
Contents

EDITORIAL	
<i>Graham Jackson</i>	3
BASIC ARTICLE	
Erectile dysfunction as an early indicator of cardiovascular and metabolic disease	
<i>Kevin L. Billups</i>	5
MAIN CLINICAL ARTICLE	
Managing sexual dysfunction in the cardiac patient	
<i>Adolph M. Hutter Jr.</i>	10
NEW THERAPEUTIC APPROACHES	
Safety and efficacy of the medical treatment of erectile dysfunction	
<i>Graham Jackson</i>	14
FOCUS ON VASTAREL MR	
Efficacy and safety of trimetazidine and phosphodiesterase type-5 inhibitors	
<i>Graham Jackson</i>	22
CASE REPORT	
Erectile dysfunction as a marker of silent ischemia	
<i>Michael Kirby</i>	25
REFRESHER CORNER	
The hemodynamics of sex	
<i>Ian Eardley</i>	29
FEATURED RESEARCH	
Abstracts and commentaries	32
GLOSSARY	
<i>Gary Lopaschuk</i>	36

Sex and the Heart

Graham Jackson

Cardiothoracic Centre, St. Thomas' Hospital, London, UK

Correspondence: Dr Graham Jackson, Consultant Cardiologist, Cardiothoracic Centre, St. Thomas' Hospital, London SE1 7EH, UK. E-mail: gjcardiol@talk21.com

Erectile dysfunction is common affecting over 50% of men aged 50–70 years. It increases with age so that men over 70 years of age have three times the incidence of men in their 40s. It is an important cause of relationships breaking down with the man losing self-esteem, feeling inadequate, and a failure. The commonest cause is organic though psychological consequences will result and both aspects of management need to be addressed. Vascular disease (endothelial dysfunction) is the common denominator in over 70% of cases which is why this issue of *Heart and Metabolism* focuses on the cardiovascular aspects of erectile dysfunction. Female sexual dysfunction is also an important management concern but it is not as clearly linked to cardiovascular problems and as it is a more complex subject needing specialised therapists we have not included it in this issue.

The recognition that male sexual ED (erectile dysfunction) can be a marker for cardiovascular ED (endothelial dysfunction) has led to the recognition that sexual ED can be an early indicator of cardiovascular disease in a man otherwise asymptomatic from the cardiac perspective. The importance of this observation, which applies to both chronic and acute cardiac presentations, has led to the belief that early aggressive risk factor reduction may delay or prevent a cardiovascular presentation. The articles by Kevin Billups and Michael Kirby cover this concept with erectile dysfunction assuming the status of "cardiovascular equivalent" in the same way we view diabetes.

The clinical articles take us from the haemodynamics of sex through cardiac risk to safe management. The phosphodiesterase type 5 (PDE5) inhibitors have transformed the management of erectile dysfunction but cannot be used in the presence of oral or sublingual nitrates due to an unpredictable profound fall in blood pressure. Here there is a role for trimetazidine as a non haemodynamic nitrate alternative (pages 22–24) - the presence of nitrates should not be a bar to PDE5 therapy without considering whether they are needed at all or whether they can be substituted.

For 4 years now I have run a male cardiovascular health clinic with Emma Waring who is a fully trained

cardiac nurse specialist with a diploma in sexual medicine. So far we have treated 342 cardiac patients with erectile dysfunction who have been followed up and we have an 85% success rate in restoring couples to sexual intercourse using PDE5 inhibitors in 95% of these. We have experienced no acute cardiac events in this carefully supervised outpatient clinic. However writing about the successes is not a match for the patient expressing his views in his own words. The following email says it all in two paragraphs – the first a typical light-hearted approach then the second vividly illustrating the pain and suffering. Sadly there is little cardiological interest in sexual ED but if we think of it as a means for early detection (another ED) of vascular disease cardiologists clearly need to be involved in both its evaluation and management – however the email alone should be convincing enough. ED is too important to be left to the urologists, we need a multidisciplinary approach which actively involves cardiologists.

"I was married in the Philippines on the 4th July 2005, something I would only have dreamed about until I came to your clinic, "Dare I say this"? My wife is 18 years younger than me, and very fit in all departments, "Boy oh Boy" did we have a really great honeymoon? We sure did. Please tell Dr. Jackson from me, "I was as good, or even better than "Way back when" I most certainly didn't let the side down –

Joking Apart – May I say a big THANK YOU, without the kind care, consideration, professionalism of your clinic towards making a 'man out of me again' I certainly would have never gained a priceless gift – someone to love and be loved, my new wife. No more "nuptial shame, embarrassment, "sickening self-loathing" for being this inadequate, incomplete, incompetent "half-man". Always One Big Guilty Secret. Too Scared to Woo a Lady. "No More"." Thank you both Again. Very Best Wishes.

Further Reading

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Erectile dysfunction as an early indicator of cardiovascular and metabolic disease

Kevin L. Billups

The EpiCenter for Sexual Health & Medicine, Edina and Department of Laboratory Medicine & Pathology, University of Minnesota School of Medicine, Minneapolis, Minnesota, USA

Correspondence: Dr Kevin L. Billups, 7455 France Avenue South, Suite 362, Edina, MN 55435, USA. Tel: +1 (612) 202 9082, fax: +1 (952) 226 3808, e-mail: klbillups@earthlink.net

Abstract

Erectile dysfunction is now commonly thought of as an early indicator of cardiovascular and metabolic disease. Current clinical research suggesting that the penile vascular bed is a sensitive indicator of systemic endothelial cell and smooth muscle dysfunction is based on sound principles of anatomy and physiology. Erectile dysfunction is probably an early marker for the development of significant cardiovascular risk factors, in addition to being one of the first symptoms of clinical vascular disease. The diagnosis of erectile dysfunction and the subsequent evaluation of underlying cardiovascular risk factors could become a powerful clinical tool to help with timely detection of atherosclerotic disease.

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Keywords: Erectile dysfunction, atherosclerosis, cardiovascular disease, endothelium, smooth muscle, oxidative stress

Introduction

Over the past decade, the cascade of events that occur between the development of cardiovascular risk factors and the onset of symptomatic clinical cardiovascular disease has been intensively investigated and well characterized on a cellular and molecular level. Cardiovascular risk factors are known to lead to the development of asymptomatic subclinical cardiovascular disease (CVD), followed by symptomatic clinical CVD and organ damage as an endstage event (*Figure 1*).

There are a number of traditional (age \geq 45 years, high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, hypertension, diabetes, smoking), underlying (obesity, sedentary lifestyle, atherogenic diet), and emerging (insulin resistance/metabolic syndrome) cardiovascular risk factors that initiate the process of atherosclerosis and CVD [1]. These factors are known to cause

oxidative stress and inflammatory changes that are responsible for endothelial cell and smooth muscle dysfunction, which are hallmark events for early atherosclerosis and subclinical CVD. The endothelial and smooth muscle dysfunction eventually progress to the occlusive vascular disease seen with symptomatic clinical CVD and characterized by vascular events such as angina, myocardial infarction, stroke, claudication, or sudden death (*Figure 1*).

Erectile dysfunction is defined as the persistent inability to maintain or achieve a penile erection sufficient for satisfactory sexual performance. There are a number of traditional, underlying, and emerging cardiovascular risk factors that are shared between erectile dysfunction and cardiovascular disease [2–4]. Evidence is emerging that endothelial dysfunction is an important common denominator between these two conditions [5,6]. In fact, a burgeoning literature is now available that suggests that erectile dysfunction may indeed be an early marker for atherosclerosis,

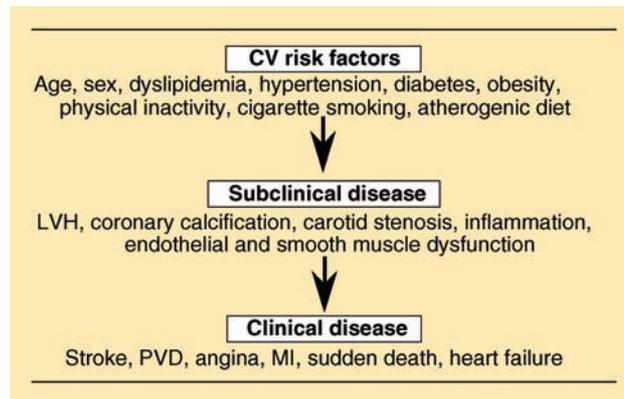


Figure 1. The cascade of atherosclerosis and cardiovascular disease. Atherosclerosis is an insidious disease process that starts with the development of cardiovascular risk factors and progresses to the onset of symptomatic clinical vascular disease. CV, cardiovascular; LVH, left ventricular hypertrophy; MI, myocardial infarction; PVD, peripheral vascular disease. (Modified with permission from Kevin L. Billups, MD.)

cardiovascular risk, and subclinical CVD [7,8]. The symptom of erectile dysfunction is present at every stage of the CVD cascade, from development of risk factors to the onset of clinical symptoms (Figure 2).

This article will examine the role of erectile dysfunction in the overall cascade of atherosclerosis and the development of cardiovascular disease. Unique aspects of penile anatomy and erectile physiology that make the penis an ideal early warning system will be discussed. Selected clinical research studies supporting the concept of erectile dysfunction as an early marker for atherosclerosis and cardiovascular disease will also be reviewed.

Unique aspects of penile anatomy and erectile physiology

It is now widely accepted that organic erectile dysfunction in a substantial majority of men is attributable to underlying vascular causes, especially

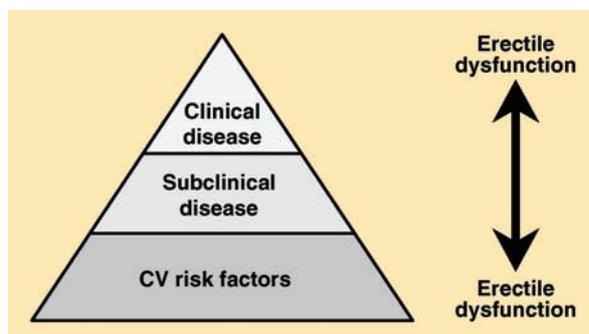


Figure 2. The link between erectile dysfunction and the development of cardiovascular disease. The symptom of erectile difficulty is present at every stage along the pathway from development of cardiovascular risk factors to the occurrence of an adverse vascular event. CV, cardiovascular. (Modified with permission from Kevin L. Billups, MD.)

atherosclerosis [9–14]. Many men will note the onset of erectile dysfunction – specifically, difficulty being able to maintain a firm erection – before they are diagnosed with cardiovascular disease. The anatomic structure of the penis and the physiology of achieving and maintaining an erection provide clues as to why the penile vascular bed has some unique properties that facilitate early detection of systemic vascular disease.

Penile erection is the result of a complex and coordinated series of events involving vascular response, neuronal pathways, and psychosomatic stimulation. The nitric oxide pathway is activated upon sexual stimulation, and nitric oxide is released into penile smooth muscle from both the vascular endothelium of the penis and the autonomic, cavernous nerve terminals. Within the penile smooth muscle, nitric oxide activates guanylyl cyclase, which increases the concentration of the second messenger, cyclic guanosine monophosphate (cGMP). The increased concentrations of cGMP result in relaxation of arterial smooth muscle in the penis and increased inflow of blood. In addition, cGMP relaxes trabecular smooth muscle, which facilitates engorgement of the sinusoidal spaces and compression of the subtunical venules (Figure 3). The net result is complete occlusion of penile venous outflow and trapping of blood within the corpus cavernosa [9]. A functioning nitric oxide pathway is therefore a primary determinant of smooth muscle tone, arterial inflow, and restricted venous outflow in the physiology of erection. Disruption of any of these factors can lead to erectile dysfunction. Endothelial dysfunction, which is associated with impaired release and activity of nitric oxide, underlies the pathophysiology of vascular erectile dysfunction [5,6,8].

