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Endothelial dysfunction/Erectile dysfunction: Common mechanisms, common management

BY JUAN CARLOS MONGE MD

Endothelial dysfunction, considered by many to be at the root of atherosclerotic vascular disease, shares many common risk factors with erectile dysfunction. In addition, they frequently occur in the same patients. A common mechanism that may explain the coexistence of these two seemingly disparate conditions is a decrease in the bioavailability of nitric oxide (NO), a small unstable molecule that mediates many of the normal functions of the endothelium. NO is also responsible for neurally-induced vasomotor changes at the level of the corpora cavernosa that underlie penile erection. A state of increased oxidative stress not only renders NO inactive, but also, through the reaction of oxygen-free radicals with NO, may lead to the formation of potentially toxic products. Therefore, addressing common risk factors is important because it may reduce cardiovascular events and improve erectile function. In addition, control of risk factors may increase the possibility of safely resuming sexual activity in the patient with coronary artery disease (CAD), although this has yet to be proven in properly designed randomized trials. Most cardiac patients, when appropriately risk-stratified and managed, can resume sexual activity safely, while many who also exhibit erectile dysfunction are eligible for first-line therapeutic modalities, including phosphodiesterase-5 inhibitors such as sildenafil. This issue of *Cardiology Rounds* examines the research linking endothelial with erectile dysfunction and discusses patient management.

In October 1998, some of the major national and international media outlets announced that the Nobel Prize for Physiology and Medicine had been awarded to three American researchers for "the discovery of the Viagra principle." By the following day, some local and secondary media organizations had transformed this news to "Viagra discoveries win Nobel Prize for Medicine." It should have come as no surprise that the link between the Nobel Prize-winning discoveries of Furchgott, Ignarro, and Murad and sildenafil, the novel therapy for erectile dysfunction, was so quickly established by the media, given the great interest of the media and the public following the release of sildenafil. However, the Nobel-winning discoveries – starting with the description by Furchgott of an endothelium-derived relaxing factor (EDRF) – were actually related to a simple molecule called nitric oxide (NO). NO, besides being the biologic principle responsible for EDRF activity, is also, among many other functions, the physiological mediator of penile erection.[1-5]

The search for catchy headlines notwithstanding, the media, perhaps inadvertently, were right in establishing a link between endothelial dysfunction and erectile dysfunction. Furchgott discovered the former condition when he observed that arteries denuded of endothelium contracted in response to acetylcholine, while normal arteries dilated. Endothelial dysfunction is caused by a decrease in the bioavailability of endothelial NO and erectile dysfunction is very often also caused by a decrease in NO of endothelial or neural origin. Therefore, both conditions share the same mechanisms and in many cases, the same risk factors. It is reasonable to postulate that addressing common mechanisms and modifying common risk factors may be indicated in the management of patients with erectile dysfunction.

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Nitric oxide: a key biologic mediator

Nitric oxide is a volatile gas formed during the conversion of L-arginine to L-citrulline by an enzyme called nitric oxide synthase. Three isoforms of NO synthase are known:

- Endothelial NO synthase (eNOS) is expressed mainly, but not exclusively, in endothelial cells and this expression is a hallmark of endothelial health.
- Brain or neuronal NO synthase (bNOS) is expressed in central and peripheral nervous tissues, including cavernous nerves.
- Inducible NO synthase (iNOS); expression can be induced in macrophages and other cell types in response to infection or inflammation.

NO is a rather unstable and short-lived molecule that acts locally, near the cells that produce it. After its secretion, it can follow one of three directions. First, it can act on guanylyl cyclase located in a target cell to generate cGMP, and if the target cell is a vascular smooth muscle cell, this leads to vasodilatation. Second, it can be exposed to hemoglobin and be inactivated. Third, it can react with oxygen-free radicals such as superoxide, leading not only to its inactivation, but also to the formation of potentially toxic compounds such as peroxynitrite.

