The Penis as a Barometer of Endothelial Health

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Erectile dysfunction (ED) has only within the past 25 years been recognized as being largely organic in cause. The introduction of phosphodiesterase-5 inhibitor therapy represents a major breakthrough in the treatment of ED and has resulted in a fast-growing body of knowledge regarding the etiology of the disorder, including its close association with cardiovascular disease. ED symptoms are often an early manifestation of endothelial dysfunction and, as such, should prompt further evaluation of not only the sexual dysfunction but also cardiovascular risk. This article discusses the importance of recognizing ED as much more than a quality-of-life issue.
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Only during the past 30 years has penile dysfunction been associated with organic disease processes. In the middle ages, erectile dysfunction (ED) was considered a sign of possible demonic possession, to be cured by exorcism. In the early to mid-19th century, ED was believed to be to the result of masturbation and sexual excesses, to be cured by anti-masturbation belts and

prostatic urethra electrical stimulation. Sigmund Freud and his colleagues introduced the concept that penile function was ultimately controlled by the mind and that, by exploring and understanding subconscious conflicts with psychoanalysis, erectile function could be restored. Masters and Johnson hypothesized that the problem was behavioral and could be resolved with behavior modification. Their concept of organic ED was that it was purely hormonal. Because most men with ED had normal hormone levels, they inferred that ED must have a psychological basis.

In 1974, with the introduction of the penile implant, the urologic community was forced to explore the association between ED and organic disease. Aside from the obvious cases associated with advanced diabetes, trauma, spinal cord injury, or post–major pelvic radiation or postsurgery status, the cause was not always apparent. Fearing an inundation of unnecessary penile implants, insurance companies were mandating "proof" that the cause of ED was organic before they would consider reimbursement for implantation surgery. Psychiatric consultations, hormonal profiles, penile Doppler ultrasonography, nocturnal penile tumescence studies, penile angiography, and cavernosometry were performed to document the organic dysfunction. Because normal standards were lacking and results were frequently ambiguous, the indiscriminate use of these tests only added to the confusion over the ED etiology. The deluge of implants never materialized, and the criteria for implantation reimbursement relaxed. We did, however, learn something important from all the tests conducted: ED was strongly associated with cardiovascular disease processes.

Anecdotal, experimental, and epidemiologic evidence increasingly demonstrates a clear link between ED and the risk factors for atherosclerotic cardiovascular disease.[1] In a recent study of 154 men with ED, 44% had hypertension, 23% had diabetes mellitus, 16% used tobacco, 79% had a body mass index greater than 26 kg/m^2, and 74% had a low-density lipoprotein cholesterol level greater than 120 mg/dL.[2] The 10-year follow-up of the Massachusetts Male Aging Study has validated its original epidemiologic findings linking ED with cardiovascular risk factors.[1,3,4]

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As new therapeutic interventions were developed—intracavernosal and intraurethral prostaglandin and, eventually, sildenafil—there seemed to be no need to understand the underlying etiology of ED. If the recommended therapy was the same regardless of the results of the diagnostic workup, why bother with understanding the etiology? Most urologists adopted a goal-directed approach that de-emphasized the importance of the diagnostic workup. The patient was educated about the therapeutic options and left to make a decision.

Before March 27, 1998, the date of US Food and Drug Administration approval of the phosphodiesterase-5 (PDE-5) inhibitor sildenafil, ED was almost exclusively treated by urologists. This rapidly changed and, by the end of 1998, 75% of new sildenafil prescriptions were being written by non-urologist physicians. The primary treatment of ED has landed squarely in the laps of non-urologists, most of whom received only the briefest education in male sexual dysfunction in their medical school training. As of this year, fewer than 15% of new sildenafil prescriptions are written by urologists.

After the approval of sildenafil, the "Process of Care" model was developed to help guide non-urologist physicians in the treatment of ED.[5] This comprehensive consensus monograph, written by leading experts in the field of male sexual dysfunction, was to serve as a guide for non-urologists to the clinical approach to ED. Again, the emphasis was on patient choice.

ED continues to be perceived by physicians, patients, and third-party payers as a quality-of-life issue. In the era of managed and capitated care, with tremendous economic pressure to increase patient load and volume, spending time eliciting discussion from patients about such a "quality-of-life issue" is viewed as time poorly spent. Physicians expect patients to bring up the issue, and patients are waiting for their physicians to ask them the question. Although the public is now vastly more educated about ED, many patients are still embarrassed by the subject. Physician and patient resistance has resulted in fewer than 25% of men with ED seeking medical care for this problem.