The penis as a vascular organ may be very sensitive to changes in oxidative stress, inflammation, and

Basic article

Erectile dysfunction as an early indicator of disease

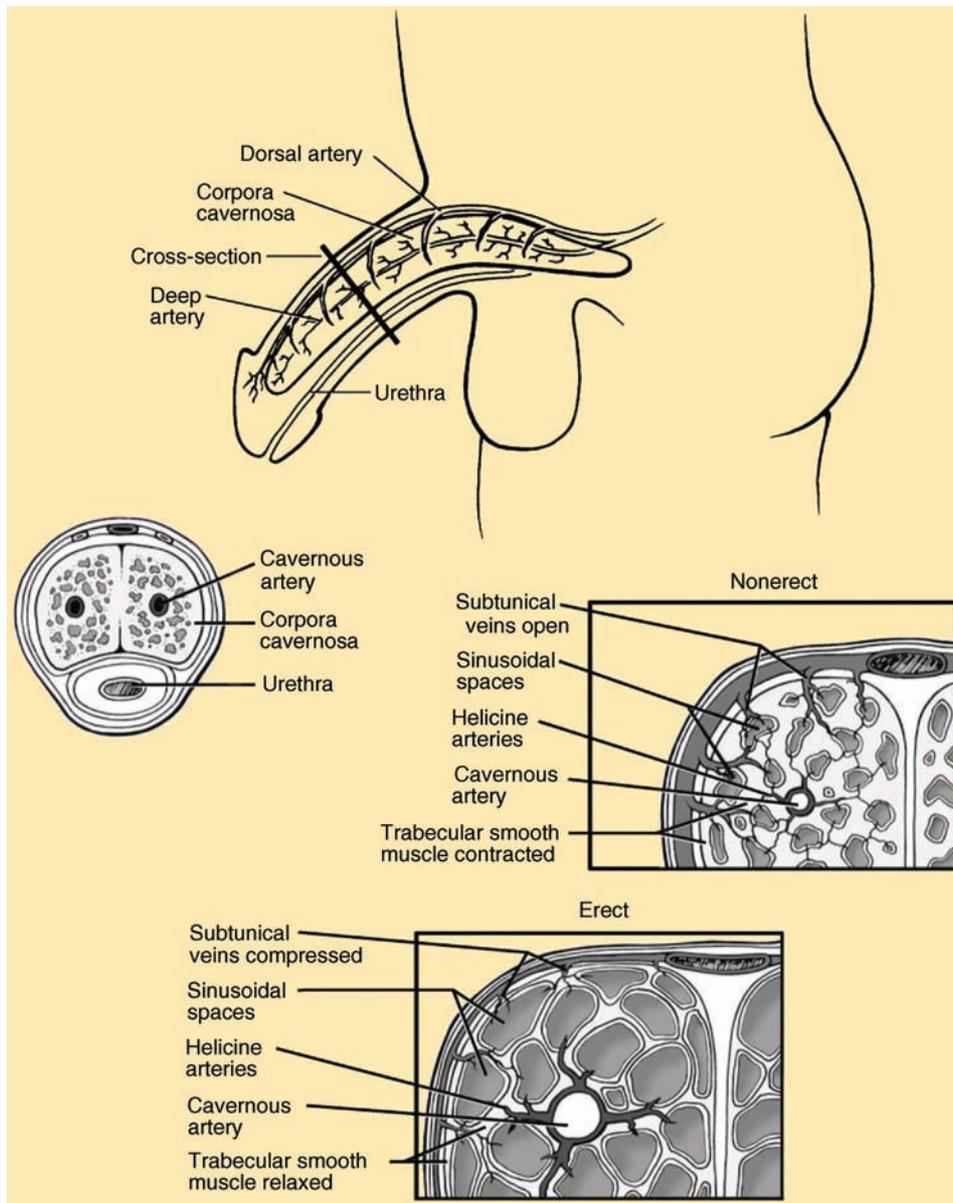


Figure 3. Anatomy of penile erection and detumescence. (Modified with permission from Kevin L. Billups, MD.)

systemic nitric oxide concentrations for several reasons. The small diameter of the cavernosal arteries and the high content of endothelium and smooth muscle on a per gram of tissue basis (compared with other organs) may make the penile vascular bed a sensitive indicator of systemic vascular disease. Therefore, erectile dysfunction can be the result of any number of structural or functional abnormalities in the penile vascular bed. For instance, it may result from occlusion of the cavernosal arteries by atherosclerosis (structural vascular erectile dysfunction), impairment of endothelium-dependent or -independent smooth muscle relaxation (functional vascular

erectile dysfunction), or a combination of these two factors. Erectile dysfunction caused by functional vascular factors occurs early and is probably linked to oxidative stress, inflammatory changes, and decreased availability of nitric oxide. These functional factors initially result in a poor relaxation of penile endothelium and smooth muscle that presents clinically as erectile dysfunction – in particular, difficulty maintaining a firm erection. This early clinical symptom of poor maintenance caused by functional endothelial cell dysfunction probably occurs before the development of structural, occlusive penile arterial disease, and may be one of the

earliest signs of systemic cardiovascular disease [6,7,15,16].

Clinical research studies supporting the idea of erectile dysfunction as an early marker of cardiovascular disease

Recently conducted studies that measured early markers of cardiovascular disease and endothelial dysfunction demonstrated that damage to the penile vascular bed occurs before clinically apparent CVD [17,18]. In one study, 30 men with Doppler-proven erectile dysfunction and no clinical evidence of cardiovascular disease (mean age 46 years) were compared with 27 healthy, age-matched controls across a number of measures for peripheral vascular structure and function (rapid computed axial tomography scan imaging for coronary calcification, aortic pulse wave velocity, and carotid intima media thickness [IMT]) and were not found to differ. However, they differed with respect to measures that assessed systemic endothelial function using flow-mediated brachial artery vasodilatation studies: when compared with controls, the men with erectile dysfunction exhibited significantly lower brachial artery flow-mediated, endothelium-dependent vasodilatation ($P \leq 0.05$) and endothelium-independent vasodilatation (blunted response to 0.4 mg sublingual nitroglycerin; $P = 0.02$) [17].

In another study, biochemical markers of endothelial cell activation were used to compare 45 men with erectile dysfunction but no clinical cardiovascular disease with 25 age-matched normal individuals. Biochemical and structural markers compared between the erectile dysfunction and normal men included carotid IMT, soluble P-selectin, intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1, and endothelin-1. Results revealed no difference in carotid IMT scores between the two groups, but soluble P-selectin, ICAM-1, VCAM-1, and endothelin-1 concentrations were significantly greater in the men with erectile dysfunction and no cardiovascular disease [18].

Results from these two clinical studies support the idea that erectile dysfunction precedes overt structural occlusion of larger blood vessels and is often an early manifestation of atherosclerosis and CVD. Erectile dysfunction probably begins as a nonobstructive, functional process caused by endothelial and smooth muscle dysfunction. As atherosclerosis and CVD progress, erectile dysfunction becomes more of a structural disease caused by occlusion of the penile cavernosal and helicine arteries.

Conclusions

Results from clinical research studies are suggesting that erectile dysfunction must now be considered an early marker of subclinical or undiagnosed cardiovascular and metabolic disease. The symptom of erectile difficulty occurs at all stages of the CVD cascade (Figure 2). Erectile dysfunction should be considered, not only as an early symptom of cardiovascular disease, but also as an emerging risk factor that significantly influences overall global cardiovascular risk and aggressive risk factor management strategies in men aged 25 years and older [19]. Such a fundamental shift in thinking could profoundly affect preventive vascular medicine.

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Managing sexual dysfunction in the cardiac patient

Adolph M. Hutter Jr

Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

Correspondence: Dr Adolph M. Hutter Jr, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA.

Abstract

The cardiac patient is more likely than the general population to have erectile dysfunction, because the risk factors are common to both diseases. Thus the physician should ask about erectile dysfunction as part of the overall assessment of the patient. The phosphodiesterase type 5 inhibitors are effective in treating erectile dysfunction, and can be safely used in the vast majority of patients with cardiovascular disease, including patients with stable coronary artery disease, Class II–III congestive heart failure, and hypertension. A good history and physical examination can identify most patients who are at low risk for sexual intercourse and the use of these drugs. In some cases, a stress test can provide useful guidance.

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Keywords: Erectile dysfunction, cardiovascular disease, PDE-5 inhibitors

Exploring the issue with the patient

Patients with cardiovascular disease, particularly coronary artery disease, are more likely to have erectile dysfunction, and vice versa. Indeed, the risk factors (hypertension, diabetes, hyperlipidemia, smoking) for one problem are also the risk factors for the other [1–3]. Endothelial dysfunction is seen in both coronary artery disease (CAD) and erectile dysfunction [4]. Consequently, when a physician sees a patient with erectile dysfunction, exploration for the presence of these risk factors, and the possible presence of CAD, should be undertaken. Similarly, the physician seeing the patient with CAD, congestive heart failure, diabetes, hypertension, or hyperlipidemia should inquire about the adequacy of sexual function. Erectile dysfunction is a common problem, but one that is infrequently raised by either the patient or the physician. Since we now have so many advances that have made CAD a chronic disease that a patient can live with rather than die of, quality of life becomes important. Sexual activity is an important aspect of a good quality of life for most patients.

The availability of oral phosphodiesterase type-5 (PDE-5) inhibitors (sildenafil, tadalafil, and vardenafil) has opened a wide window of opportunity to help men with erectile dysfunction, including those with cardiovascular disease. It is very helpful to involve the partner in these discussions. This not only gives a more accurate picture of any problems in the area of sexual relations, but also provides reassurance to the partner as the evaluation process proceeds.

Safety of PDE-5 inhibitors

The PDE-5 inhibitors have now been used in thousands of patients. A number of drug–placebo and open-label studies have shown the overall safety of sildenafil and tadalafil in patients with cardiovascular disease. They have been shown not to increase the incidence of myocardial infarction or cardiovascular death compared with placebo treatment [5–10].

Coronary artery disease

Sildenafil has been shown to have no deleterious effects on exercise in patients with stable CAD.

Arruda-Olson et al [11] performed a randomized placebo-controlled trial with sildenafil in patients with CAD and positive stress imaging tests. Compared with placebo, sildenafil decreased the resting systolic and diastolic blood pressures slightly, with no difference in the resting heart rate. There was no difference in exercise capacity, blood pressure, or heart rate. There was also no difference in symptoms with exercise, positive electrocardiogram changes, exercise-induced wall motion abnormalities, or rest or exercise ejection fraction. Fox et al [12] showed that sildenafil did not adversely affect the exercise performance of patients with stable angina. Compared with placebo, there was no difference in time to 1 mm ST-segment depression or total exercise time. Sildenafil actually prolonged the time to angina. Thadani et al [13] studied men with reproducible angina on exercise and showed that vardenafil 10 mg did not change the total exercise time or time to angina compared with placebo and actually increased the time to ischemic ST-segment changes. In a small number of patients with stable CAD, Patterson et al [14] showed that tadalafil 10 mg caused no difference in total exercise time or time to ischemia compared with placebo. Thus all three agents have been shown to have no deleterious effects on the exercise performance of men with stable CAD and angina, and even perhaps to have some benefit.

Congestive heart failure

The American College of Cardiology and American Heart Association (ACC/AHA) published an Expert Consensus Report on the safety of sildenafil in patients with cardiovascular disease in 1999. Concerns were raised about patients with congestive heart failure and patients receiving several antihypertensive agents [15].

Sildenafil has subsequently been shown to be safe with regard to the exercise performance of patients with congestive heart failure. Bocchi et al [16] studied 23 patients with this condition. Compared with placebo, sildenafil reduced the resting heart rate and systolic and diastolic blood pressures, but actually increased the exercise time, increased oxygen consumption, and attenuated the increment in heart rate with exercise. Lepore et al [17] studied sildenafil in patients with Class III heart failure and found that the drug increased work efficiency, peak oxygen consumption, exercise cardiac output, and stroke volume, while decreasing rest and exercise pulmonary vascular resistance and post capillary wedge pressure without a significant change in arterial blood pressure.

Hypertension

The PDE-5 inhibitors are mild vasodilators and may cause a small decrease in systolic and diastolic blood

pressure, which is generally of little consequence. The ACC/AHA expert consensus report expressed caution about using these drugs in patients with hypotension and hypovolemia [15]. It was also stressed that all vasodilators should be used with caution in patients with aortic stenosis and left ventricular outflow obstruction. At the time of that report, concerns were raised about using these drugs in patients receiving several antihypertensive agents. However, a large number of studies have since shown that the PDE-5 inhibitors have little effect on the systolic blood pressure when used in the presence of a single or several antihypertensive agents [18].

If there is concern that the blood pressure may be too low to allow the safe use of a PDE-5, a simple trial of a low dose and a check of the blood pressure about 30 min later can allay that concern. If there is no decrease in blood pressure, the patient can then use that dose for the purpose of sexual intercourse, without concern to him or his partner. If he requires a higher dose for efficacy, a repeat check of the blood pressure after the higher dose can be performed to make sure that the higher dose does not induce hypotension.

Nitrates

Combining PDE-5 inhibitors with nitrates can result in a profound decrease in blood pressure that is unpredictable in the individual concerned. Although the average decrease in blood pressure may be modest, the decrease in an individual patient may be severe. This phenomenon can be evaluated by determining the number of “outliers” – that is, the number of individuals who have a minimum standing systolic blood pressure of less than 85 mm Hg – after the use of nitrates combined with the PDE-5 inhibitor, in comparison with placebo. Merely averaging the decrease in blood pressure will not detect these individual marked responses. Thus the use of PDE-5 inhibitors is absolutely contraindicated in patients receiving nitrates. Nitrates should be avoided for 24 h after the use of the shorter-acting sildenafil and vardenafil [15], and 48 h after the use of a longer-acting tadalafil [19].

