The Relationship Between Erectile Dysfunction and Cardiovascular Disease. Part I: Pathophysiology and Mechanisms

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There is increased awareness regarding the close association between cardiovascular disease and erectile dysfunction, especially because both conditions share common risk factors such as diabetes mellitus, hypertension, smoking, hyperlipidemia, and a sedentary lifestyle. Recent studies suggest that erectile dysfunction could be considered a potential marker for underlying silent cardiac or vascular disease processes. Endothelial dysfunction seems to play a major role in both sexual dysfunction and heart disease. With the initiation in 1998 of vasoactive drugs such as the phosphodiesterase-5 inhibitors for the treatment of erectile dysfunction, the underlying vascular components of erectile dysfunction have become a more prominent focus of attention in the clinical and research setting. This review critically examines the background, pathophysiology, and mechanisms behind erectile dysfunction and its close correlation to cardiovascular disease.

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Key words: Erectile dysfunction • Coronary artery disease • Endothelial dysfunction • Nitric oxide • Hypertension • Heart failure

Erectile dysfunction (ED) is defined as the persistent inability to achieve and/or maintain a penile erection sufficient for satisfactory sexual performance.[1] In the Massachusetts Male Aging Study, 52% of men ages 40 to 70 reported some degree of ED.[2] In the past decade, there has been a substantial increase in interest among health care providers, the pharmaceutical industry, the media, and the public concerning ED and associated comorbidities. In part, this interest is explained by the increased awareness among both physicians and patients that ED is considered a (vascular) disease and not merely a symptom.

Normal sexual function is an interplay of psychological, hormonal, vascular, and neurological factors. At a molecular level, nitric oxide (NO) plays an important role in the maintenance of homogeneity in erectile tissue. NO is secreted by endothelial cells and causes the smooth muscle of the corpora cavernosa to relax, thereby producing a penile erection.[3,4] Disruption of the endothelial lining by stressors may cause an imbalance between vasodilating and vasoconstricting capabilities, which results in the signs and symptoms of ED.

A recent estimate revealed that ischemic heart disease will be the leading cause of global disability and the fourth most common cause of death by the year 2020. The association between cardiovascular disease and ED is evident because both conditions share common risk factors such as atherosclerosis,[5] diabetes mellitus,[6] hypertension, obesity, smoking,[7] sedentary lifestyle,[8] and hyperlipidemia[6] (Table 1).

Phosphodiesterase-5 (PDE-5) inhibitors are a class of medications approved by the Food and Drug Administration for the treatment of ED. They act primarily by inhibiting the phosphodiesterase enzyme, causing an NO-associated vasodilation that facilitates erection. In addition to their use in ED, PDE-5 inhibitors are now being evaluated for other vascular disease processes. We will discuss these other uses in detail in an upcoming issue of *Reviews in Cardiovascular Medicine*.

Table 1
Risk Factors/Associations of Erectile Dysfunction

Diabetes
Hypertension
Atherosclerosis
Hyperlipoproteinemia
Smoking
Alcohol/drugs/medication
Chronic diseases
Psychosocial problems

ED and Coronary Artery Disease

Atherosclerosis is a systemic phenomenon that affects all parts of the body, including penile tissue. It is the most common cause of vasculogenic ED in elderly men.[9] Kloner and colleagues[10] showed that 75% of men with documented coronary artery disease (CAD) had coexistent ED. In a study by Solomon and coworkers,[11] 65% of patients with angiographically documented CAD had ED. This rate was 49% in a study by Montorsi and associates,[12] which also showed that 67% of the men with ED had had symptoms prior to the onset of cardiovascular disease—on average, 39 months prior. These data suggest that ED could be a possible marker for cardiovascular disease. In addition, a penile peak systolic blood-flow velocity of less than 35 cm/s had a 100% specificity for predicting ischemic heart disease.[13]

