dysfunction: The Link Between Vasculogenic ED and Macrovascular Disease

Results from the Massachusetts Male Aging Study confirmed the association of ED with CAD, finding for patients with heart disease a 39% probability of complete ED, and subsequent studies have shown ED rates in patients with CAD as high as 75%.[2,4,16] Vascular endothelial dysfunction is the probable pathophysiologic link between the two disorders. The severity of ED has been associated with the extent of angiographically confirmed CAD.[17] CAD in patients with ED makes the presence of similar obstructive lesions between the aortic bifurcation and the distal internal pudendal artery more likely, and patients with ED have high rates of macrovascular atherosclerosis, as well as its main precursor, hyperlipidemia.[18,19] Further, a recent meta-analysis of 740 patients from 6 clinical trials in 4 countries found that treatments for cardiac risk factors (lifestyle modifications and pharmacotherapy) were associated with significant increases in International Index of Erectile Dysfunction (IIEF-5) score and improvements in sexual function, indicating a common pathophysiological process for ED and cardiovascular disease.[20]

Early impairment of endothelial-dependent vasodilation and late obstructive changes are seen in both vasculogenic ED and CAD. The inability of vascular smooth muscle cells to relax impedes vasodilation. Platelet aggregation and other indices of coagulation, surrogates for endothelial function possibly mediated by nitric oxide, have been shown to be lower in diabetic men with ED compared to diabetic patients without ED.[21] In addition, patients with ED have higher levels of asymmetric dimethylarginine, a known inhibitor of NO synthase.[22]

Given that many common risk factors for atherosclerosis, including smoking, diabetes mellitus, hyperlipidemia, and obesity are prevalent and causative in patients with ED, it is likely that metabolic factors play a crucial role in the link between the two disorders. The impact that insulin resistance, obesity, dyslipidemia, and testosterone deficiency have on endothelial dysfunction, and thus ED and CAD, is well documented. This interplay provides a unifying physiological, endocrinological and behavioral model for the association between ED and CAD. In 1980, McCulloch et al directly associated the increased incidence of ED in diabetics with age, time since onset of diabetes, and the common diabetic complications of peripheral neuropathy and retinopathy.[23] Subsequently, Virag et al studied 440 men with ED and found that 64% were smokers, 30% had diabetes, and 34% had hyperlipidemia. Notably, the severity of their ED was associated with the number and severity of their arterial risk factors.[24] This latter finding was supported by a prospective study of 132 men with ED that utilized penile papaverine injections and duplex ultrasound to assess penile vascular dysfunction in relation to smoking, diabetes, and hypertension (Figure 2).[25]

Men with ED have a high incidence of obesity, metabolic syndrome, and insulin resistance, which has been shown to damage the vascular endothelium and impair NO release.[26-28] In rat models, an insulin-resistant state also portends lower levels of vascular endothelial growth factor and its receptors, as well as a pro-apoptotic state in the penile tissue.[29] Insulin administration relieves diabetes-associated ED in rats and increases mean intracavernous pressure following electrostimulation of the cavernous nerves, which is a surrogate for erectile function.[30] Similarly, the expression of insulin-like growth factor binding protein, which regulates the availability of insulin-like growth factor, is increased in hyperglycemic rats while treatment with IGF-1 results in improvement in rat intracavernosal pressure and expression of endothelial NO-synthase.[31-33] In a prospective, randomized clinical trial of 30 men without diabetes, the addition of metformin to sildenafil resulted in improved erectile function, further indicating that insulin, even without overt diabetes mellitus, is involved in the endothelial dysfunction underlying vasculogenic ED.[34]

Another large prospective study conducted over 4 years found that in 3250 men, each 1 mmol/L increase in total cholesterol and each 1 mmol/L decrease in high-density lipoprotein were associated with a 1.32-fold and 2.6-fold greater risk of ED, respectively.[35] In men without CAD, circulating soluble oxidized low-density lipoprotein (LDL) receptor levels, which play a role in oxidized-LDL induced damage, are associated with ED.[36]