Oxidative stress – A common element of endothelial dysfunction and some forms of erectile dysfunction

An enhanced state of oxidative stress is present in all common cardiovascular risk factors associated with endothelial dysfunction, such as diabetes mellitus, hyperlipidemia, hypertension, or smoking. Indeed, the production of superoxide is increased in these conditions and leads to inactivation of NO and the production of peroxynitrite. Experimental studies have demonstrated that cardiovascular risk factors enhance the production of superoxide in the same endothelial cells where NO is being produced, leading to an immediate decrease in NO bioavailability, even if normal amounts are produced.[6,7] Therefore, the amount of biologically-active NO is a function of the state of oxidative stress in the endothelium, as much as of the total amount of NO synthesized by eNOS and, in the case of penile erection, also by bNOS.

The two EDs (endothelial and erectile dysfunction): Common presentations

Erectile dysfunction is occasionally the presenting symptom in patients who have a variety of diseases characterized by endothelial dysfunction, (eg, diabetes mellitus, CAD, arterial hypertension, and hyperlipidemia). As an example of this association, a recent study assessed the incidence of lipid abnormalities and penile arterial insufficiency in men presenting with erectile dysfunction and no other known vascular abnormalities. This study included 57 men presenting to a clinic over a 3-month period with erectile dysfunction and no history of heart disease, diabetes, hypertension, hyperlipidemia, peripheral vascular disease, or stroke. The patients were evaluated with a fasting lipid profile and penile Doppler ultrasound to assess blood flow. Patients were divided into two groups: normal cholesterol (total cholesterol <5.2 mmol/L) comprising 40% of patients, or abnormal cholesterol (60% of patients). In the abnormal cholesterol group, 91% had Doppler evidence of penile arterial disease, a finding that was also present in 83% of the patients in the normal cholesterol group. However, nearly 90% of the patients with abnormal Doppler studies and normal total cholesterol values had LDL cholesterol levels that were above the recommended target of 2.5 mmol/L for patients with CAD.[8]

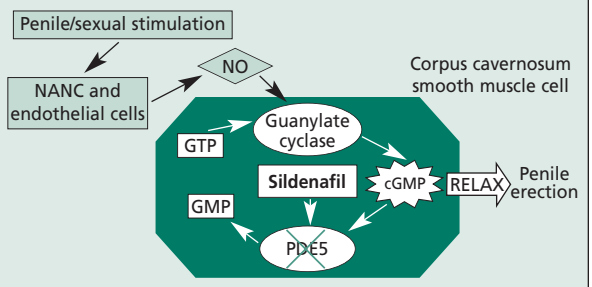
Another study evaluated the relationship between the severity of CAD and impairment of erectile function in 40 men, aged 40-73, who were undergoing coronary angiography to evaluate symptoms of ischemic heart disease. The patients completed a standardized questionnaire on sexual function and their cardiovascular risk factors were documented. Men with 2- or 3-vessel CAD had significantly fewer erections during a 30-day period and also scored lower on an index of erection firmness than men with single-vessel disease. This study also confirmed that diabetic patients scored significantly worse on both parameters than nondiabetics.[9]

The levels of cardiovascular risk factors present in men seeking treatment for erectile dysfunction were the subject of another study. The investigator evaluated the results of cardiovascular stress testing, risk profile analysis, and coronary angiography (not performed in all subjects) in 50 asymptomatic men with erectile dysfunction of presumed vascular origin. Multiple risk factors were present in 80% of the subjects, including smoking in 80% and a total cholesterol level >5.2 mmol/L in 70%. Graded exercise testing was positive in 28/50 patients and following this test, coronary angiography was performed in 20 of them, revealing severe left main or 3-vessel disease in 6, 2-vessel disease in 7, and single-vessel disease in 7. This study demonstrates the high prevalence of cardiac risk factors and significant CAD in men presenting with no symptoms other than erectile dysfunction.[10] This finding is likely explained by the common mechanism underlying both endothelial dysfunction and erectile dysfunction of vascular origin, namely the decreased availability of NO.