Screening the cardiovascular patient before sexual activity

The Princeton Consensus Conference developed a risk stratification algorithm to determine the amount of cardiovascular risk associated with sexual activity in men with different degrees of cardiovascular disease [20]. These recommendations have recently been updated [21] (*Figure 1*).

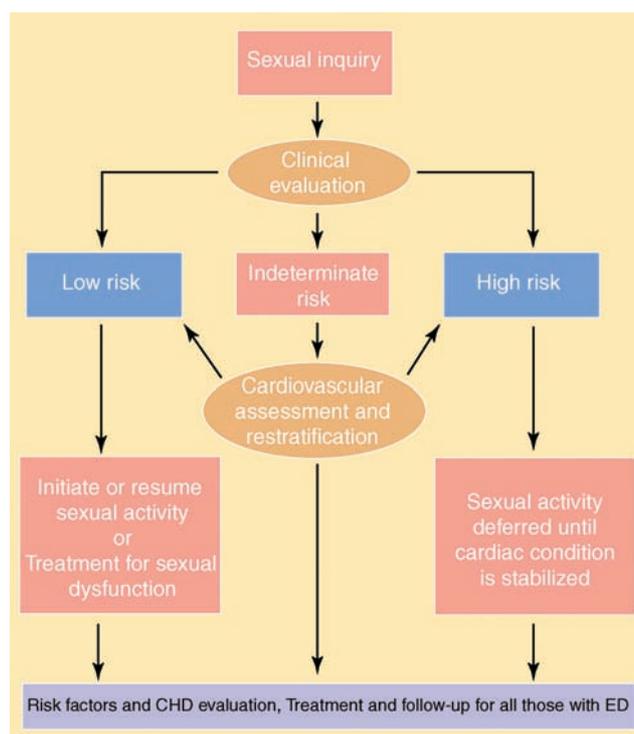


Figure 1. Princeton Consensus Panel recommended procedure for stratification of cardiovascular risk associated with sexual activity, treatment, and follow-up, in men with cardiovascular disease. CHD, coronary heart disease; ED, erectile dysfunction.

Risk stratification involves a careful history and physical examination, and identification of the various risk factors for cardiovascular disease (age, male sex, hypertension, diabetes, smoking, hyperlipidemia, sedentary lifestyle, family history). A screening exercise test can be very helpful. A patient who is able to exercise at a moderate level of activity without problems is generally at low risk: the work load of sexual activity is actually rather modest, and similar to walking a mile in 20 min or climbing two flights of stairs in 10 s [22]. This would be similar to achieving stage one of a Bruce protocol or 4–6 metabolic equivalent of task units [3]. In general, an exercise electrocardiogram is 65% sensitive for identifying CAD causing ischemia, whereas an exercise perfusion study with either sestamibi or thallium or an exercise wall-motion study with echocardiography is 85–90% sensitive [23,24]. Even if a physician is clinically confident that the patient is at low risk for sexual activity, the documentation of good exercise capacity without ischemia may provide marked psychological benefit in terms of reassurance, not only for the patient, but also for his partner.

Management of the patient with acute coronary syndrome after using a PDE-5 inhibitor

Patients who present with chest pain consistent with acute coronary syndrome or myocardial infarction

and who have recently used a PDE-5 inhibitor should not receive nitrate therapy, which is absolutely contraindicated, but can receive all other appropriate therapy, including aspirin, heparin, thrombolytic agents, glycoprotein IIb/IIIa agents, β -blockers, and, if indicated, calcium channel blockers. It is important for the patient to tell the emergency personnel and for the emergency personnel to ask the patient about the possible use of a PDE-5 inhibitor, so that nitrate therapy is not given inadvertently.

Management of the hypotensive patient who received a combination of PDE-5 inhibitor and nitrates

The patient who presents with hypotension after a combination of PDE-5 inhibitor and nitrate therapy should be treated with volume resuscitation and, if necessary, an intravenous α -blocker such as phenylephrine, which will support the blood pressure by causing peripheral vasoconstriction without increasing cardiac work (contractility). If necessary, an intra-aortic counterpulsation balloon can be used to stabilize the systemic circulation [15].

Summary

The vast majority of patients with cardiovascular disease can safely use the PDE-5 inhibitors. We, as

physicians, should inquire about erectile dysfunction in our patients with cardiovascular disease and, if it is present, explain that we have ways of helping them in this regard. A clinical evaluation, often including an exercise test, can quickly identify those patients who may safely resume sexual activity and use PDE-5 inhibitors. ■

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Safety and efficacy of the medical treatment of erectile dysfunction

Graham Jackson

Cardiothoracic Centre, St Thomas' Hospital, London, UK

Correspondence: Graham Jackson, Consultant Cardiologist, Cardiothoracic Centre, St Thomas' Hospital, London SE1 7EH, UK. E-mail: gjcardiol@talk21.com

Abstract

Erectile dysfunction and vascular disease commonly coexist. They share the same risk factors, and endothelial dysfunction is the common denominator. Erectile dysfunction may develop in an otherwise asymptomatic male and be an important predictor of subsequent acute or chronic cardiac events. It may therefore offer an opportunity for risk assessment and therapeutic intervention to reduce the chance of a subsequent cardiac presentation. Cardiac patients with erectile dysfunction need a careful assessment to judge the safety of sexual activity and their suitability for treatment of their erectile dysfunction. When correctly assessed and counseled, patients can safely enjoy sexual activity. Treatment of erectile dysfunction with phosphodiesterase type-5 inhibitors is safe and effective, provided the patient and their partner are advised as to their use and potential drug interactions, especially with nitrates.

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Keywords: Erectile dysfunction, sexual activity, cardiac patients

Introduction

When advising cardiac patients concerning sexual activity, it is important to individualize the advice. Although we have a statistical framework that supports our recommendations, each person being advised will have, in addition to a general cardiac condition (eg, post myocardial infarction), varying degrees of restriction of effort – determined by the size of the infarction, for example. In addition, each person will have personal concerns regarding safety of sexual activity, treatment of erectile dysfunction, and their confidence in returning to normal activities, including sex. As we advise on sexual function and activity, we need to remember that these problems may have preceded the cardiac event, with important implications for personal relationships as a consequence.

Cardiovascular response to sexual activity

Several studies performed using ambulatory electrocardiography and blood pressure monitoring have

compared the heart rate, electrocardiographic, and blood pressure responses to sexual activity with those to other normal daily activities [1]. The energy requirement during sexual intercourse is not excessive for couples in a long-standing relationship. The average peak heart rate is 110–130 beats/min and the peak systolic blood pressure 150–180 mm Hg, resulting in a rate–pressure product of 16 000–22 000. Expressed as a multiple of the metabolic equivalent of task units (METs) of energy expenditure in the resting state (MET = 1), sexual intercourse is associated with a work load of 2–3 MET before orgasm and 3–4 MET during orgasm. Younger couples, who are not usually the individuals we advise, may be more vigorous in their activity, expending 5–6 MET. The average duration of sexual intercourse is 5–15 min. Therefore, sexual intercourse is not an extreme or sustained cardiovascular stress for patients in a long-standing relationship who are comfortable with each other. Casual sexual intercourse, which must be separated from extramarital sexual intercourse with a long-standing 'other partner', may involve a greater cardiac workload because of lack

New therapeutic approaches

Safety and efficacy of treatment of erectile dysfunction

Table I. Metabolic equivalent of task units (METs) as a guide to relating daily activity to sexual activity.

Daily activity	METs
Sexual intercourse with established partner	
Lower range (normal)	2–3
Lower range orgasm	3–4
Upper range (vigorous activity)	5–6
Lifting and carrying objects (9–20 kg)	4–5
Walking 1.6 km (1 mile) on the level in 20 min	3–4
Golf	4–5
Gardening (digging)	3–5
Do-It-Yourself, wallpapering, etc.	4–5
Light housework; eg, ironing, polishing	2–4
Heavy housework; eg, making beds, scrubbing floors, cleaning windows	3–6

of familiarity and age mismatch (usually older men with younger women), with different activities and expectations [2].

By using our knowledge of METs in the clinical setting, we can advise on sexual safety by comparing sexual intercourse with other activities. Some daily activities and their METs are shown in *Table I*.

Exercise testing

Using METs, sexual intercourse is equivalent to 3–4 min of the standard Bruce treadmill protocol. Where doubts exist as to the safety of sexual intercourse, an exercise test can help guide decision making. If a person can manage at least 4 min on the treadmill without significant symptoms, electrocardiogram (ECG) evidence of ischemia, a decrease in systolic blood pressure, or dangerous arrhythmias, it will be safe to advise on sexual activity [2,3]. Using ambulatory ECGs and bicycle exercise tests, Drory et al [4,5] studied 88 men with coronary artery disease (CAD) who were not receiving medication. On ambulatory ECGs, one-third of the men had ischemia during sexual intercourse and all had ischemia on the bicycle exercise ECG. All those who did not exhibit ischemia on the exercise test ($n = 34$) also had no ECG changes during sexual intercourse. All ischemic episodes during sexual intercourse were associated with an increasing heart rate, identifying a potentially important therapeutic role for drugs that decrease the heart rate (β -adrenoreceptor antagonists, verapamil, diltiazem).

If a patient is unable to perform an exercise test because of mobility problems, a pharmacological stress test should be utilized (e.g. dobutamine stress echocardiography).

A man who cannot achieve 3–4 MET should be further evaluated by angiography if appropriate [2].

Advice on METs in the clinical setting and relating this advice to sexual intercourse should also include

advice on the avoidance of stress, a heavy meal, or excess alcohol consumption before sexual intercourse.

Positions

As long as the couple are not stressed by the sexual position they use, there is no evidence of increased cardiac stress to a man or woman. Man on top, woman on top, side to side, oral sex and masturbation are cardiologically equivalent. In homosexual relationships, other than casual, anal intercourse is not associated with increased cardiac stress, provided proper lubrication is used and amyl nitrate ('poppers') is not used in conjunction with a phosphodiesterase type-5 (PDE-5) inhibitor.

Cardiac risk

There is only a small risk of myocardial infarction associated with sexual activity. The relative risk of a myocardial infarct during the 2 h after sexual intercourse is shown in *Table II* [6]. The baseline absolute risk of a myocardial infarction during normal daily life is low – 1 chance in a million per hour for a healthy adult, and 10 chances in a million per hour for a patient with documented cardiac disease. Therefore, during the 2 h after sexual intercourse, the risk increases to 2.5 in a million for a healthy adult and 25 in a million for a patient with documented cardiac disease; importantly, there is no increased risk in those who are physically active.

A similar study from Sweden has reported identical findings [7]. If we take a baseline annual rate of 1% for a 50-year-old man, as a result of weekly sexual activity, the risk of a myocardial infarction increases to 1.01% in those without a history of a previous myocardial infarction and to 1.1% in those with a previous history.

Coital sudden death is very rare. In three large studies, death related to sexual activity was 0.6% in Japan, 0.18% in Frankfurt, and 1.7% in Berlin. Extramarital sex was responsible for 75%, 75%, and 77% respectively, and the victims were men in 82%, 94%, and 93% of cases, respectively [1]. The partnership of

Table II. Relative risk of myocardial infarction during the 2 h after sexual activity: physically fit equals sexually fit.

Patient type	Relative risk (95% CI)
All patients	2.5 (1.7–3.7)
Men	2.7 (1.8–4.0)
Women	1.3 (0.3–5.2)
Previous myocardial infarction	2.9 (1.3–6.5)
Sedentary life	3.0 (2.0–4.5)
Physically active	1.2 (0.4–3.7)

CI, confidence interval.

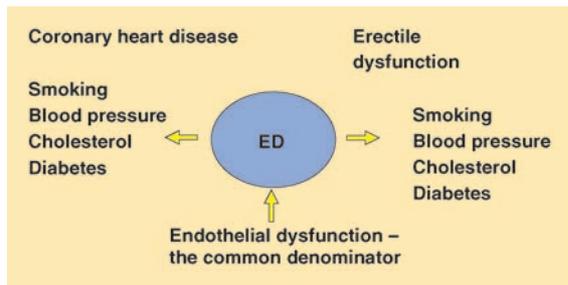


Figure 1. Risk factors for erectile dysfunction and coronary heart disease. ED, erectile dysfunction.

an older man with a younger woman was the most common setting.