There is also evidence that ED could serve as an early marker for vascular dysfunction and associated diseases.[14] In one study, 92% of men (47 out of 51) who did not respond to a pharmacologic erection test with prostaglandin E1 had 1 or more cardiovascular risk factors, compared with 78% (36 out of 46) in the responder group ($P = .081$).[15] Sixteen percent of patients (8 out of 51) in the nonresponder group showed ischemic changes on an electrocardiogram during a stress test, whereas none of the 46 patients in the responder group demonstrated objective signs of ischemia ($P < .05$). The presence of arteriogenic ED (using penile Doppler ultrasonography) has been associated with a high prevalence of clinically apparent atherosclerosis, particularly in men older than 50.[5] In addition, one study showed a positive correlation between ED and the number of occluded coronary arteries.[16]

There is overwhelming evidence that endothelial dysfunction is a central etiological factor in the development of atherosclerosis and systemic vascular disease. Alteration in the homogeneity of the endothelial environment forms the baseline for both ED and cardiovascular disease. The vascular damage caused by certain risk factors leads to endothelial dysfunction that predisposes to atherosclerosis and, consequently, impairment in vascular flow to the penile tissue, resulting in ED. Alterations in the endothelial L-arginine-NO mediated smooth muscle relaxation pathway have been demonstrated in atherosclerotic coronary arteries of humans and in animal models in several studies.[6-9] These findings are similar to those seen in the penile L-arginine-NO pathway and support the concept that vasculogenic changes in the penile vascular bed mirror those in the coronary arteries.

Bocchio and associates[17] studied the biochemical marker in patients with ED and cardiovascular risk factors. Forty-five patients with ED and cardiovascular disease risk factors were compared with 45 patients who had ED but no cardiovascular risk factors. There was no difference in the carotid intima-media thickness scores between the 2 groups. The men with ED but without cardiovascular disease had significantly higher levels of soluble P-selectin, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and endothelin-1 than the men who had both ED and cardiovascular disease. The results support the concept that

symptoms of ED may precede overt structural occlusion of larger vessels, thereby confirming the concept that ED is an early manifestation of systemic vascular disease.

ED and Hypertension

Hypertension is considered a highly prevalent risk factor for the development of cardiovascular disease. According to data from the National Health and Nutrition Examination Survey, approximately 50 million people suffer from hypertension in the United States.[18,19] The close association between hypertension and ED has been highlighted in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[20] The authors concluded that the age-dependent decline in sexual function is accelerated in patients with hypertension. Use of antihypertensive agents may further impair sexual function because of drug-specific side effects.

There is no doubt, however, that the deleterious effects associated with uncontrolled hypertension are stronger than any of the potential side effects caused by drugs, especially in regard to sexual dysfunction. In the Massachusetts Male Aging Study, the probability of sexual dysfunction was directly correlated with concomitant hypertension, heart disease, and diabetes mellitus.[2] Hypertension has been associated with increased risk of ED (odds ratio 1.4; 95% CI, 0.7-3.2).[21] Moreover, the Cologne Male Survey study showed a higher prevalence of ED in men with hypertension.[22] Results from 832 men ages 30 to 69 who took the International Index of Erectile Dysfunction questionnaire indicated that the risk for ED increased in men with cardiac disease, diabetes, and hypertension.[23] In one study, 44% of patients with known ED had concomitant hypertension.[24] The frequency of hypertension in men with ED compared with the general population, however, was not significantly different. In a study comparing 110 newly diagnosed, untreated patients with hypertension with 110 healthy volunteers, patients with hypertension reported 25% fewer sexual intercourse episodes.[25] Hypertension therefore appears to be strongly associated with the development of ED and is considered an independent risk factor for its development.

More recently, hypertension—among other vascular risk factors—has been shown to contribute to the development of female sexual dysfunction.[26] Antihypertensive medications, in particular thiazide diuretics and β-blockers, are known to have some degree of negative effects on both male and female sexual function. For example, it is postulated that β-adrenoreceptor blockers act on the corporal smooth muscle sodium pump. The inhibition of this pump results in the contraction of the corporal smooth muscle, leading to impaired vasorelaxation and erection. The diuretic spironolactone also has well known antiandrogenic properties that cause a decrease in sexual function.