Mechanism of penile erection

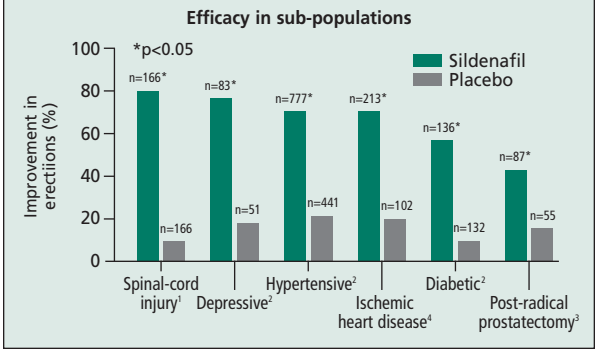
Neural impulses resulting from sexual stimulation lead to the release of NO by bNOS located in nonadrenergic, noncholinergic cavernous nerves. Similarly, cholinergic nerves release acetylcholine that acts on the surface receptors of the endothelial cells, leading to activation of eNOS and, in the healthy endothelium, a release of significant levels of bioactive NO.[11] In the presence of an increased state of oxidative stress, much of the NO would be inactivated; otherwise, it diffuses to the trabecular smooth muscle cells surrounding the sinusoidal spaces and acts on guanylyl cyclase. The cGMP thus generated mediates

Figure 1: Mechanism of action of sildenafil[12]



NO=nitric oxide. cGMP=cyclic guanosine monophosphate. PDE5=phosphodiesterase type 5. GTP=guanosine triphosphate. NANC=nonadrenergic-noncholinergic neurons.

Figure 2: Sildenafil – Improvement in erections



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relaxation of the smooth muscle, allowing an inflow of blood into the sinusoidal spaces and engorgement of the penis. Release of norepinephrine from the adrenergic nerves, coupled with the endothelial release of endothelin (a potent vasoconstrictor whose synthesis is increased in endothelial dysfunction), induce smooth muscle cell contraction and hinder penile erection. These mechanisms provide the common link between the two EDs, erectile and endothelial dysfunction.

Development of phosphodiesterase inhibitors and treatment of erectile dysfunction

Phosphodiesterases are enzymes that catabolize cyclic nucleotides such as cGMP. Because of the vasodilatory effects of cGMP, phosphodiesterase inhibitors were felt to be a good target for development of inhibitors that, by enhancing cGMP levels, would be of potential benefit for the treatment of hypertension and angina pectoris. Sildenafil, the first phosphodiesterase inhibitor approved for the treatment of erectile dysfunction, exhibits high affinity for the phosphodiesterase-5 (PDE-5) isoform that is abundant in the corpus cavernosum, but is also present in platelets, skeletal muscle, and visceral and vascular smooth muscle cells.

Sildenafil was originally developed as a cardiovascular drug of potential antianginal and antihypertensive efficacy. However, the observation of interesting "side-effects" led to its study in the management of erectile dysfunction where it was proven to be highly effective (Figure 1).[12,13] Sildenafil is a modest vasodilator, similar to a weak nitrate, and it has no direct cardiac effects given the absence of PDE-5 in the myocardium. By itself, sildenafil results in a modest 10/5 mm Hg reduction in blood pressure that is not dose-related within and beyond the recommended dose range. There are additive blood-pressure lowering effects when combined with other antihypertensive drugs and special caution must be exercised in patients taking multiple agents. A particularly striking synergistic effect is observed when sildenafil is co-administered with nitrates, explained by the induction of cGMP synthesis that is the mechanism of action of these agents. Thus, sildenafil is absolutely contraindicated in patients on regular oral or topical nitrates and in those requiring frequent doses of sublingual nitrates for symptomatic relief of angina pectoris.[14]

Sildenafil has been shown to improve erections significantly in patients with ischemic heart disease and in those with risk factors like hypertension and diabetes. It is also helpful in the management of erectile dysfunction due to nonvascular causes such as depression, spinal cord injury, or following radical prostatectomy (Figure 2). Due to the potentially disastrous interactions with nitrates and the additive effects with antihypertensive agents, reasonable concerns have been raised regarding the use of sildenafil in the cardiovascular patient. However, in 53 clinical trials with sildenafil that included over 6000 patients, no excess incidence of myocardial infarction (MI) or death was observed.[15] Similarly, in a prescription event-monitoring study of more than 5000 men conducted in the United Kingdom, there was no increased incidence of MI, ischemic heart disease, death or total mortality, compared with the overall UK population.[16]