Vasculogenic erectile dysfunction

Vascular diseases are the most common cause of erectile dysfunction, with endothelial dysfunction now recognized as the common denominator (Figure 1) [8]. Erectile dysfunction and CAD share the same risk factors, which explains the endothelial link (Table III) [9]. However, before attributing erectile dysfunction to a purely vascular cause, it is important to evaluate the patient thoroughly, as other factors may be contributing to the problem or, occasionally, may be the cause. As men age, there may be comorbid conditions that need to be addressed (endocrine, cellular, neural, or iatrogenic such as drug treatment), and organic erectile dysfunction will have psychological consequences for which they require counseling and support.

A large number of drugs, whether prescribed or recreational, can affect sexual function [2]. Their negative impact may be on erections, ejaculation, or sex drive. These drugs include:

- Cardiovascular drugs: thiazide diuretics, β -adrenoceptor antagonists, calcium channel antagonists, centrally acting agents (eg, methyl-dopa, clonidine, reserpine, ganglion blockers), digoxin, lipid-decreasing agents, angiotensin-converting enzyme inhibitors, and recreational drugs such as alcohol (ethanol), marijuana, amphetamines, cocaine, anabolic steroids, and heroin (diamorphine).
- Psychotropic drugs: major tranquilizers, anxiolytics and hypnotics, tricyclic antidepressants, selective serotonin reuptake inhibitors.
- Endocrine drugs: antiandrogens, estrogens, gonadotropin-releasing hormone analogs, testosterone.
- Others: cimetidine, ranitidine, metoclopramide, carbamazepine.

There is little evidence that changing cardiovascular drug therapy will restore erectile function, suggesting it is the underlying disease process that is more important. However, if there is a strong temporal relationship between the commencement of treatment and the onset of erectile dysfunction (2–4 weeks), it is logical to change the treatment if it is safe to do so. Antihypertensive agents, especially thiazide diuretics, are the most frequently incriminated, and a switch to angiotensin II receptor antagonists or α -adrenoceptor antagonists should be considered [10]. When drugs are prognostically important, such as β -adrenoceptor antagonists used after myocardial infarction, the decision to discontinue treatment should be approached with caution, and undertaken only after overall risks have been considered [3].

Erectile dysfunction and cardiovascular disease

The Massachusetts Male Aging Study [11] was a random-sample, cross-sectional, observational study in 1709 healthy men aged 40–70 years, undertaken to assess the impact of aging on a wide range of health-related issues. Fifty-two percent of respondents reported some degree of erectile dysfunction (17% mild, 25% moderate, 10% complete), and the prevalence increased with age. Cardiovascular disease was significantly associated with erectile dysfunction. The incidence was doubled in patients with hypertension and tripled in diabetic patients; in those with established coronary disease, it was quadrupled. Cigarette smoking increased the prevalence twofold for all these conditions, and a positive relationship was found between reduced high-density lipoprotein cholesterol concentrations and erectile dysfunction.

The association between hyperlipidemia and erectile dysfunction has been studied in apparently

Table III. Shared risk factors for coronary artery disease and erectile dysfunction (data from [9]).

Coronary artery disease	Erectile dysfunction
Age	Age
Dyslipidemia	Dyslipidemia
Hypertension	Hypertension
Diabetes	Diabetes
Smoking	Smoking
Sedentary lifestyle	Sedentary lifestyle
Obesity	Obesity
Depression	Depression
Male sex	Coronary artery disease, peripheral vascular disease

healthy men who complained of erectile dysfunction [12]. More than 60% had hyperlipidemia and 90% of these had evidence of penile arterial disease on Doppler ultrasound. Diabetes is commonly associated with erectile dysfunction, with a prevalence of 50% (range 27–70% depending on age and disease severity). The onset of erectile dysfunction usually occurs within the first 10 years of the diagnosis of diabetes [13].

Men older than 50 years who have established CAD have an incidence of erectile dysfunction of 40%; in those who have suffered myocardial infarction or vascular surgery, the incidence ranges from 39% to 64%, depending on diagnostic criteria [14].

Erectile dysfunction as a marker of vascular disease

As erectile dysfunction and vascular disease share the same risk factors, the possibility arises that erectile dysfunction in otherwise asymptomatic men may be a marker of silent vascular disease, especially CAD [15]. This has now been established to be the case and represents an important new means of identifying those at risk of vascular disease.

Pritzker [16] studied 50 men aged 40–60 years who were asymptomatic other than for erectile dysfunction, and had cardiovascular risk factors (several such factors were present in 80% of the group). Exercise ECG was abnormal in 28 of the men and subsequent coronary angiography in 20 men identified severe CAD in six, moderate two-vessel disease in seven, and significant single-vessel CAD in a further seven. In a study of 132 men attending for day-case angiography, 65% had experienced erectile dysfunction before their CAD had been diagnosed [17]. Erectile dysfunction also correlates with the severity of CAD, patients with single-vessel disease having less difficulty in obtaining an erection [18].

The smaller penile arteries (diameter 1–2 mm) suffer obstruction from plaque burden earlier than do the larger coronary (3–4 mm), carotid (5–7 mm), or iliofemoral (6–8 mm) arteries; hence erectile dysfunction may be symptomatic before the occurrence of a coronary event [19]. Addressing cardiovascular risk early after the presentation of erectile dysfunction, and aggressive intervention to reduce risk, may have long-term symptomatic and prognostic cardiac benefits [20]. Most acute coronary syndromes follow from the rupture of asymptomatic lipid-rich plaques, and erectile dysfunction may therefore be a marker for reducing the risk of this happening [21].

Billups and colleagues [22] have developed a risk assessment and management algorithm for primary care patients with erectile dysfunction, with the aim of

facilitating early diagnosis, intervention, and prevention of cardiovascular disease.

Any asymptomatic man who presents with erectile dysfunction that does not have an obvious cause (eg, trauma) should be screened for vascular disease and have blood glucose, lipids, and blood pressure measured. Ideally, all patients at risk should undergo an elective exercise ECG to facilitate risk stratification [23].

Treating erectile dysfunction in patients with cardiovascular disease

Recognizing the need for advice on management of erectile dysfunction, two consensus panels (in the UK and the USA) have produced similar guidelines dividing cardiovascular risk into three practical categories, with recommendations for management [2,3]. The Princeton consensus guidelines have recently been updated (*Table IV*) [3]. It is recommended that all men with erectile dysfunction should undergo a full medical assessment (*Figure 2*). Baseline physical activity needs to be established, and cardiovascular risk graded as low, intermediate, or high. Most patients with low or intermediate cardiac risk can have their erectile dysfunction managed in the outpatient or primary care setting.

There is no evidence that treating erectile dysfunction in patients with cardiovascular disease increases cardiac risk; however, this is with the provisos that the patient is correctly assessed and that the couple or individual (self-stimulation may be the only form of sexual activity) is appropriately counseled. Oral drug treatment is the most widely used, because of its acceptability and effectiveness, but all treatments have a place in management. The philosophy is to be always positive during what, for many men and their partners, is an uncertain time.

Phosphodiesterase type-5 inhibitors

To say that sildenafil has transformed the management of erectile dysfunction would be a substantial understatement. Its mechanism of action by blocking the degradation of cyclic guanosine 3′/5′-monophosphate (cGMP) by PDE-5 promotes blood flow into the penis and the restoration of erectile function. Vardenafil and tadalafil have been added to this family of drugs [24,25]. Because their mechanism of action is the same, there is no reason to assume there will be any significant differences in their effectiveness in treating erectile dysfunction, but their half-life may be of cardiac clinical importance.

Hemodynamically, PDE-5 inhibitors have mild nitrate-like actions (sildenafil was originally intended to be a drug for the treatment of stable angina) [26]. As

New therapeutic approaches

Graham Jackson

Table IV. Risk from sexual activity in cardiovascular diseases: Second Princeton Consensus Conference.

Low risk: typically implied by the ability to perform exercise of modest intensity without symptoms
Asymptomatic and < 3 major risk factors (excluding sex) Major CVD risk factors include age, male sex, hypertension, diabetes mellitus, cigarette smoking, dyslipidemia, sedentary lifestyle, and family history of premature CAD
Controlled hypertension β-Blockers and thiazide diuretics may predispose to erectile dysfunction
Mild, stable angina pectoris Non-invasive evaluation recommended Antianginal drug regimen may require modification*
Post revascularization and without significant residual ischemia ETT may be beneficial to assess risk
Post myocardial infarction (> 6–8 weeks), but asymptomatic and without ETT-induced ischemia, or post revascularization If post revascularization or no ETT-induced ischemia, intercourse may be resumed 3–4 weeks after myocardial infarction
Mild valvular disease May include selected patients with mild aortic stenosis
LVD (NYHA class I) Most patients are low-risk
Intermediate or indeterminate risk: evaluate to reclassify as high or low risk
Asymptomatic and ≥ 3 CAD risk factors (excluding sex) Increased risk for acute myocardial infarction and death ETT may be appropriate, particularly in sedentary patients
Moderate, stable angina pectoris ETT may clarify risk
Myocardial infarction within previous 2–6 weeks Increased risk of ischemia, reinfarction, and malignant arrhythmias ETT may clarify risk
LVD/CHF (NYHA class II) Moderate risk of increased symptoms Cardiovascular evaluation and rehabilitation may permit reclassification as low risk
Non-cardiac atherosclerotic sequelae (peripheral arterial disease, history of stroke, or transient ischemic attacks) Increased risk of myocardial infarction Cardiological evaluation should be considered
High risk: defer resumption of sexual activity until after cardiological assessment and treatment
Unstable or refractory angina Increased risk of myocardial infarction
Uncontrolled hypertension Increased risk of acute cardiac and vascular events (ie, stroke)
CHF (NYHA class III, IV) Increased risk of cardiac decompensation
Recent myocardial infarction (within 2 weeks) Increased risk of reinfarction, cardiac rupture, or arrhythmias, but impact of complete revascularization on risk is unknown
High-risk arrhythmias Rarely, malignant arrhythmias during sexual activity may cause sudden death Risk is decreased by an implanted defibrillator or pacemaker
Obstructive hypertrophic cardiomyopathies Cardiovascular risks of sexual activity are poorly defined Cardiological evaluation (ie, ETT and echocardiography) may guide patient management
Moderate to severe valve disease Use vasoactive drugs with caution

CAD, coronary artery disease; CHF, congestive heart failure; CVD, cardiovascular disease; ETT, exercise tolerance test; LVD, left ventricular dysfunction; NYHA, New York Heart Association.

PDE-5 is present in smooth muscle cells throughout the vasculature and the nitric oxide/cGMP pathway is involved in the regulation of blood pressure, PDE-5 inhibitors have a modest hypotensive action. In healthy men, a single dose of sildenafil 100 mg transiently decreased blood pressure by an average

of 10/7 mm Hg, with a return to baseline at 6 h after the drug was given. There was no effect on heart rate [26]. As nitric oxide is an important neurotransmitter throughout the vasculature and is involved in the regulation of vascular smooth muscle relaxation, a synergistic and clinically important interaction with

New therapeutic approaches

Safety and efficacy of treatment of erectile dysfunction

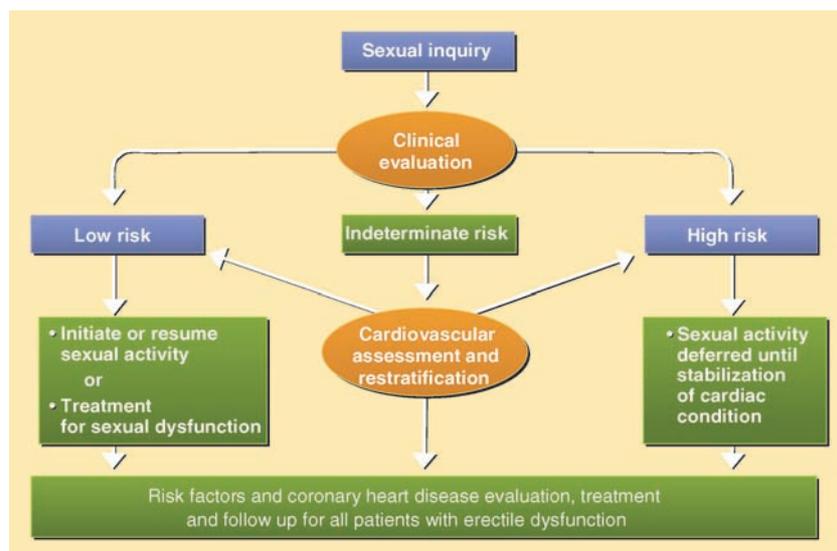


Figure 2. The Princeton II algorithm for the evaluation of men with erectile dysfunction.

oral or sublingual nitrates can occur, and a profound decrease in blood pressure can result. The mechanism involves a combination of increased formation of cGMP when nitrates activate guanylate cyclase, and decreased breakdown of cGMP as a result of the action of PDE-5 inhibitors. The concomitant administration of PDE-5 inhibitors and nitrates is thus contraindicated, and this recommendation also extends to other nitric oxide donors such as nicorandil. Clinical guidelines recommend that sublingual nitrate should be taken 12 h after the PDE-5 inhibitors sildenafil or vardenafil [3]; tadalafil, which has a longer half-life, ceases to react with nitrates only after 48 h [27]. Oral nitrates are not prognostically important drugs, and they can therefore be discontinued and, if necessary, alternative agents substituted [28]. After cessation of oral nitrate, and provided there has been no clinical deterioration, PDE-5 inhibitors can be used safely. It is recommended that the time interval before the use of a PDE-5 inhibitor be five half-lives, which equates to 5 days in the case of most popular once-daily oral nitrate agents.