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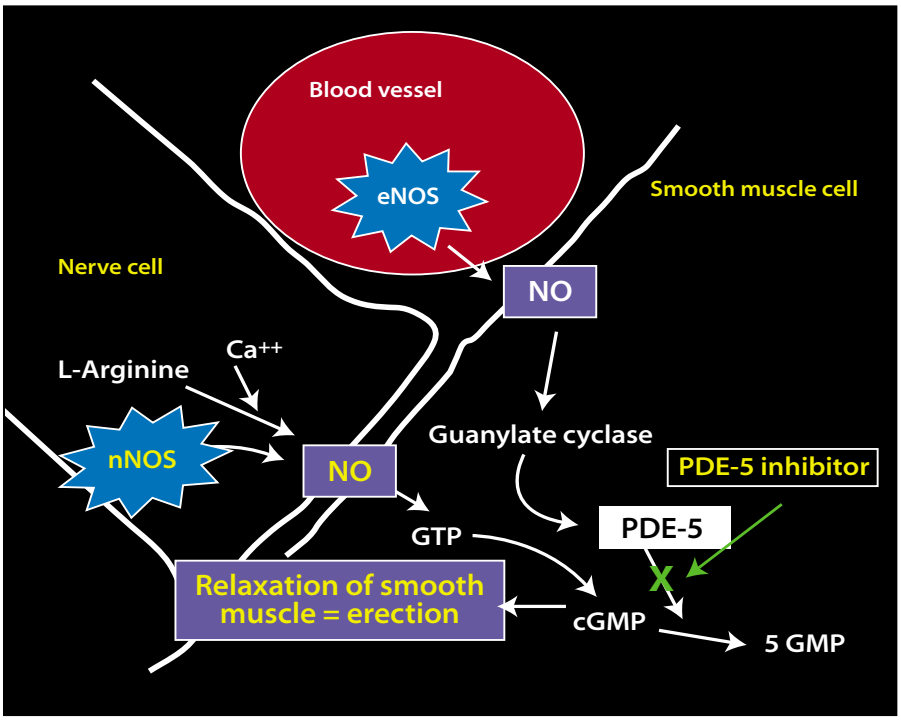

Figure 1. *Schematic of the biochemical pathway for erectile function and mode of action of phosphodiesterase-5 (PDE-5) inhibitors. NO, nitric oxide; eNOS, endothelial nitric oxide synthase; nNOS, neuronal nitric oxide synthase; GTP, guanosine triphosphate; GMP, guanosine monophosphate; cGMP, cyclic GMP.*

The crucial questions are: What is the significance of the presence of ED? Is ED a quality-of-life issue or a possible diagnostic clue that the patient is manifesting an early sign of peripheral vascular disease?

The Penis and the Endothelial System

The penis is a sensitive hydraulic organ that is responsive to sympathetic and nervous parasympathetic tone, active vascular flow, and passive veno-occlusion. It is composed of an extensive endothelial surface interlaced with smooth muscle. In order for a man to achieve an erection, there must be a decrease in sympathetic smooth muscle tone, an increase in parasympathetic smooth muscle relaxation, an increase in arterial inflow, a filling of the endothelial spaces (enabled by corporal smooth muscle relaxation), and a passive pinching off of the venules exiting the tunica albuginea.

The entire process is exquisitely sensitive to the availability of both neuronal and endothelial nitric oxide, which is in turn dependent on the presence of both neuronal and endothelial nitric oxide synthase (nNOS and eNOS, respectively), the crucial enzyme responsible for the production of nitric oxide gas (Figure 1).[6] The penis, richly innervated and with its vast endothelial system, is a natural repository for NOS.[7] Consequently, any disease process that reduces the levels of nNOS or eNOS will decrease erectile function. Whereas a reduction in nNOS level is usually iatrogenic, the result of prostatic or pelvic surgery or irradiation, the conditions that reduce the eNOS level are those associated with cardiovascular disease and endothelial dysfunction (Table 1).[8]

The experimental evidence linking NOS deficiency and ED has come from studies of aging and diabetic rats.[9-11] In addition, data are accumulating linking polymorphism of eNOS to coronary artery disease in humans.[12] Damage to the endothelium often precedes the development of clinically manifest vascular disease.[13]

Despite the strong association between ED and endothelial dysfunction, ED is not always related to decreased NOS levels. The 18-year-old male who has anxiety about his first sexual experience and loses his

Table 1
Conditions Associated With Reduced nNOS and eNOS

Endothelial disease
- Age
- Hypertension
- Hyperlipidemia
- Diabetes
- Obesity
- Smoking
- Pelvic radiation

