

EDITORIAL COMMENT

Erectile Dysfunction: The Earliest Sign of Generalized Vascular Disease?*

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Until sildenafil, the first effective oral agent for erectile dysfunction (ED), was introduced, only genitourinary physicians concerned themselves with this problem. Certainly cardiologists rarely asked their patients with cardiovascular disease about difficulty developing or maintaining a penile erection. Physicians knew that ED could be caused by atherosclerosis of the internal iliac arteries, the smaller vessels supplying the penis, neural damage frequently related to radical prostatectomy, certain medications, and a deficiency of testosterone. Lacking these, ED was attributed to psychologic problems.

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With the development of sildenafil, the first guanosine monophosphate (GMP)-specific phosphodiesterase (PDE-5) inhibitor, there has been a major increase in the interest in the problem of ED, and with this increased interest, a realization that the prevalence of ED in patients with cardiovascular disease is higher than that of the general population. There will soon be other PDE-5 inhibitors approved by the Food and Drug Administration, such as vardenafil and tadalafil, each with slightly different properties, so physicians will soon have several effective drugs with which to treat these patients. In the Massachusetts Male Aging Study, 34.8% of men ages 40 to 70 years have moderate-to-complete ED, and 15% of men aged 70 have complete ED. The risk increases markedly with age, with men ages 50 to 59 having 3.6 times the risk of men age 18 to 29 (1). Studies have shown a high prevalence of ED in patients with cardiovascular disease (1). There is a significant correlation between the severity of ED and the number of vessels involved in patients with coronary artery disease (CAD) (2). The age-adjusted prevalence of complete ED is 1.5 times higher in men with hypertension than the prevalence in the entire population studied (1). Erectile dysfunction also is prevalent in smokers (3), diabetics (4), and patients with hypercholesterolemia (5), all of the same risk factors as for CAD. Conversely, patients with ED have an increased prevalence of vascular disease, including CAD and peripheral vascular disease (5).

The common denominator for these apparently disparate problems is endothelial dysfunction, a major etiology of ED (6). Penile erection occurs through neural stimulation of the endothelial lining of penile vessels and the lacunae of the corpus cavernosum, releasing nitric oxide. This activates guanylate cyclase—converting guanosine triphosphate into the second messenger cyclic GMP (cGMP), which through cGMP-dependent protein kinase phosphorylates numerous ion channels and pumps sequestering intracellular Ca^{2+} in the endoplasmic reticulum, decreasing cytosolic Ca^{2+} and resulting in smooth muscle relaxation, arteriolar vasodilation, and relaxation of the corpus cavernosum lacunae. Intercourse stimulates the bulbocavernous reflex, and the contracting ischiocavernosus muscles compress the base of the engorged corpus cavernosum. The lacunae fill with arterial blood under arterial pressure, swelling the penis, compressing the penile veins against the tough tunica albuginea, and trapping blood in the corpus cavernosum under arterial pressure (7). Detumescence occurs because the cGMP is hydrolyzed to GMP by an enzyme, PDE-5, one of a family of 11 PDE enzymes, allowing vasoconstriction and lacunae to contract with release of blood from the penis (8). Sildenafil, a PDE-5 inhibitor, prolongs the action of cGMP and, therefore, smooth muscle relaxation.

Our present understanding of the genesis of atherosclerosis also begins with damage to the intima of arteries, accelerated by the risk factors such as smoking, hypertension, and so on, resulting in endothelial dysfunction. Excessive production of superoxide radicals and other reactive oxygen species oxidizes lipoproteins, nucleic acids, and other proteins. It also decreases nitric oxide bioavailability and results in a procoagulant surface (9). Therefore, the earliest events in the development of atherosclerosis are similar to the earliest events in the development of ED.

Because of the high prevalence of vascular disease in patients with ED, physicians must be aware of the relationship and evaluate the patient for the presence of vascular disease. Similarly, patients being examined for vascular disease should be questioned about the presence of ED, first because ED may be an important factor in degrading the quality of life in some, if not all patients, and second because we have an effective therapy that can markedly improve the ED.

In this issue of the *Journal*, Kaiser et al. (10) have reported a study of 30 patients with ED, with no clinical evidence of arterial disease, who had most of the known risk factors associated with coronary disease ruled out. Kaiser and colleagues age-matched these patients with a control group of normal subjects without clinical evidence of arterial disease and without ED and searched for early signs of atherosclerosis with carotid ultrasound, measuring thickness of the intima-media, carotid and brachial artery compliance and distensibility, aortic pulse wave velocity as a measure of arterial stiffness, coronary calcification by rapid computed

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tomography, and brachial artery endothelium-dependent and -independent vasodilatation.

They found no differences in intimal-medial thickness, coronary calcification, or pulse wave velocity or aortic distensibility, all presumably surrogates for atherosclerosis, from the control subjects. They found abnormal endothelial-dependent flow-mediated vasodilatation in the brachial arteries in the patients with ED, indicating a widespread abnormality of endothelial function in men with ED as has been shown in patients with CAD (11) and CAD risk factors (12). Their conclusion was that ED is the earliest manifestation of vascular disease and that these patients may be at increased risk of later developing clinically apparent arterial disease, including CAD. Furthermore, they noted that endothelial dysfunction occurred in the absence of the usual atherosclerosis risk factors in these patients. The question arises as to whether all known risk factors were ruled out: lipoprotein (a), elevated homocysteine, glucose intolerance, and insulin resistance were not examined. It is possible that the patients had risk factors predisposing them to atherosclerosis. Still, the earliest sign before any demonstrable vascular disease was the development of ED.

There are etiologies of ED other than endothelial dysfunction, such as damage to the penile autonomic innervation as seen in radical prostatectomy (13). However, in this study ED was determined to be vascular in etiology by using a Doppler technique to determine cavernosal artery velocity as a measure of penile blood flow. Even if atherosclerosis and some patients with ED have a common abnormality of endothelial dysfunction, there are patients where ED may be related to any of the stages in the cascade of chemical processes that produce smooth muscle relaxation and vasodilatation. For instance, the cGMP-dependent protein kinase activation of the Ca^{2+} -sensitive potassium channels, which hyperpolarize the arterial and cavernosal smooth muscle cell membranes causing relaxation, appears to be compromised with aging and may not be associated with a higher incidence of development of arterial disease (14). This abnormality is at the level of the smooth muscle cell. Corporeal veno-occlusive dysfunction, a smooth muscle problem that causes venous leakage from the penis, is another etiology of ED that does not produce decreased blood flow into the corpus cavernosum (15) and yet may not be a harbinger of atherosclerosis.

An interesting finding in this study is that both endothelial-dependent and endothelial-independent vasodilatation were abnormal in patients with ED. The implication is that, in these ED patients without signs of early atherosclerosis, the problem is not only endothelial dysfunction but also a problem with smooth muscle relaxation itself. A possible explanation for this finding is that with long-standing penile vascular disease, either atherosclerotic or due to endothelial dysfunction, a loss of smooth muscle and fibrosis occur in the corpus cavernosum, which will cause the ED to persist despite reversal of the original vascular

abnormality (16,17). Still, evidence that there is a smooth muscle abnormality beyond the endothelial dysfunction in ED is an intriguing finding and certainly will have to be confirmed by other studies.

The important message here is that many patients with ED have a vascular mechanism similar to that seen in atherosclerosis and that its presence should alert the clinician to the possible presence or future development of vascular disease. To paraphrase Richardson and Vinik: "a flagging penis should raise the red flag of warning to evaluate the patient for arterial disease elsewhere" (18).

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