Sildenafil

Sildenafil was the first oral treatment for erectile dysfunction and is the most extensively evaluated [26]. Overall success rates of 80% or more in patients with cardiovascular disease have been recorded, with no evidence of tolerance. Patients with diabetes, with or without additional risk factors, in whom the pathophysiology is more complex and extensive, have an average success rate of 60%. To date, randomized trials, open-label studies, and outpatient monitoring studies have not found the use of sildenafil to be

associated with any excess risk of myocardial infarction, stroke, or mortality [29–31].

In patients with stable angina pectoris, there is no evidence of an ischemic effect caused by coronary steal, and in one large, double-blind, placebo-controlled exercise study, sildenafil 100 mg increased exercise time and diminished ischemia [32]. A study of the hemodynamic effects of sildenafil in men with severe CAD identified no adverse cardiovascular effects, and a potentially beneficial effect on coronary blood flow reserve [33]. Studies in patients with and without diabetes have demonstrated improved endothelial function acutely and after long-term oral administration, which may have implications beyond the treatment of erectile dysfunction [26]. Sildenafil has also been shown to attenuate the activation of platelet IIb/IIIa receptor activity [34]. Hypertensive patients receiving monotherapy or being treated with several drugs have experienced no increase in adverse events, with the exception of those receiving doxazosin, a non-selective α -adrenoceptor antagonist. Occasional postural effects have occurred with sildenafil when it was taken within 4 h of doxazosin 4 mg; advice to avoid this time interval is now in place. Sildenafil has also been proved to be effective in patients with heart failure who were deemed suitable for treatment of erectile dysfunction [35]; the incidence of erectile dysfunction in patients with heart failure is 80%, making this finding of major clinical importance. On average, the dose of sildenafil is 50 mg; 25 mg is advised initially for those older than 80 years, because of delayed excretion. A dose of 100 mg is invariably needed in patients with diabetes. An empty stomach and the avoidance of alcohol or cigarette smoking facilitate the effect of the drug. Sildenafil 100 mg has no adverse cardiac effects

additional to those associated with the 50-mg dose, and should be routinely prescribed if, after four attempts, the 50-mg dose is not effective.

The short half-life of sildenafil makes it the drug of choice in patients with more severe cardiovascular disease, allowing early use of supportive treatment if an adverse clinical event occurs.

Tadalafil

Tadalafil also has been extensively evaluated in patients with cardiovascular disease, and has a safety and efficacy profile similar to that of sildenafil [36]. Studies have shown no adverse effects on cardiac contraction, ventricular repolarization, or ischemic threshold. A similar hypotensive effect has been recorded with a dose of doxazosin 8 mg, so caution is needed: as hypotension does not occur when the patient is in the supine position, and as tadalafil has a long half-life, it is suggested that tadalafil is taken in the morning and doxazosin in the evening. There is no interaction of tadalafil with the selective α -adrenoceptor antagonist, tamsulosin, which can, therefore, be prescribed as an alternative to doxazosin for benign prostate hypertrophy [37].

Because of its long half-life, tadalafil may not be the drug of first choice for patients with more complex cardiovascular disease. However, as 80% of patients with cardiovascular disease stratify as low risk, it does represent an alternative for the majority.

Vardenafil

Because vardenafil has a chemical structure very similar to that of sildenafil, it is not surprising that it has a similar clinical profile. One study has reported no impairment of exercise ability in patients with stable CAD receiving vardenafil 20 mg [38]. Similar clinical efficiency for all three agents has been observed in patients with diabetes.

Other treatments

When oral agents are not effective, intracavernous injection therapy, transurethral alprostadil, or a vacuum pump are alternatives, requiring specialized referral and advice [2,3]. There is no evidence of increased cardiovascular risk from the use of any of these therapeutic options. If surgical intervention with general anesthesia is being anticipated, a full cardiovascular risk evaluation is recommended.

Conclusion

Erectile dysfunction is common in patients with cardiovascular disease, and should be routinely inquired about. The cardiac risk of sexual activity

in patients with cardiovascular disease is minimal in those who are correctly assessed. The restoration of a sexual relationship is a possibility for the majority of patients with cardiovascular disease and erectile dysfunction, by means of oral PDE-5 inhibitors, which have an excellent safety profile (provided the use of nitrates is avoided). Erectile dysfunction is both a marker for cardiovascular disease and its consequence; therefore, its identification (in the asymptomatic male) provides the opportunity to address other cardiovascular risk factors and detect silent but significant vascular pathology. ■

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New therapeutic approaches

Safety and efficacy of treatment of erectile dysfunction

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Efficacy and safety of trimetazidine and phosphodiesterase type-5 inhibitors

Graham Jackson

Cardiothoracic Centre, St Thomas' Hospital, London, UK

Correspondence: Dr Graham Jackson, Consultant Cardiologist, Cardiothoracic Centre, St Thomas' Hospital, London SE1 7EH, UK. E-mail: gjcardiol@talk21.com

Abstract

Erectile dysfunction is a common problem in men with ischemic heart disease and can be successfully treated with phosphodiesterase type-5 (PDE-5) inhibitors (sildenafil, tadalafil, vardenafil). Nitrates are frequently prescribed for these patients, but their use is an absolute contraindication to the PDE-5 inhibitors because of an unpredictable interaction leading to a profound decrease in blood pressure. Nitrates have no prognostic value and can therefore be discontinued or substituted in patients with stable coronary artery disease. Trimetazidine, unlike nitrates, has no hemodynamic actions. It is a proven effective anti-ischemic agent that does not interact with the PDE-5 inhibitors, allowing their safe use for the treatment of erectile dysfunction.

■ *Heart Metab.* 2005;28:22–24.

Keywords: Erectile dysfunction, ischemic heart disease, nitrates, PDE-5 inhibitors, trimetazidine

Introduction

Coronary artery disease (CAD) is a manifestation of endothelial dysfunction and is commonly associated with erectile dysfunction [1]. Vascular disease is the most common cause of erectile dysfunction, which increases in frequency with age, affecting more than 50% of men aged 40–70 years [2]. It is estimated that erectile dysfunction affects more than 150 million men worldwide [3]. It increases in incidence with age (a man older than 70 years has 3 times the incidence of a man of 40 years), and it has been estimated that, as our population ages, by the year 2025 the number of men with erectile dysfunction will have doubled to 300 million [3].

As a consequence of erectile dysfunction, distress is commonly felt by many couples, affecting not only a man's self esteem but the entire marital (or partner) relationship. In up to 20% of all relationship breakdowns, erectile dysfunction is a major contributing factor [4]. Treatment has been transformed by the phosphodiesterase type-5 (PDE-5) inhibitors (sildenafil [Viagra], tadalafil [Cialis], and vardenafil [Levitra]), with therapeutic success rates of 80–85% in non-

diabetic men and 60–70% in those with diabetes [5]. PDE-5 inhibitors potentiate the action of nitric oxide by competing with PDE-5, which degrades cyclic guanosine monophosphate (cGMP), an important mediator of smooth muscle relaxation and hence erectile function [6]. cGMP is derived from the stimulation of guanylate cyclase by nitric oxide. Organic nitrates donate nitric oxide, which can lead to an accumulation of cGMP in the presence of a PDE-5 inhibitor (*Figure 1*). This can result in an unpredictable and significant vasodilatory interaction, leading to a profound decrease in blood pressure which may be fatal. Oral nitrate treatment is therefore an absolute contraindication to the use of a PDE-5 inhibitor. Even though some men may have no hypotensive sequelae, it is the so-called "outliers" who do determine the recommendation.

Oral nitrates are, however, relatively weak anti-anginal agents and are of no proven prognostic value [7]. They can be of use for the symptomatic treatment of angina pectoris, but in the presence of optimum β -blockade or calcium antagonist therapy, or both, there is little, if any, evidence of clinical benefit. The possibility arises, therefore, that they could be

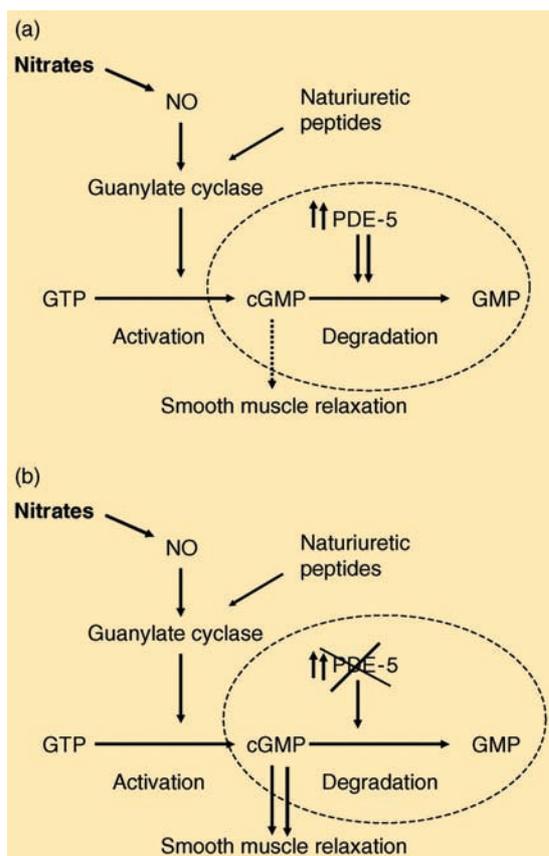


Figure 1. (a) By degrading cyclic guanosine monophosphate (cGMP), phosphodiesterase type-5 (PDE-5) reduces smooth muscle relaxation, and the resulting effect on penile blood flow may cause erectile dysfunction. (b) A PDE-5 inhibitor reduces the degradation of cGMP, promotes smooth muscle relaxation, and improves penile blood flow. In the presence of nitrates, there may be an exaggerated vasodilatory response throughout the vasculature, leading to profound hypotension.

discontinued or substituted in patients whose condition is stable, to allow for the introduction of a PDE-5 inhibitor, provided other anti-ischemic therapy is in place.

Changing treatment

In patients whose condition is stable and who are not restricted or only mildly restricted in their exercise ability, the therapy can be re-assessed. In addition, after percutaneous or surgical intervention many men are symptom free, but continue to receive nitrates for no evidence-based reason; they can therefore have their nitrates stopped. Trimetazidine (Vastarel) is a metabolic anti-ischemic agent that is widely used in the treatment of stable angina, with an efficacy that is comparable or superior to that of oral nitrate therapy [8]. As trimetazidine has no hemodynamic actions and does not exert its effects through the nitric oxide

pathway, it offers an alternative approach to nitrates that would, in turn, allow for the safe use of a PDE-5 inhibitor.

Rosano and colleagues [9] studied 38 men aged 57 ± 6 years with proven CAD and stable symptoms. Their patients underwent 24-h ambulatory electrocardiographic monitoring at baseline and after 2 weeks of treatment with oral mononitrates (20 mg three times daily) and trimetazidine (also 20 mg three times a day) in a single crossover study. The study was double-blind and erectile dysfunction was not a criterion for entry. Patients engaged in sexual intercourse 1 h after sildenafil 100 mg or placebo (nitrate group) on the last day of each treatment period. Compared with baseline, the total ischemic burden decreased significantly after both trimetazidine and isosorbide mononitrate. There was a nonsignificant trend in favor of trimetazidine for decreased frequency of silent ischemic episodes. Ischemia was less during sexual intercourse with trimetazidine plus sildenafil than with nitrates plus placebo/sildenafil. No serious adverse effects were reported.