Low testosterone is independently associated with hormonal causes of ED, but the pivotal role of androgens in the regulation of NO-synthase and PDE-5 highlights their relationship to vascular endothelial dysfunction, and underscores the resistance of some patients to treatment with PDE-5 inhibitors.[26] Low levels of total testosterone in eugonadal patients with ED are associated with higher body mass index (BMI), waist circumference, metabolic syndrome, and insulin resistance and treatment with testosterone can reduce central adiposity and insulin resistance.[37-39] Independent of age, BMI, and cholesterol, testosterone is associated with endothelial dysfunction, measured via flow-mediated vasodilation on brachial artery ultrasound.[40]

ED Precedes CAD

ED and CAD are distinct manifestations of the same disease process, evidenced by common independent predictors and a clear association between both disorders. There is a growing body of research supporting ED as the likely incident diagnosis, preceding the development of symptomatic CAD. Multiple studies have documented the occurrence of ED 2-5 years prior to CAD presentation.[24,41,42] In 2003, Montorsi et al queried 300 consecutive patients presenting to Italian emergency departments with acute coronary syndromes and angiographically significant CAD for the presence of ED. A total of 71% had symptoms of sexual dysfunction prior to the onset of CAD symptoms, and a similar relationship has been shown in patients with asymptomatic diabetes.[16,43] A large, prospective study of more than 9000 men ≥55 years old found that ED was associated with a hazard ratio of 1.45 (P<.001) for subsequent cardiovascular events and a meta-analysis of 12 prospective cohort studies involving 36,744 patients found that men with ED had 1.48 times the risk of developing cardiovascular disease overall, 1.46 for CAD, and 1.35 for stroke.[44,45] Furthermore, the duration of preceding sexual dysfunction is related to the severity of CAD at presentation and to the number of involved coronary arteries at the time of angiography.[41] The cardiovascular risk portended by ED appears to be especially significant in men <60 years old, the reasons for which are currently unclear.[46,47]

Montorsi et al proposed the artery size hypothesis as the likely reason that ED precedes CAD and other symptomatic vascular disease.[48] If we assume that atherosclerosis progresses at relatively the same pace throughout all major arterial beds, symptoms indicative of disease in smaller arterial branches will manifest first, since larger vessels can better tolerate the same extent of plaque buildup. The literature supports the claims of this hypothesis, namely the low prevalence of occult CAD in ED, the high prevalence of ED in patients with CAD, and the typical appearance of ED symptoms before those of CAD. [4,16,24,41,49]

Non-Invasive Evaluation of ED

The accumulation of evidence supporting ED as a predictor of CAD indicates the need for physicians to consider and recognize the former as a warning sign of more severe systemic disease. Along with an adequate medical history and physical examination, there are non-invasive diagnostic methods to assess ED. Similar to the ankle-brachial index for peripheral artery disease diagnosis, the penile-brachial index demonstrates the relationship between the brachial systolic arterial pressure and penile arterial pressure. While a penile to brachial pressure ratio of 1.0 is normal, a ratio of <0.6 is considered the threshold for diagnosis of vasculogenic ED; however, with only 70% accuracy, this test is not particularly sensitive or specific.[50] Doppler ultrasound with intracavernosal vasodilator injection is another imaging modality that measures peak systolic flow velocity in the cavernosal arteries, considered the most accurate indicator of arterial disease, as well as cavernosal artery diameter, degree of arterial dilatation, and acceleration time.[51] Doppler ultrasound can diagnose vascular pathology, including arterial insufficiency and veno-occlusive disease, with 93.8% sensitivity and 77% specificity. Furthermore, the dose required for erection after injection of the intracavernosal agent correlates with findings from Doppler ultrasound, cavernosography, and arteriography.[50]

Standard Treatment

Standard therapy for ED requires first the identification and treatment of reversible, non-vasculogenic causes. Initial non-invasive treatment methods include sexual counseling, lifestyle changes, and incident medication dose alterations or discontinuation.