Several studies have shown a relationship between the use of antihypertensive drugs and the prevalence of ED. In a study published by the Medical Research Council in 1981, patients received the diuretic bendrofluazide, the β-blocker propranolol, or a placebo.[27] After 2 years of treatment, the prevalence of impotence was 10% in the placebo group, 13% in the propranolol group, and 23% in the bendrofluazide group. Similarly, in the Trial of Antihypertensive Interventions and Management, sexual dysfunction was diagnosed in 28% of patients receiving chlortalidone, 11% of patients receiving atenolol, and 3% of patients receiving placebo ($P < .05$).[28]

Interestingly, both hypertension and the use of antihypertensive drugs seem to contribute to the worsening and, eventually, the development, of ED. In contrast, some anecdotal reports state that agents such as the angiotensin II receptor blocker valsartan might improve sexual dysfunction.[29] A randomized, double-blind, crossover study compared the effects of carvedilol (50 mg/d) with valsartan (80 mg/d) in 120 newly diagnosed hypertensive patients. It showed increased sexual activity in the valsartan group at 16 weeks ($P < .05$).[29]

In summary, adequate control of elevated blood pressure is the ultimate goal to prevent cardiovascular problems, including sexual dysfunction, which—in most cases—can be considered a vascular problem. The choice for antihypertensive agents, however, should be dictated by the potential side effects. Side effects might not always be related to the class of a particular drug, so treatment may require several attempts with different drugs as well as different drug classes.

ED and Heart Failure

The prevalence of heart failure is increasing worldwide, and the condition is currently the number one reason for hospitalizations, morbidity, and mortality in the elderly. Patients with heart failure, when treated adequately, might be relatively stable for a certain period of time. Therefore, quality-of-life issues, such as a satisfactory sexual life, are gaining prominence. Only limited data are available on the prevalence of ED in the heart failure population.[30] In one cohort of 62 male and female clinic outpatients with heart failure, 71% reported compromised libido and ED.[31]

The cause of ED in heart failure patients is multifactorial; decreased cardiac capacity, deconditioning, generalized atherosclerosis, endothelial dysfunction, arterial insufficiency, neurohormonal changes, and medication side effects all play important roles.[32] Moreover, heart failure is associated with elevated endothelin levels that cause vasoconstriction. In the setting of impaired vasodilatory mechanisms, elevated endothelin levels further amplify ED.[33,34] Vascular smooth muscle abnormalities also contribute to the worsening of ED. It has been suggested that a decrease in arterial compliance and impaired endothelium-independent vasodilation result in an altered response of the NO-dependent pathway, thereby contributing to ED.

Sexual activity and function are closely linked to exercise tolerance and conditioning. Jaarsma and colleagues[31] found a significant relationship between sexual function and the 6-minute walk test. In addition, psychological factors such as depression, performance anxiety, and fear of cardiac damage or death may exist in patients with reduced cardiac capacity or heart failure. In particular, fear of death during sexual activity appears to contribute to the worsening of sexual function.[35] As mentioned earlier, several drugs used in the treatment of heart failure, such as β-adrenoreceptor blockers, digoxin, and diuretics, are also known to contribute to the development of ED.[32] Arginine vasopressin (AVP) is elevated in heart failure, even in asymptomatic states. Recently, it was shown that AVP inhibits sexual behavior in female rats.[36] Even though this link is not proven in humans, elevated AVP might further contribute to reduced sexual activity in patients with chronic heart failure (Table 2).

Table 2
Possible Causes of Erectile Dysfunction in Patients With Heart Failure

Arterial insufficiency
Endothelial dysfunction
Endothelins
Psychogenic (depression/performance anxiety)
Medication side effects (digoxin, β-blockers, spironolactone, thiazide diuretics)
Exercise intolerance, reduced cardiac capacity
Deconditioning
Arginine vasopressin