The implications of this study for men with erectile dysfunction are extremely important. Trimetazidine is a safe and effective agent as monotherapy or combination therapy for the treatment of stable angina and it has, in addition, important metabolic effects at the cellular level, leading to improved myocardial function. Given its efficacy similar to that of oral nitrates, its absence of erectile dysfunction as an adverse effect, and its potentially beneficial effects on ischemia in combination with a PDE-5 inhibitor, it represents a means of allowing men receiving nitrates to have their therapy substituted in order to allow the opportunity for PDE-5 inhibitors to improve their erectile dysfunction and relationships.

Stopping nitrates

In our unit we have recently completed a study of discontinuing oral nitrates in patients with erectile dysfunction whose condition is stable and who continued to receive treatment with a β -blocker or calcium antagonist, or both [10]. We prospectively evaluated 425 men with erectile dysfunction and cardiac disease in our outpatient cardiac sexual advice clinic, and found that 88 (21%) were using oral nitrates. Fifty-five (63%) had a good exercise ability, and their nitrates were discontinued. They were reviewed 1 week later, and only three had restarted their nitrates because of an increase in symptoms. A PDE-5 inhibitor was effective in treating erectile dysfunction in 85%, with no adverse cardiac events. Oral nitrate therapy should therefore not be an absolute barrier to prescribing PDE-5 inhibitors, but a reason for cardiovascular re-assessment and cessation of nitrate therapy if appropriate.

Conclusions

Erectile dysfunction is common in cardiac patients who are low risk as a result of modern medical and interventional management. Those with a good exercise ability and no restrictive symptoms can have their oral nitrate therapy discontinued or substituted with trimetazidine. PDE-5 inhibitors are safe and effective in carefully assessed cardiac patients whose condition is stable and who may be denied this treatment if nitrates have been prescribed. Although other treatments for erectile dysfunction are available, oral therapy is preferred by the majority of those affected.

Sex, the heart and erectile dysfunction represent an important issue for many couples and their health care professionals. Nitrates must not be allowed to prevent patients enjoying the benefits of PDE-5 inhibitors; where they appear to, a careful re-assessment of the clinic situation is indicated. ■

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Erectile dysfunction as a marker of silent ischemia

Michael Kirby

The Nevells Road Surgery, Letchworth Garden City, Herts, UK

Correspondence: Professor Michael Kirby, Hertfordshire Primary Care Research Network, The Surgery, Nevells Road, Letchworth Garden City, Herts SG6 4TS, UK. E-mail: kirbym@globalnet.co.uk

Abstract

The case is reported of a 44-year-old man who presented in 1991 with erectile dysfunction. At this time he was smoking heavily (30 cigarettes per day) and described himself as a stressed executive. Alcohol consumption was a bottle of red wine each night and his symptoms were initially attributed to psychological causes. He was underweight (body mass index 19.6 mg/kg²), and he played football regularly. Five months later, the patient presented with atypical chest pain; he had increased cardiac enzyme concentrations and there were some changes on his electrocardiogram suggestive of inferolateral ischemia. Lipid tests showed an increased cholesterol concentration of 7.4 mmol/L. A subsequent angiogram demonstrated a 70% stenosis in the left anterior descending coronary artery. He was admitted for angioplasty, which was performed at the lesions in the anterior descending and the first and second obtuse marginal branches of the circumflex arteries, with an excellent result. In the subsequent 14 years, a wealth of evidence has accumulated demonstrating that erectile dysfunction is an early marker for coronary artery disease. Patients presenting with erectile dysfunction should be screened for diabetes and cardiovascular risk factors. This presents a major opportunity for prevention.

■ *Heart Metab.* 2005;28:25–28.

Keywords: Erectile dysfunction, ischemic heart disease, endothelial dysfunction, marker

Case report

A 44-year-old man presented in primary care in 1991, initially complaining of pain in the back. During the consultation, he also mentioned that he had been noticing difficulties with both achieving and maintaining an erection. A general enquiry by his practitioner about his lifestyle revealed that he was, in his words, “a stressed executive”. He was smoking 30 cigarettes a day, working long hours and drinking at least a bottle of red wine each night. He made time to play football each week, but otherwise had little leisure time. His blood pressure was normal, but no other clinical examination was made. It was noted that he was underweight and the discussion with his doctor focused on psychological causes for his erectile problems. He was advised to reduce his alcohol consumption, stop smoking and to try and find more time for leisure activities. He was offered the opportunity of a review, but did not return until he presented

5 months later with atypical chest pain, which led to his admission to hospital.

It was confirmed that the patient had suffered an inferolateral myocardial infarction, confirmed by increasing cardiac enzymes and typical changes on his electrocardiogram (ECG). Lipid tests showed an increased cholesterol concentration of 7.4 mmol/L, with increased concentrations of low-density lipoprotein cholesterol and reduced high-density lipoprotein cholesterol. Risk factors for coronary artery disease included a positive family history: his father had died of a myocardial infarct aged 56 years and his mother was hypertensive. He had been a regular smoker.

After this admission to hospital, the patient was discharged, but continued to experience ischemic pain. Medication included isosorbide mononitrate, diltiazem, and cholestyramine. He described a hollow sensation throughout his anterior chest occurring on a daily basis, with occasional radiation to his throat. The pain was precipitated by stress and

Case report

Michael Kirby

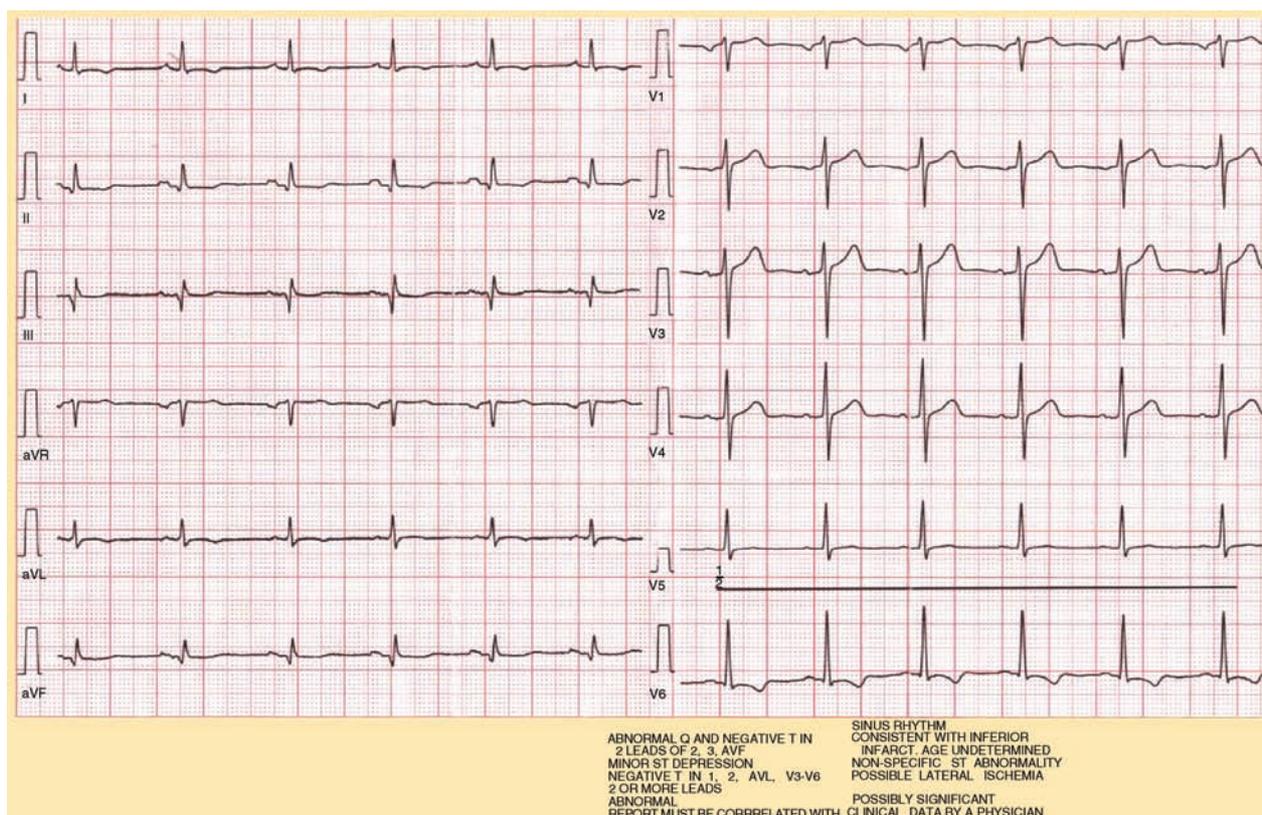


Figure 1. The patient's electrocardiogram at the time of his second admission to hospital.

overworking, but not by physical exertion. He experienced some pain every day, variable in intensity and duration, lasting several minutes, up to 24 h, and variably relieved by nitrates. He did not associate the pain with meals. He denied any tenderness in the chest wall and had not noticed any exacerbation of his symptoms with exertion.

In January 1992, the patient experienced a more severe episode of chest pain, which lasted several hours. He was re-admitted to hospital. ECG performed on the second admission (Figure 1) revealed T-wave inversion in the inferior and lateral leads and no acute ST-segment changes. A coronary angiogram was performed that showed left ventricular function to be slightly impaired. There was a 70% stenosis in the left anterior descending coronary artery after the first septal branch. There were no significant stenoses in the proximal right coronary artery, but there was a lesion in the obtuse marginal branch of the circumflex. A subsequent exercise tolerance test showed that he could achieve 12.5 min of exercise, but at this stage he developed chest pain and a 4 mm ST-segment depression in the anterior leads.

In July 1992, coronary angioplasty was performed at the lesions in the anterior descending artery and the first and second obtuse marginal branches of the circumflex arteries, with excellent results. Since undergoing this procedure, the patient has had no further chest pain and has been regularly followed up,

with comprehensive secondary prevention measures including ramipril, pravastatin, metoprolol, and aspirin. No further mention was made of the erectile dysfunction until the launch of sildenafil, which prompted him to seek help once again. After a negative exercise treadmill test, the patient was prescribed sildenafil, with a good response, and he continues to use the drug regularly. Management of such patients has been facilitated by a practical consensus statement [1].

Comment

Since the early 1990s, there has accumulated a wealth of medical literature providing evidence that erectile dysfunction is an early sign of cardiovascular disease [2–5]. It is an important marker of vascular disease throughout the arterial tree, including coronary artery disease (CAD), stroke, and diabetes. Epidemiological studies have confirmed that there is a close association between erectile dysfunction and vascular disease. A study of 76 men with stable CAD showed that 75% had erectile dysfunction to some degree [6]. It is also recognized that risk factors for erectile dysfunction – hypertension [7], smoking [8], abnormal lipid profile [9], and diabetes [10–12] – are also risk factors for CAD. The link between erectile dysfunction and vascular disease is endothelial dysfunction [5,13,14].

Case report

Erectile dysfunction as a marker of silent ischemia

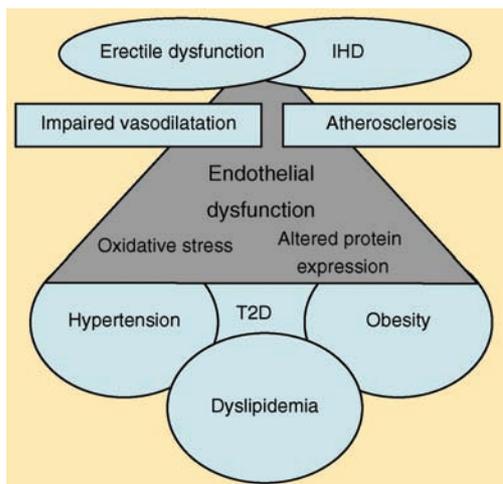


Figure 2. Relationship between baseline risk factors for coronary heart disease and subsequent erectile dysfunction. Underlying disease/risk factors lead to endothelial dysfunction, followed by impaired vasodilatation and development of atherosclerotic lesions. IHD, ischemic heart disease; T2D, Type 2 diabetes.

The Massachusetts Male Aging Study, a random sample cohort of men aged 40–70 years, investigated the relationship between baseline risk factors for coronary heart disease (CHD) and subsequent erectile dysfunction (Figure 2). The premise was that sub-clinical arterial insufficiency might well first manifest itself as erectile dysfunction. Results in 513 men with no erectile dysfunction at baseline revealed that cigarette smoking almost doubled the risk of erectile dysfunction over 8–10 years of follow-up (24%, compared with 14% adjusted for age and covariates; $P = 0.01$). Being overweight (body mass index [BMI] $>28 \text{ kg/m}^2$) and a composite coronary risk score also significantly predicted incident erectile dysfunction. Associations were also seen for hypertension and dietary intake of cholesterol and saturated fat [15].