Selective PDE-5 inhibitors (sildenafil, vardenafil, and tadalafil) enhance NO-mediated relaxation of the corpus cavernosum via increased intracavernosal cGMP levels, resulting in erection initiation and maintenance.[16] Given their ease of use and excellent safety profile, PDE-5 inhibitors are recommended as first-line drug therapy; however, these drugs demonstrate lower response rates in older men. The reasons for this age discrepancy include an age-associated decrease in

endogenous NO production, which is further diminished by other comorbidities.[9] Of the 30%-40% of patients who do not initially respond, counseling and daily low-dose administration may be helpful, as well as exogenous testosterone, which can increase the bioavailable NO in the cavernous smooth muscle tissue and improve drug efficacy.[52] Furthermore, any condition that disturbs the integrity of the NO-cGMP pathway will diminish the efficacy of PDE-5 inhibitors, which depend on the presence of endogenous NO. Such conditions are the same as those that contribute to CAD and PAD, specifically diabetes, endothelial dysfunction, metabolic syndrome, and hypercholesterolemia, and may explain why up to 50% of men have a suboptimal response to pharmacological therapy.[4,18]

Sublingual apomorphine is another type of oral pharmacotherapy, which is a centrally acting non-selective dopamine agonist. This drug enhances natural pro-erectile signals to the brain and is most effective in mild-moderate ED. It has limited utility in older patients with decreased NO stores, but may be helpful in combination with PDE-5 inhibitors.[9]

For patients who do not wish to take oral medications or whose ED is refractory, vacuum constriction devices offer a manual mechanism to achieve erection. Another second-line treatment is intracavernosal and intraurethral administration of vasoactive agents such as prostaglandin E1, phentolamine, and papaverine. These agents elevate intracavernosal cGMP and block local α-receptors, resulting in cavernous smooth muscle relaxation independent of endogenous supply of NO. Consequently, overall satisfaction rates with intracavernous therapy are up to 80%, but long-term use can lead to priapism and penile fibrosis.[9] Lastly, surgical treatment of ED commonly utilizes a penile prosthesis, which results in both patient and partner satisfaction rates as high as 98%, but carries the risks of infection, erosion, and mechanical failure.[53] In the case of vasculogenic ED, the aforementioned therapies may improve erectile function, but will not alter the natural history of the disease.

Endovascular Diagnostic and Therapeutic Techniques

Up until the early 2000s, surgical penile revascularization, in which an epigastric artery is used to bypass significant inflow disease and is anastomosed to the deep dorsal vein or the cavernosal artery, was the only revascularization option for patients with vasculogenic ED. Despite a 50%-70% overall initial success rate, cavernosal fibrosis, vessel leak, and distal arteriogenic disease typically result in failure over time.[15] More recently, endovascular diagnostic and therapeutic techniques have been proposed and studied.

Arteriography can aid in the diagnosis of macrovascular causes of ED by demonstrating significant atherosclerotic lesions proximal to the dorsal penile arteries. A reduction of luminal diameter by more than 50% in these vessels is thought to be significant.[18] First described in 1976 by Ginestie and Romieu, Valji et al identified a vasculogenic etiology in 57 out of 132 patients undergoing arteriography for ED and found that the most common sites for significant stenoses were the distal internal pudendal and proximal penile arteries.[54,55] Bahren et al used bilateral selective pudendal arteriography in 126 young patients with chronic ED (mean age, 46 years), and found that 34 patients had significant stenoses in the internal pudendal arteries.[56] A recent study of 10 patients with ED undergoing cardiac catheterization for the evaluation of CAD found that of the 9 patients with significant CAD, all had evidence of internal pudendal artery disease.[18]