ED and Endothelial Dysfunction

The erectile mechanism involves the integrated coordination of output from parasympathetic, sympathetic, and somatosensory neural pathways to result in the vasodilation of the penile arteries, the increase of blood flow to the penis, and the increase of volume capacity within the penile vascular structures. The endothelium lining the smooth muscle of the corpus cavernosum is a key regulator of erectile function. Although a number of neurotransmitters are important for erection, NO is probably the most important. It is synthesized from endogenous L-arginine by a reaction catalyzed by nitric oxide synthase (NOS).[37] NO is derived from both cavernous nerves (neuronal NOS) and the endothelium (endothelial NOS), and both sources of NO are important for penile erection.[38] Evidence suggests that in the initial phases of the erectile response, NO is released from nerve terminals in relatively short bursts followed by a more sustained release from endothelial cells throughout the duration of the erection. NO diffuses into the cells and activates the enzyme guanylate cyclase in the cytosol, which converts 5-guanosine triphosphate to the second messenger, 3′,5′-cyclic guanylate monophosphate.[1] The resulting calcium changes of the sarcoplasm cause relaxation of the smooth muscle in the corpora cavernosa, which leads to an erection through reduced sinusoidal resistance and increased arterial inflow. Alteration in endothelial function or impaired NO synthesis causes an imbalance between vasodilating and vasoconstriction factors that can result in ED (Figure 1).

A number of studies have supported the role of endothelial dysfunction as a marker for ED. Pegge and colleagues[38] studied 33 men ages 35 to 65 years with ED (20 diabetic, 13 nondiabetic). The group consisted of 15 sildenafil responders and 18 nonresponders, who were compared with age- and risk-matched controls. Endothelial function was assessed by changes in brachioradial and femorotibial arterial pulse-wave velocity during reactive hyperemia, and was expressed as a percentage of endothelium-dependent dilation. The mean respective changes in pulse-wave velocity in the arm and leg were:

- 0.71% (standard deviation [SD], 6.5) and 3.5% (SD, 6.4) in the impotent diabetic men.
- 0.7% (SD, 7.6) and 2.4% (SD, 5.9) in the nondiabetic impotent men.
- 0.68% (SD, 5.7) and 1.31% (SD, 7.2) in the nonimpotent diabetic men.
- 7.7% (SD, 3.7) and 7.6% (SD, 3.4) in controls.

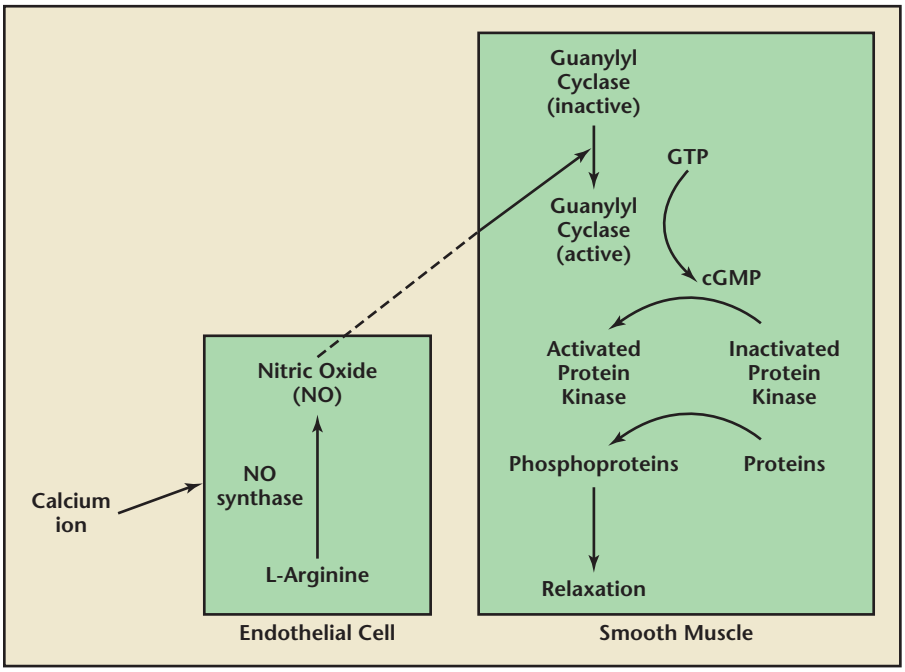

Figure 1. *The interaction between endothelial cells and smooth muscle of the corpus cavernosum. Endothelial dysfunction affects the nitric oxide mediated pathway, hence impairing smooth muscle relaxation and penile erection. GTP, guanosine triphosphate; cGMP, cyclic guanosine monophosphate.* www.medreviews.com

The results demonstrated that ED in both diabetic and nondiabetic men is characterized by marked endothelial dysfunction (in contrast to nondiabetic controls).