Sexual activity in patients with CAD

Sexual activity can be associated with a transient increase of 50-60 bpm in heart rate and 50-60 mm Hg in systolic blood pressure. The risk of non-fatal MI transiently doubles following sexual activity, but the absolute risk is quite small. In individuals free of cardiac disease, weekly sexual activity would only increase the annual risk of MI from 1% to 1.01%. In subjects with a prior MI history, sexual activity transiently doubles the risk from 10 in a million per hour to 20 in a million per hour. Nevertheless, the absolute risk remains low since, in the clinically high-risk patient, weekly sexual activity increases the risk of MI from 10% to 10.2%.[17]

In order to assess whether a cardiac patient is fit to resume sexual activity, it is crucial to obtain a history of the activities that the patient is able to perform and correlate them with the workload required for sexual intercourse. The workload can be expressed in metabolic equivalents or METs. One MET is the amount of oxygen consumed at rest, which is 3.5 ml/kg/minute. Other activities can then be measured against this standard. For instance, walking at 2 mph requires 2-3 METS, gardening or digging requires 5-6 METS, swimming 9-10 METS, whereas sexual activity

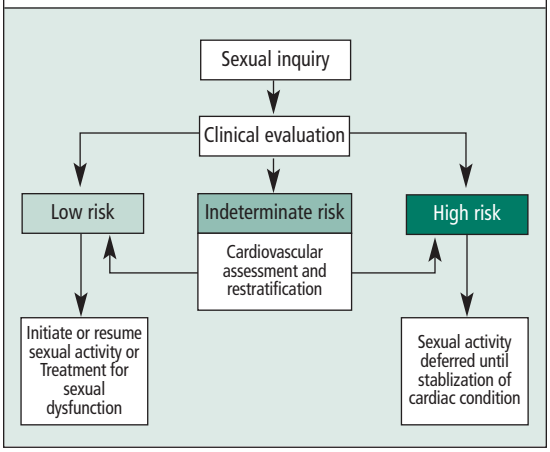
Table 1: Energy requirements of selected physical activities (in METs)

Walking 2 mph, level	2-3
Walking 3 mph, level	3-3.5
Sexual activity*	3-5
Painting, masonry	4-5
Golf, carrying clubs	4-5
Cycling 10 mph, level	5-6
Gardening, digging	5-6
Cycling 12 mph, level	7-8
Swimming – front crawl	9-10
Shoveling 16 lb/min	9-12

*(With usual partner)

Pashkow and Dafoe, Eds. Clinical Cardiac Rehabilitation, Appendix A. ©1999.

Figure 3: Algorithm for sexual activity and cardiac risk



with the usual partner requires only 3-5 METS. Sexual intercourse with an extramarital or much younger partner is associated with significantly greater energy requirements and a higher risk of MI (Table 1). If necessary, an exercise test can be obtained to determine objectively the patient's exercise tolerance and workload achieved in METS. A patient who is able to achieve 6 METS on a treadmill (for instance, following the Bruce protocol) without any symptoms, ECG changes, arrhythmias, or hemodynamic instability, can resume sexual activity safely, provided that there are no other absolute contraindications.