Though percutaneous coronary intervention is now the most common therapeutic procedure performed in hospitals, endovascular repair of internal pudendal stenoses for the treatment of ED has just recently been examined. While long occlusions and intrapenile lesions are unlikely to benefit from angioplasty, short smooth stenoses (2-3 mm) in the internal pudendal and proximal common penile arteries, where approximately 70% of lesions are found, are amenable to percutaneous transluminal angioplasty (PTA). Historically, few small studies have investigated the efficacy of PTA in the treatment of ED. One such study of 35 patients with aortoiliac or above-the-knee atherosclerotic disease found that of the 8 patients with ED who underwent PTA, only 1 patient experienced a return to functional potency, though distal common penile lesions and veno-occlusive insufficiency were not ruled out prior to PTA.[57]

Despite the less than promising historical evidence regarding PTA, endovascular interventions for the treatment of vasculogenic ED are gaining popularity given the increasingly evident association between ED and CAD and the artery size hypothesis as a theoretical model for success. In addition, the past 20-30 years have seen the success of percutaneous coronary intervention and the resultant commonality of stenting for cardiovascular and peripheral arterial diseases. The classic example is Leriche's syndrome, the triad of claudication, diminished femoral pulses, and ED, which is classically due to a distal abdominal aortic occlusion. With aorto-bifemoral bypass or endovascular repair of bilateral iliac arteries, both the claudication and ED improve. Even in the case of unilateral claudication associated with a significant common iliac lesion, endovascular repair can significantly improve coexisting ED, by way of improved penile arterial flow (Figure 3).

Recently, clinical trials have investigated the utility of internal pudendal artery stenting for the treatment of ED. The Zotarolimus-Eluting Peripheral Stent System for the Treatment of Erectile Dysfunction in Males with the Suboptimal Response to PDE-5 Inhibitors (ZEN) trial was the first ED trial to evaluate stenting of internal pudendal artery stenoses.[58] The primary endpoints were safety at 30 days, defined by device or procedure-related death, perineal gangrene, or necrosis, or need for perineal, penile, or anal surgery, and feasibility at 3 months, defined as an improvement in IIEF-5 scores of greater than 4 points. Pertinent exclusion criteria included non-vascular ED, veno-occlusive disease, and non-target lesions of the common iliac, internal iliac, or common penile arteries with >70% stenosis. Of the 383 subjects screened, only 89 (23%) qualified for arteriography, and of those, only 30 (7.8%) qualified for intervention, highlighting the need for appropriate patient selection. Forty-five lesions were treated with stents, and technical success was achieved in each of these patients, with no deaths or perineal gangrene at up to 6 months of follow-up. There was a non-significant increase in peak systolic velocity within