Neurologic trauma
- Surgical trauma: radical prostatectomy or cystectomy
- Pelvic radiation
- Accidental trauma
- Neurologic disease: Parkinson disease, multiple sclerosis, etc

erection most certainly has an overactive sympathetic system that is not allowing his corporal smooth muscles to relax and, hence, his penis does not fill or detumesces prematurely. In men younger than 35 years who have no significant underlying endothelial disease or neurologic risk factors and are using no medications or drugs, the cause of ED is usually psychogenic. In this population, ED is not a major epidemiologic problem: the prevalence of ED in men younger than 35 years is less than 10%. Given the impact of the central nervous system on erectile function, it is highly probable that all men with ED, even those whose condition has a clearly organic basis, will have some performance anxiety that undermines their residual erectile function.

With such a strong relationship between ED and endothelial dysfunction, is there clinical utility in diagnosing ED? Might penile dysfunction be an important diagnostic clue to endothelial dysfunction and, hence, be more than a quality-of-life issue?

Why Should We Diagnose ED?

Assessing the Severity of Underlying Disease

It is generally acknowledged that ED can be a manifestation of an underlying "more serious" pathophysiology. Although this is true, physicians do not have to ask questions about erectile function to determine what medications a patient is taking and whether the patient is hypertensive, hyperlipidemic, obese, diabetic, or aging. The facts speak for themselves. Most primary care physicians will know the patient's age, weight, blood pressure, serum glucose level, and lipemic profile before entering the examination room, whether or not the patient has ED.

However, the important point is not that the comorbid conditions are associated, but that ED is an early end-organ manifestation of the disease process—one that manifests much earlier than a critical arterial stenosis of the coronary arteries,[14] diabetic peripheral neuropathy, retinopathy, or hypertensive cardiomyopathy. It is the body's "early warning system." For example, when assessing whether to give diet counseling only or to prescribe medication for a 52-year-old man with dyslipidemia, the presence of ED is a diagnostic clue that his endothelium is "screaming for attention" and that a more aggressive approach may be indicated. The same is true of the sedentary hypertensive patient or cigarette smoker. Whether or not the ED is problematic is irrelevant to the importance of asking about it. Inquiring about ED is an easy way to assess the severity of a man's endothelial disease.

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Drug Compliance

Many of the conditions treated in medicine are not perceptible to the patient. In general, a patient is not aware of his increased diastolic pressure or his elevated cholesterol level but is painfully aware of the side effects of his treatment. There is little doubt that the development of ED can undermine compliance with antihypertensive therapy.[15,16] As many as 44% of hypertensive men in whom ED develops ascribe the onset of ED to drug initiation.[17] Most partnered hypertensive men in their sixth decade of life will have established patterns of sexual activity, frequently centered on weekends. A man who perceives his ED to be drug-induced is likely to stop his medication midweek in order to maximize his weekend function. These bursts of treatment will undoubtedly result in poor control of hypertension.

The etiology of medication-induced sexual dysfunction is unclear. Although certain classes of drugs are more frequently associated with ED than others, modification of the drug regimen infrequently results in amelioration of the ED. The etiology is more likely a combination of the lowering of the blood pressure, end-organ disease, and the direct effect of the medication.[18] Regardless of the cause, the end result is the same: poor compliance with drug therapy. A proactive approach on the part of the physician in addressing any potential sexual side effects will reassure the patient that, should side effects occur, they can be summarily addressed. The patient need not sacrifice his sexual function for the treatment of an asymptomatic disease. Use of the Sexual Health Inventory for Men before initiation of antihypertensive therapy can potentially identify men with latent ED,[19,20] for whom ß-blockers and loop diuretics might not be the best initial choices.[21]

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Assessment of Disease Progression

Most conditions treated in medicine

have an inexorably progressive course. Our responsibility as physicians is to identify and manage these chronic conditions. Control of hypertension and dyslipidemia have irrefutably been associated with the prevention of cardiovascular complications. Tighter glycemic control is associated with fewer retinal and nephrologic complications.[22] We frequently rely on laboratory testing and radiographic studies to alert us to disease progression, whereas physical examination findings usually represent the latest manifestations of the disease. Our most powerful tool remains the patient history. In the follow-up of a diabetic patient, physicians will assiduously inquire about the new onset of exertional chest pain or dyspnea, claudication, and urinary frequency, yet they will neglect to mention a glaringly obvious symptom of endothelial disease—ED. In a multinational study of 26,000 men and women aged 40 to 80 years, only 14% of diabetic patients were asked about their sexual health.[23]