The management of erectile dysfunction in patients with cardiovascular disease

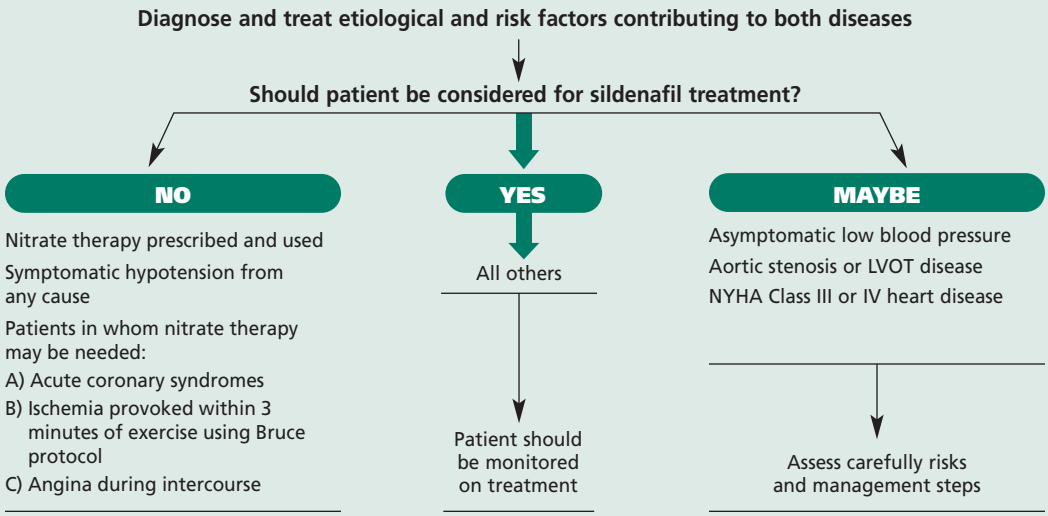
Establishing whether a patient is eligible to receive therapy with sildenafil requires a determination of the patient's risk. The Princeton Consensus Panel in the United States suggests stratifying the patients in low-risk, intermediate- or indeterminate-risk, or high-risk categories.[18]

- The low-risk category includes subjects with no significant cardiac risk associated with sexual activity (ie, asymptomatic individuals or those with <3 cardiac risk factors). Also in the low-risk group are patients with controlled hypertension, mild stable angina, prior successful coronary revascularization, uncomplicated prior MI, mild valvular disease, and NYHA class I heart failure patients. Patients in the low-risk category require no special cardiac testing or evaluation prior to resuming sexual activity or initiating therapy for erectile dysfunction. All the first-line treatment modalities, including sildenafil, can be considered in these patients.
- Individuals at intermediate- or indeterminate-risk include those with ≥3 cardiac risk factors, moderate stable angina, recent MI (>2, but <6 weeks), NYHA class II heart failure, or significant manifestations of noncoronary vascular disease such as peripheral arterial disease or stroke. These patients must be reclassified to the low- or high-risk categories based on cardiac testing, including a graded exercise test and an echocardiogram. In some cases, a cardiology consultation may be necessary.
- Patients in the high-risk category are those who have a cardiac condition sufficiently severe or unstable that sexual activity may constitute significant risk. This category includes patients with unstable or refractory angina, uncontrolled hypertension, NYHA class III or IV heart failure, recent MI (within 2 weeks), high-risk arrhythmias, hypertrophic obstructive or other cardiomyopathies, and moderate to severe valvular heart disease. These patients should have high priority for referral to a cardiovascular specialist and the initiation of sexual activity should be deferred until the cardiac condition is stabilized or managed appropriately and a specialist determines that it can be safely resumed (Figure 3).

Sildenafil in the cardiovascular patient: Position of the Heart and Stroke Foundation of Canada and the Canadian Cardiovascular Society

These two organizations have jointly stated that the majority of cardiovascular patients can be treated with sildenafil except those already taking any form of nitrates. Patients for whom nitrate therapy is essential must be considered for other forms of therapy for erectile dysfunction. Patients who are receiving multiple, concomitant, antihypertensive therapy must be assessed carefully to ensure that there is no symptomatic hypotension. Of great interest is the recommendation that etiological and risk factors contributing to both cardiovascular disease and erectile dysfunction be diagnosed and treated.[19] This may prove to be remarkable foresight by the authors of the recommendations. Although the hypothesis that treating endothelial dysfunction also improves erectile

Figure 4: Decision tree for treating patients with cardiovascular disease and ED with sildenafil[19]



function has yet to be studied in randomized controlled trials, the biological plausibility is strong. As discussed above, treating the risk factors or etiologies of endothelial dysfunction would lead to a reduction in oxidative stress and an increase in the bioavailability of NO leading, theoretically, to an increase in the efficacy of an agent like sildenafil. At the very least, treatment of risk factors for endothelial dysfunction with agents such as statins or ACE inhibitors, would reduce the risk of coronary events and possibly make the initiation of therapy for erectile dysfunction and the resumption of sexual activity safer.