The Rancho Barnado Study was designed to discover whether risk factors for CHD measured in midlife could predict the incidence of erectile dysfunction an average of 25 years later. The study assessed seven classic risk factors for CHD in community-dwelling men aged 30–69 years, between the years 1972–74. They were reviewed again in 1978. The investigators found that mean age, BMI, cholesterol, and triglyceride concentrations were significantly associated with an increased risk of erectile dysfunction [16].

Further evidence has come from a prospective study that confirmed that 1 in 4 men with erectile dysfunction (aged 40–69 years), but without known CAD, will develop symptomatic CAD in the subsequent 12 years [17]. It has also been demonstrated that symptoms of erectile dysfunction occurred before

symptoms of CAD in 67% of men presenting with chest pain and angiographically documented CAD. Of particular note, all patients with type 1 diabetes and erectile dysfunction developed sexual dysfunction before the onset of CAD ($P < 0.001$) [18].

The rationale as to why erectile dysfunction may present before other signs of CVD is that penile artery diameter is 1–2 mm, compared with a coronary artery that is 3–4 mm; the carotid artery is 5–7 mm. Symptoms associated with oxidative stress and decreased blood flow occur sooner in tissues supplied by the smaller vessels, hence the penis is a barometer of cardiovascular health [19,20].

Several studies have demonstrated that cardiovascular assessment of men with erectile dysfunction enables the detection of CVD. A cohort of 174 men with erectile dysfunction presenting to a urologist were subsequently investigated. Thirty percent were found to be at significant risk of CVD, and their erectile dysfunction treatment had to be deferred until further cardiovascular evaluation could establish them to be at low risk [21]. The severity of erectile dysfunction correlates with the burden of vascular risk factors and severity of cardiovascular disease [22,23]. Routine inquiries about erectile function would therefore be an important way to detect early vascular disease in middle-aged men. This would then provide an opportunity to assess CVD risk factors. The potential time that could be gained was illustrated in a study of 300 consecutive male patients presenting with acute chest pain that was diagnosed as CAD. Forty-nine percent of these men had erectile dysfunction, and this dysfunction had preceded CAD symptoms in 67% of them. The mean time interval between the onset of erectile dysfunction and CAD was 38.8 months (range 1–168 months) [18].

“Erectile dysfunction” is commonly represented by the abbreviation “ED”. It is a noteworthy coincidence that ED also stands for “endothelial dysfunction”, “early detection”, and, for the purpose of this paper, “education and debate” [24]. ■

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Case report

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The hemodynamics of sex

Ian Eardley
St James University Hospital, Leeds, Yorks, UK

Correspondence: Dr Ian Eardley, Department of Urology, St James University Hospital, Beckett Street, Leeds LS9 7TF, UK. Tel: +44 (0) 113 2066994, fax: +44 (0) 113 2064920

Abstract

Penile erection is a vascular event involving relaxation of penile vascular smooth muscle in response to parasympathetic nerve stimulation. The primary neurotransmitter is nitric oxide which produces the smooth muscle relaxation via the cyclic GMP second messenger system. Vascular smooth muscle relaxation results in arteriolar dilatation, relaxation of the trabecular smooth muscle and venous occlusion. Sympathetic stimulation leads to smooth muscle contraction with detumescence.

■ *Heart Metab.* 2005;28:29–31.

Keywords: Smooth muscle relaxation, nitric oxide

Introduction

A penile erection is a vascular event in which the degree of tumescence depends upon the balance between arterial inflow and venous outflow, such that when inflow is low and outflow balances it, the penis is flaccid, but when inflow increases and outflow decreases, tumescence occurs. An erection can be initiated in a number of ways. Some form of erotic stimulus, be it visual, auditory, olfactory, or imaginative, can initiate a process that acts via the hypothalamus to initiate descending parasympathetic activity. An alternative neural pathway involves tactile stimulation of the genitals, with afferent impulses traveling via the pelvic nerves to the spinal cord. The efferent nerves that produce an erection are parasympathetic and arise from the 2nd, 3rd, and 4th segments of the sacral spinal cord. They pass forward around the rectum to the pelvic plexus at the base of the bladder. From there, cavernous nerves pass posterolateral to the prostate before leaving the pelvis beneath the pubic arch, where they penetrate the corpora cavernosa of the penis. They then spread out to innervate the smooth muscle, blood vessels, and endothelium of the penis.

When the parasympathetic nerves are activated, they release a cocktail of neurotransmitters that lead to smooth muscle relaxation within the penis [1]. These include acetylcholine, vasoactive intestinal polypeptide, and nitric oxide, of which the last is by far the most important. In addition to this neural release of

nitric oxide, during an erection there is also release of nitric oxide from the vascular endothelium surrounding the sinusoidal spaces. The nitric oxide penetrates the smooth muscle cell, where it stimulates the enzyme guanylate cyclase to produce cyclic guanosine 3'5'-monophosphate (cGMP), which is the active second messenger within the cell. The production of cGMP ultimately leads to smooth muscle relaxation.

While the parasympathetic nerves are pro-erectile, the sympathetic nervous system provides the primary anti-erectile innervation, with the main stimulator of smooth muscle contraction within the penis being norepinephrine. In this respect, the actions of the sympathetic and parasympathetic nervous systems are reciprocal.

Vascular changes during erection

The penis is a vascular organ consisting of three tubes, one of which serves primarily to transmit urine, while the other two (the corpora cavernosa) have the primary erectile function. They are anchored to the pelvis, so that they are stable when erect, and they have a tough fibrous outer layer (called the tunica albuginea). They are filled with spongy tissue within which are vascular spaces (sinusoids) surrounded by walls (trabeculae) containing smooth muscle. The sinusoids are lined with endothelium. The main arterial inflow comes via the central penile arteries,

Table 1. Cardiovascular consequences of sexual activity (data from [3]).

	Heart rate (beats/min)		Systolic BP (mm Hg)		Oxygen consumption (mL/min per kg)		Workload (MET)	
	Baseline	Orgasm	Baseline	Orgasm	Baseline	Orgasm	Baseline	Orgasm
Masturbation	65	102	151	173	3.9	6.3	1.1	1.8
Woman on top	66	110	147	169	4.5	8.7	1.3	2.5
Man on top	62	127	148	167	4	11.7	1.1	3.3

BP, blood pressure; MET, metabolic equivalent of task units.

which give off several helicine arterioles, which in turn feed the sinusoidal spaces. Venous blood drains from the sinusoidal spaces via a plexus that lies beneath the tunica albuginea, and from which efferent veins penetrate out to the superficial venous system. Passive closure of these venous channels (emissary veins) by the expanding sinusoidal tissue is a crucial part of normal erectile physiology.

When the penis is flaccid, the sympathetic nervous system is dominant in keeping the arterioles constricted and the cavernosal smooth muscle contracted. Blood flow through the penis is low. Erection is brought about under the influence of parasympathetic stimulation, which leads to arteriolar dilatation and trabecular smooth muscle relaxation. Eight separate phases of erection have been identified [2]:

Phase 0: The flaccid phase – Sympathetic tone predominates. The arterial inflow is low and the trabecular smooth muscle is contracted. The sinusoids are relatively empty at this stage.

Phase 1: The filling phase – Parasympathetic stimulation leads to arteriolar dilatation, with a massive increase in arterial flow. Trabecular relaxation leads to sinusoidal filling, without any significant increase in intracavernosal pressure.

Phase 2: The tumescent phase – Parasympathetic stimulation is maintained. As blood continues to pool in the sinusoids, the sinusoidal pressure increases, resulting in a decrease in the arterial inflow. As the pressure increases above diastolic blood pressure, flow continues only during the systolic phase. Furthermore, as the sinusoids expand there is compression of the subtunical venous plexus.

Phase 3: The full erection phase – The intracavernosal pressure continues to increase to around 90% of systolic blood pressure. The arterial flow into the penis decreases further, but is still greater than during the flaccid phase. The expanding sinusoids compress the subtunical venous plexuses, which results in reduced flow into the emissary veins. The mechanism by which the venous outflow from the penis ceases is called the “veno-occlusive mechanism”.

Phase 4: The rigid erection phase – Under the influence of the pudendal nerve, the ischiocavernosus

muscle contracts, squeezing the crura and increasing the intracavernosal pressure above systolic blood pressure. The penis becomes fully rigid and erect. Arterial inflow ceases and the emissary veins are completely closed, such that the penis acts as a closed space. As the skeletal muscle fatigues, there is a decrease in the intracavernosal pressure back to those values seen during the full erection phase, allowing circulation to return to the cavernosal tissue.

Phase 5: The initial detumescence phase – There is a small transient increase in intracavernosal pressure, probably induced by sympathetic stimulation against a closed venous outflow.

Phase 6: The slow detumescence phase – The trabecular smooth muscle contracts, the penile arterioles constrict, and the intracavernosal pressure decreases, leading to reduced compression of the subtunical veins and increased venous outflow.

Phase 7: The fast detumescence phase – Sympathetic stimulation leads to a rapid decrease in both arterial inflow and intracavernosal pressure, with an increase in venous outflow and rapid detumescence.

Cardiovascular effects of sexual activity

Coitus is physical activity, and there are changes in the blood pressure, heart rate, and cardiac output which reflect this and which have been recognized for some years [3]. Both heart rate and blood pressure increase with foreplay, stimulation, and orgasm and, in general, coital activity produces larger changes than does masturbation. The changes reach a peak during orgasm, but then rapidly return to normal (Table 1). There are relatively minor differences relating to the position of the partners during intercourse.

Oxygen consumption also increases during sexual activity and, in this respect, there is some evidence that the “man on top” position is associated with increased oxygen consumption. When converted into the metabolic equivalent of task units (METs) of energy expended in the resting state, sexual activity seems to be associated with a workload between 3 and 4 METs

in older men and 5 and 6 METs in younger men, who may be more energetic in their sexual activity. Clearly then, sexual activity is mild exercise and should be within the physical capacity of most men.

Conclusion

Penile erection is a vascular event under neural control. Parasympathetic stimulation leads to smooth muscle relaxation that results in an active increase in arterial inflow, active relaxation of the cavernosal sinusoids, and a passive reduction in venous outflow (the veno-occlusive mechanism). Sexual activity is

accompanied by a modest increase in heart rate and blood pressure, and can be thought of as being “mild” exercise, within the capacity of almost all men. ■

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Abstracts and commentaries

Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial

Nissen SE, Tuzcu EM, Libby P, et al, for the CAMELOT Investigators. *JAMA*. 2004;292:2217–2226.

The effect of antihypertensive drugs on cardiovascular events in patients with coronary artery disease (CAD) and normal blood pressure remains uncertain. In a double-blind, randomized, multicenter, 24-month trial (enrollment April 1999–April 2002), we compared amlodipine or enalapril with placebo in 1991 patients with angiographically documented CAD (>20% stenosis by coronary angiography) and diastolic blood pressure <100 mm Hg. A substudy of 274 patients measured progression of atherosclerosis by intravascular ultrasound (IVUS). Patients were allocated randomly to groups to receive amlodipine 10 mg, enalapril 20 mg, or placebo. IVUS was performed at baseline and study completion.

The primary efficacy parameter was incidence of cardiovascular events for amlodipine compared with placebo. Other outcomes included comparisons of amlodipine and enalapril, and enalapril and placebo. Events included cardiovascular death, nonfatal myocardial infarction, resuscitated cardiac arrest, coronary revascularization, admission to hospital for angina pectoris or congestive heart failure, fatal or nonfatal stroke or transient ischemic attack, and new diagnosis of peripheral vascular disease. The IVUS endpoint was change in percent atheroma volume.

Baseline blood pressure averaged 129/78 mm Hg for all patients; it increased by 0.7/0.6 mm Hg in the placebo group and decreased by 4.8/2.5 mm Hg and 4.9/2.4 mm Hg in the amlodipine and enalapril groups, respectively ($P < 0.001$ for both compared with placebo). Cardiovascular events occurred in 151 (23.1%) placebo-treated patients, 110 (16.6%) amlodipine-treated patients (hazard ratio [HR] 0.69;

95% confidence interval [CI] 0.54 to 0.88; $P = 0.003$), and in 136 (20.2%) enalapril-treated patients (HR 0.85; 95% CI 0.67 to 1.07; $P = 0.16$). Primary endpoint comparison between enalapril and amlodipine was not significant (HR 0.81; 95% CI 0.63 to 1.04; $P = 0.10$). The IVUS substudy showed a trend toward less progression of atherosclerosis in the amlodipine group compared with placebo ($P = 0.12$), with significantly less progression in the subgroup with systolic blood pressures greater than the mean ($P = 0.02$). Compared with baseline, IVUS showed progression in the placebo group ($P < 0.001$), a trend toward progression in the enalapril group ($P = 0.08$), and no progression in the amlodipine group ($P = 0.31$). For the amlodipine group, correlation between blood pressure reduction and progression was $r = 0.19$ ($P = 0.07$).