A man may deny his symptoms of angina by taking an elevator instead of the stairs or paying for his groceries to be delivered to the car instead of carrying them himself. Likewise, he may avoid sexual intimacy with his partner, but he knows that his penis is malfunctioning. Questions about ED belong not in a discussion of the genitourinary system but after questions about angina and claudication. A man may wonder why a question about his erectile function follows questions about his heart, at which point the physician has an opportunity to educate the patient about the connection between ED and cardiovascular disease. "Medicalizing" ED in this way can also lessen the stigma associated with the condition. Many patients retain the notion that ED is primarily psychogenic, even after radical prostatectomy, a surgery that uniformly results in organic ED.

PDE-5 Inhibitor Failures and the Need for Follow-up

Diagnosing ED and recommending oral therapy is not enough. Following up on the treatment is as important as the diagnosis. (It would be considered malpractice for physicians to prescribe antihypertensive medication without a follow-up blood pressure check.) The therapeutic efficacy of PDE-5 inhibitors in the nonsurgical patient is well over 75%, a level of success not often found in medicine. Not only is the therapy largely successful but it also usually results in improved quality of life, unlike treatments for many asymptomatic conditions.

Treatment failures with oral PDE-5 inhibitors should be taken seriously. Fifty percent of failures can be salvaged with re-instruction; the other 50% of these men may have relationship issues that are not conducive to re-establishing sexual intimacy, be unable to tolerate the side effects, or have advanced endothelial disease and peripheral vascular disease. The success rate of PDE-5 inhibitors is clearly related to the severity of the underlying peripheral vascular disease. The more serious the disease, the poorer the response to PDE-5 inhibitors. If PDE-5 inhibitor therapy fails in a patient who has followed all of the medication instructions,

Main Points

- Only recently has erectile dysfunction (ED) been recognized as an organic disorder. The various studies that established it as such led to the discovery of ED's association with cardiovascular disease.
- The process of penile erection is dependent on the availability of neuronal and endothelial nitric oxide synthase (nNOS and eNOS); a reduction in nNOS level is usually the result of prostatic or pelvic surgery or irradiation, whereas the conditions that reduce the eNOS level are those associated with cardiovascular disease and endothelial dysfunction.
- It is important that primary care physicians be educated in the management of ED (most prescriptions for sildenafil are written by non-urologists) and that they question patients about ED symptoms, which can be an early manifestation of a serious vasculopathy.
- A proactive approach to addressing and treating drug-related ED can help patients adhere to their antihypertensive regimens without feeling as if they must sacrifice their sex lives.
- Following up on ED treatment is important: because the phosphodiesterase-5 inhibitors have a high success rate, failure of this therapy should be considered a sign of serious peripheral vascular disease unless another origin (eg, a psychogenic cause) is found.
- Attitudes about ED are changing: more men are seeking medical care for ED, more clinicians are recognizing it as a medical condition that involves much more than quality of life, and ED is no longer the concern of urologists only. However, the stigma and embarrassment surrounding the topic still remain relatively strong.

either a powerful psychogenic component or severe peripheral vascular disease is at work. The distinction between the man with psychogenic ED and the man with severe vasculopathy should be obvious from the patient histories.

The patient with vasculopathy should be carefully evaluated. Are his comorbid conditions being maximally managed? Has he recently had a cardiologic evaluation? If not, and if he is playing 2 sets of tennis a week, he may be a "walking time bomb." To ignore this patient would be like ignoring the patient complaining of left arm pain with exertion. True PDE-5 inhibitor failures should be considered a result of advanced peripheral vascular disease until proved otherwise. As stated earlier, endothelial disease often precedes the development of clinically manifest vascular disease.[13] The penis is an endothelial organ. Its failure to respond to PDE-5 inhibitors should be treated as a serious symptom.

Summary

We have made great strides in the treatment of ED. A little more than 5 years ago, fewer than 6% of men with ED were receiving treatment. Today, 1 in 4 men with this condition has sought medical care. A field that was dominated by urologists is now predominantly managed by nonurologist physicians. However, the stigma of ED remains strong. Physicians and patients frequently avoid the topic. The former feel that they do not have the time and that it is not a serious topic, and the latter continue to be embarrassed about bringing up the subject.

ED is, in fact, more than a quality-of-life issue. It can be an early sign of endothelial dysfunction, can lead to noncompliance with medications used to treat the sequelae of endothelial disease, and can be a marker of endothelial disease progression. The penis is truly the barometer of the health of the endothelial system. ■

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