In the Canadian recommendations, patients who should not be considered for sildenafil treatment are those for whom nitrate therapy is prescribed and used. As well, sildenafil should be avoided in patients for whom nitrate therapy may be needed, such as patients with acute coronary syndromes, ischemia provoked within 3 minutes of exercise on the Bruce protocol, and patients who develop angina during intercourse. A potential exception, and one that has to be considered with great caution, are patients taking nitrates only very sporadically. A rule-of-thumb in these patients is that sildenafil should not be used within 24 hours of any nitrate therapy and, conversely, nitrates should be avoided completely within a 24-hour period of any dose of sildenafil. Patients with symptomatic hypotension of any etiology are not eligible for treatment with sildenafil.

Patients, who may be considered for treatment with sildenafil after risk has been carefully assessed and the appropriate management instituted, include those with asymptomatic hypotension, aortic stenosis or left ventricular outflow obstruction, or heart failure patients. All other cardiovascular patients are considered eligible for treatment for erectile dysfunction with sildenafil, but it is important to emphasize that close monitoring of these patients must be continued or intensified after initiation of therapy (Figure 4).

Conclusion

In summary, NO bioavailability is at the center of both erectile and endothelial function and this could explain why erectile dysfunction and cardiovascular disease share so many common risk factors. Patients, whose presenting complaint is erectile dysfunction, may have previously unrecognized risk factors for atherosclerotic vascular disease such as hyperlipidemia, hypertension, or diabetes. Treatment of the underlying conditions common to both disorders should be instituted in the appropriate patients in order to improve endothelial function and NO bioavailability. Sexual activity usually implies a mild to moderate level of energy expenditure that could be safely achieved by many cardiac patients. It is important to stratify patients by risk and address correctable causes of structural heart disease or optimize medical therapy before the resumption of sexual activity. Most cardiac patients thus stratified and treated may be eligible for treatment of erectile dysfunction with a PDE inhibitor such as sildenafil or other first-line therapies. In patients who require therapy with nitrates or multiple antihypertensive agents, other therapeutic modalities have to considered

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Abstract of Interest

Oral sildenafil is an effective and specific pulmonary vasodilator in patients with pulmonary arterial hypertension

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Background: The prognosis of patients with severe pulmonary hypertension (PHT) is poor. To determine prognosis and guide chronic therapy, an acute trial of a selective pulmonary vasodilator, usually inhaled nitric oxide (INO), is performed during cardiac catheterization. We hypothesized that oral sildenafil, a phosphodiesterase V inhibitor, is a safe and effective alternative to INO.

Methods: We studied 12 consecutive patients (mean±SEM, 43±2 years, 8 female) referred during one year, for consideration of heart-lung transplantation or as a guide to medical therapy. All but one were functional class IV. Subjects had primary PHT (8), pulmonary arterial hypertension (2) or secondary PHT (2). Hemodynamics and serum cyclic guanosine monophosphate levels (c-GMP) were measured at baseline and at peak effects of INO (80 ppm), sildenafil (75 mg) or their combination.

Results: The decrease in pulmonary vascular resistance was similar with INO (-20±6%) and sildenafil (-25±3%) while sildenafil +INO was more effective than INO alone (-32±5%, P<0.03). Sildenafil and sildenafil + INO increased cardiac output (15±6 and 15±4%, respectively) whereas INO did not (0.3±3%, P<0.003). INO increased, whereas sildenafil tended to decrease pulmonary-capillary wedge pressure (+17±7 versus -9±8%, P<0.001). Systemic arterial pressure was similar amongst groups and did not decrease with treatment. cGMP levels increased similarly with INO and sildenafil and their combination elevated cGMP more (P<0.05).

Conclusion: A single oral dose of sildenafil is as effective and selective a pulmonary vasodilator as INO. Sildenafil may be superior to INO in that it causes greater increase in cardiac output and does not increase wedge pressure. Future studies are indicated to establish whether sildenafil could also be effective chronically.

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