Similarly, men with ED exhibit significantly lower brachial artery flow-mediated, endothelium-dependent vasodilation and endothelium-independent vasodilation compared with controls.[5] The men with ED had a blunted response to 0.4 mg sublingual nitroglycerin ($P < .05$). Yavuzgil and colleagues[39] compared brachial artery flow-mediated dilation and nitroglycerine-mediated dilation in patients with presumed vasculogenic ED and cardiac risk factors, patients with risk factors but no ED, and controls. Brachial artery flow-mediated dilation and nitroglycerine-mediated dilation were significantly reduced in patients with ED as compared with healthy controls. Patients without ED who had risk factors demonstrated a decrease in flow-mediated dilation, but not nitroglycerine-mediated dilation, as compared with controls, which suggests impairment in endothelial-independent vasodilation. Vlachopoulos and colleagues[40] investigated the role of low-grade inflammation and endothelial dysfunction in patients who had ED with or without CAD. Markers for inflammation (eg, high sensitivity C-reactive protein, interleukin-6, interleukin-1b, and tumor necrosis factor-α), endothelial prothrombotic mediators (eg, Von Willebrand factor, tissue plasmogen activator, and plasminogen activator inhibitor-1), and fibrinogen were significantly increased in patients with ED and correlated negatively with sexual performance. Bivalacqua and colleagues[41] found that RhoA/Rho-kinase suppresses endothelium NO synthase in the penis, which is a mechanism for diabetes-associated ED. Uslu and associates[42] assessed left ventricular diastolic function and forearm endothelial function in patients with ED who did not demonstrate overt cardiovascular disease. They reported that endothelium-dependent vasodilation, mitral inflow E velocity, and E/A ratio were smaller in men with ED compared with controls. The authors concluded that endothelial function and left ventricular diastolic function are

Main Points

- There is increasing evidence that erectile dysfunction (ED) could serve as an early marker for vascular dysfunction.
- Hypertension is considered a highly prevalent risk factor for the development of cardiovascular disease. However, the use of antihypertensive drugs may contribute to the development of ED.
- The possible connection between heart failure and ED could be attributed to factors such as decreased cardiac capacity, deconditioning, generalized atherosclerosis, endothelial dysfunction, arterial insufficiency, neurohormonal changes, and medication side effects.
- Nitric oxide (NO) is probably the most important neurotransmitter involved in the process of erection. Any alteration in endothelial function or NO synthesis results in an imbalance between vasodilating and vasoconstriction factors that can result in ED.

impaired in patients with ED without overt cardiovascular disease.

Conclusion

The initiation and maintenance of penile erection is a complex physiological process involving the interaction of vascular, neurological, and psychological factors. Cardiac risk factors such as diabetes, hypertension, and hyperlipidemia can affect the normal homogenous penile environment and lead to ED. There is increasing evidence of a close association between cardiovascular disease and male (and even female) sexual dysfunction. ED, at least in part, is caused by and appears similar to endothelial dysfunction. Because ED seems to occur prior to the onset of cardiovascular symptoms, it can be seen as an early marker for underlying but undiagnosed cardiovascular disorders. We believe, in contrast to former recommendations, that ED in most patients with underlying heart or vascular disease can be adequately evaluated and treated. Men with existing cardiovascular disorders should be screened for coexisting sexual dysfunction, even though cost-effective screening has not yet been established. ■

Editor's Note

In an upcoming issue of *Reviews in Cardiovascular Medicine*, the authors will discuss the role of phosphodiesterase-5 inhibition in sexual dysfunction and cardiovascular disease.

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