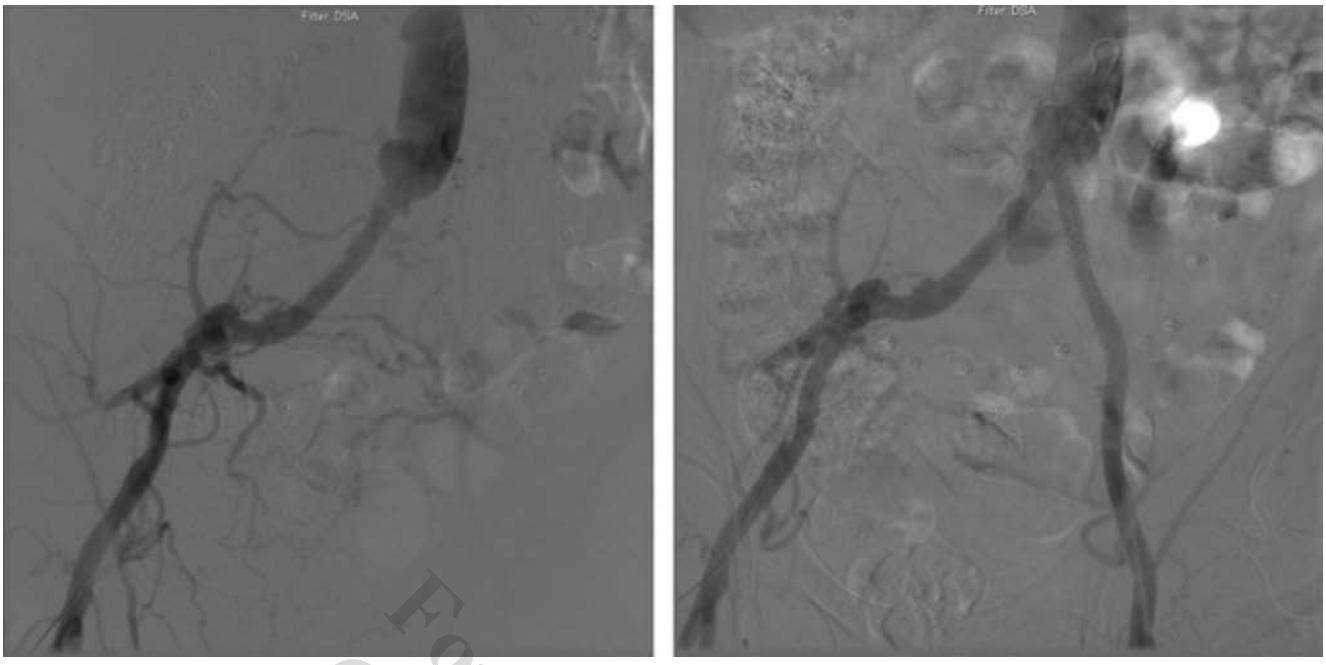

Figure 3. *Arteriography demonstrating impact of common iliac stent on erectile function.* **(A)** *Iliac angiogram of patient presenting to our clinic with worsened erectile dysfunction (ED) and marked decrease in IIEF-5 scores over previous 2 months. Previously placed left common iliac stent is occluded.* **(B)** *Patent stent after ultrasound-accelerated lytic infusion and balloon angioplasty. The patient reported marked improvement in ED with return to baseline IIEF-5 scores at 2-week follow-up exam.*

stented internal pudendal arteries, and a binary restenosis rate of 34.4% at 6 months; however, the feasibility endpoint was met with meaningful improvement in IIEF score (59.3%) at 3 and 6 months.[58] The ZEN trial was limited by the lack of a control arm and a high screen-failure rate, which highlights interventionalists' inexperience with pudendal arteriography and the need for better non-invasive screening of patients who may benefit from pudendal stents.

The Incidence of Male Pudendal Artery Stenosis in Suboptimal Erections Study (IMPASSE) was a multicenter trial enrolling 350 males ages 35-70 years undergoing angiography for CAD or PAD with follow-up at 1, 2, and 3 years. IMPASSE was intended to define the normal pelvic anatomy and correlate the pathologies of pelvic arteries to ED. Unfortunately, the study was suspended due to similar difficulties encountered in patient screening and selection. Further anatomical and interventional trials are necessary before endovascular repair of internal pudendal stenoses for the treatment of ED can be proven safe and effective.

Conclusion

The link between vasculogenic ED, CAD, and PAD is well defined. The disease processes likely represent distinct manifestations of the same atherosclerotic process. Because vasculogenic ED typically presents 2-5 years before the onset of clinically relevant CAD and PAD, it represents an ominous sign of cardiovascular pathology to come that clinicians must recognize and treat aggressively. All patients with presumed vasculogenic ED warrant aggressive modification of atherosclerotic risk factors, especially those with a suboptimal response to PDE-5 inhibition. Patients with coexisting claudication and diminished femoral pulses may have significant aortoiliac stenoses amenable to surgical or endovascular repair to target both their claudication and their ED. Endovascular repair of internal iliac, internal pudendal, or common penile stenoses is likely to provide symptomatic improvement in patients with vasculogenic ED, as outlined by the ZEN trial, though larger randomized trials are needed to demonstrate long-term safety and efficacy, and improvements in non-invasive evaluation of this arterial bed are needed to improve patient selection for this potentially impactful therapy.

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