Administration of amlodipine to patients with CAD and normal blood pressure resulted in reduced adverse cardiovascular events. Directionally similar, but smaller and nonsignificant, treatment effects were observed with enalapril. For amlodipine, IVUS showed evidence of slowing of atherosclerosis progression.

Commentary

Guidelines for risk reduction that recommend target blood pressures of less than 140/85 mm Hg in patients without diabetes and 130/80 mm Hg in those with diabetes, chronic renal disease, and established cardiovascular disease perhaps do not give the qualification “less than” sufficient emphasis to have an impact on practice. Risk reduction to a low-density lipoprotein cholesterol concentration of 2 mmol/L or less in the Treating to New Targets (TNT) [1] and Pravastatin or Atorvastatin Evaluation Infection Therapy (PROVE-IT) [2] trials has demonstrated clinical benefit from a more aggressive statin regimen (atorvastatin 80 mg) and setting a lower target. In the case of hypertension, the risk-reduction benefit

continues to a blood pressure of 115/75 mm Hg, so a study looking at decreasing blood pressure in the “normal range” in those with CAD is highly relevant to clinical practice. We already know from the European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease (EUROPA) trial [3] in individuals at high cardiovascular risk (documented CAD, previous myocardial infarct) that the addition of perindopril to the drug regimen reduced overall mortality by 14% and myocardial infarction by 24%. This benefit may well be explained by a blood pressure reduction of 5/2 mm Hg from a baseline 137/82 mm Hg. Participants in the (The comparison of Amlodipine vs Enalapril to limit occurrences of Thrombosis [CAMELOT]) trial [4] had a mean baseline blood pressure of 129/78 mm Hg; this was reduced by an additional 4.8/2.5 mm Hg with amlodipine 5–10 mg compared with placebo, and by an additional 4.9/2.4 mm Hg with enalapril 10–20 mg compared with placebo. Both regimens were once-daily, so the benefit recorded for amlodipine over enalapril (and placebo) may be a consequence of the longer half-life of amlodipine and therefore better 24 h blood pressure control. The importance of the study is the identification of clinical benefit with a lower pressure in the normal range, confirming that a lower blood pressure is a better blood pressure in patients with CAD.

It is difficult to know whether the better effect of amlodipine compared with that of enalapril is a direct one, as enalapril should have been administered twice daily (perindopril would have been a better agent for comparison). The IVUS substudy showed no progression of atheroma in the amlodipine group compared with the placebo and enalapril groups, but again this may have been a 24 h blood pressure effect, rather than drug related.

The overall results suggest that the optimal blood pressure for patients with CAD needs to be re-evaluated, given that amlodipine achieved a 31% relative risk reduction and 5.6% absolute risk reduction in adverse cardiovascular events superimposed on high rates of use of statins (>80%), aspirin (95%), and β -blockers (>75%). Perhaps, after all, the classic target of 120/80 mm Hg should be our treatment objective. The “less than” component of the target guidelines needs to be emphasized, just as it is in the case of decreasing low-density lipoprotein cholesterol concentrations.

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Graham Jackson

Influence of substrate supply on cardiac efficiency, as measured by pressure–volume analysis in ex vivo mouse hearts

How OJ, Aasum E, Kunnathu S, Severson DL, Myhre ES, Larsen TS. *Am J Physiol Heart Circ Physiol.* 2005;288:2979–2985.

In the present study we tested the reliability of measurements of pressure–volume area (PVA) and myocardial oxygen consumption (mVO_2) in ex-vivo mouse hearts, combining the use of a miniaturized conductance catheter and a fiberoptic oxygen sensor. Secondly, we tested whether we could reproduce the influence of increased myocardial fatty acid metabolism on cardiac efficiency in the isolated working mouse heart model, which has already been documented in large animal models. The hearts were perfused with crystalloid buffer containing 11 mmol/L glucose and two different concentrations of fatty acids bound to 3% bovine serum albumin: an initial concentration of 0.3 ± 0.1 mmol/L, subsequently increased to 0.9 ± 0.1 mmol/L. End-systolic and end-diastolic pressure–volume relationships were assessed by temporarily occluding the preload line. Different steady-state PVA– mVO_2 relationships were obtained by changing the loading conditions (pre- and afterload) of the heart. There were no apparent changes in baseline cardiac performance or contractile efficiency (slope of the PVA– mVO_2 regression line) in response to increased concentrations of fatty acid in the perfusate. However, all hearts ($n = 8$) showed an increase in the Y-intercept of the PVA– mVO_2 regression line after an increase in the palmitate concentration, indicating a fatty-acid-induced increase in the unloaded mVO_2 . In the present model, therefore, unloaded mVO_2 is not independent of metabolic substrate. This is, to our knowledge, the first report of the PVA– mVO_2 relationship in ex-vivo perfused murine hearts, using a PVA catheter. The methodology can be an important tool for phenotypic assessment of the relationship between metabolism, contractile performance, and cardiac efficiency in various mouse models.

Commentary

Cardiac efficiency is defined as the amount of cardiac work performed at a given level of $m\dot{V}O_2$. As the heart has a high energy demand, and almost no energy reserves, alterations in cardiac efficiency can have important consequences for heart function or heart muscle viability. This is particularly true during myocardial ischemia, when energy production in the heart is compromised as a result of a lack of adequate oxygen supply. ATP is the energy currency of the heart, and is produced by the metabolism of a variety of energy substrates, carbohydrates and fatty acids being the primary ones. The ATP produced by the heart is not only used to sustain contractile function; it is also used for noncontractile purposes, such as to maintain ionic homeostasis or basal metabolic processes in the heart. Any change in the amount of ATP needed for muscle contraction, or the amount of ATP needed for basal metabolism and ion homeostasis, has the ability to alter cardiac efficiency. One determinant of cardiac efficiency is the supply of energy substrate to the heart. In particular, an increased supply of fatty acid to the heart, and an increased use of fatty acids as a source of energy, can lead to a decrease in cardiac efficiency.

Using a sophisticated experimental approach involving the measurement of pressure–volume area (PVA) in isolated working mouse hearts, the authors of this paper have shown that exposing hearts to a high fatty acid concentration can dramatically increase the “unloaded” $m\dot{V}O_2$, which is equivalent to the oxygen used for noncontractile purposes. A 27% increase in unloaded $m\dot{V}O_2$ was seen if the fatty acid concentration was increased from 0.3 to 0.9 mmol/L. Part of this increase in $m\dot{V}O_2$ could be related to the fact that fatty acids are less efficient than glucose for the production of ATP (more oxygen is required to produce an equivalent amount of ATP). However, this would not normally account for more than 11% of the $m\dot{V}O_2$ differences. The additional difference could be the result of a high fatty-acid-induced uncoupling of oxidative phosphorylation, such that the mitochondria are less efficient at producing ATP, yet still consume oxygen. Alternatively, high fatty acid concentrations may trigger futile metabolic cycling such as an increase in triacylglycerol turnover, a process in which ATP consumption increases. A third possibility is that high concentrations of fatty acids can inhibit glucose oxidation, which will result in an increased production of lactate and protons in the heart; many of the pathways involved in the clearance of protons in the heart require ATP. As a result, fatty acid inhibition of glucose oxidation may be another mechanism by which high concentrations of fatty acids decrease cardiac efficiency.

Myocardial ischemia results in a situation in which a mismatch occurs between the oxygen demand of the heart and the oxygen supply to the heart. In most forms of clinical ischemia (during and after a myocardial infarction, during and after cardiac surgery, or during an angina attack), blood concentrations of fatty acids increase markedly and can readily exceed 1 mmol/L. These high concentrations of fatty acids may contribute to the severity of ischemia as a result of their effect in decreasing cardiac efficiency. It is therefore important to have a better understanding of the exact mechanism by which high concentrations of fatty acids produce the marked decrease in cardiac efficiency. Understanding these mechanisms may provide novel therapeutic approaches to the treatment of myocardial ischemia. It may also provide us with a better understanding of why inhibition of fatty acid oxidation (such as through the use of trimetazidine in patients with angina pectoris) has proved to be a useful therapeutic approach to the treatment of ischemic heart disease.

Gary D. Lopaschuk

Sildenafil effects on exercise, neurohormonal activation, and erectile dysfunction in congestive heart failure: a double-blind, placebo-controlled, randomized study followed by a prospective treatment for erectile dysfunction

Bocchi EA, Guimarães G, Mocelin A, Bacal F, Bellotti G, Ramires JF. *Circulation*. 2002;106:1097–1103.

Erectile dysfunction is common in patients with congestive heart failure. It reduces the quality of life, and may affect compliance, thereby impairing the success of treatment of the congestive heart failure. We have studied the effects of sildenafil in 23 men with congestive heart failure.

In the first phase (a fixed-dose, double-blind, randomized, placebo-controlled, two-way crossover study), we studied the effects of sildenafil 50 mg on exercise and neurohormonal activation. The patients underwent a 6-min treadmill-walking cardiopulmonary test (6MWT), followed by a maximal cardiopulmonary exercise test. In the second phase, patients received sildenafil, taken as required for erectile function. Sildenafil reduced the heart rate before the 6MWT from 75 ± 15 to 71 ± 14 beats/min ($P < 0.02$) and that before the exercise test from 75 ± 15 to 71 ± 15 ($P < 0.02$). It reduced the systolic blood pressure before the 6MWT from 116 ± 18 to 108 ± 18 mm Hg ($P < 0.004$) and that before the exercise test from 116 ± 15 to 108 ± 17 mm Hg

($P < 0.001$) and the diastolic blood pressure before the 6MWT from 69 ± 9 to 63 ± 11 mm Hg ($P < 0.01$) and that before the exercise test (from 70 ± 8 to 65 ± 10 mm Hg ($P < 0.004$)). In addition, it reduced the V_E/V_{CO_2} slope during the 6MWT from 32 ± 7 to 31 ± 6 ($P < 0.04$) and that during the exercise test from 33 ± 8 to 31 ± 5 ($P < 0.03$). Sildenafil attenuated the increment in heart rate during the 6MWT ($P < 0.003$) and the exercise test ($P < 0.000$), and increased the peak VO_2 from 16.6 ± 3.4 to 17.7 ± 3.4 mL/kg per min ($P < 0.025$) and the exercise time from 12.3 ± 3.4 to 13.7 ± 3.2 min ($P < 0.003$). It improved most International Index of Erectile Function scores.

Sildenafil was tolerated and effective for the treatment of erectile dysfunction in congestive heart failure, and improved the exercise capacity. The reduction in heart rate during exercise that was obtained with sildenafil could, theoretically, decrease the myocardial oxygen consumption during sexual activity.

Commentary

The prevalence of heart failure is close to 10% and is expected to increase further in the near future. Congestive heart failure is often associated with impaired sexual performance, either as a result of the disease

itself or as an adverse effect of drugs prescribed to reduce mortality and morbidity in patients with the condition. Many patients who value quality of life over prolonged survival may overtly refuse treatment and become noncompliant, in order to retain sexual activity.

Phosphodiesterase inhibitors, such as sildenafil, have been shown to improve erectile dysfunction in a variety of conditions, including heart failure. Concerns have been raised, however, as to the safety of sildenafil in patients with heart failure, either as a direct effect of the vasodilating property of the drug or as a consequence of increased sexual activity. In this study, the effects of sildenafil on exercise tolerance and quality of life were investigated in patients with heart failure. The authors report that inhibition of phosphodiesterase type-5 reduced heart rate and blood pressure under resting conditions and during exercise. Sildenafil increased maximal exercise capacity, was well tolerated, and improved erectile dysfunction.

Successful treatment of erectile dysfunction can improve, not only personal relationships, but also overall quality of life in patients with heart failure, both as a direct effect of resumed sexual activity and as a result of greater patient compliance to complex drug regimens.

Mario Marzilli

Glossary

Gary D. Lopaschuk

Nitric oxide activates guanylyl cyclase

Guanylyl cyclase is the enzyme responsible for converting guanylyl triphosphate to cyclic guanosine monophosphate (cGMP). One of the prominent effects of cGMP is smooth muscle relaxation. Release of nitric oxide by endothelial cells is a potent vasodilator. The actions of nitric oxide are now known to be due to a stimulation of guanylyl cyclase, that results in an increase in cGMP levels and smooth muscle relaxation.

Cyclic guanosine monophosphate

Cyclic guanylate monophosphate (cGMP) is produced from guanylate triphosphate (GTP) via the enzyme guanylyl cyclase. cGMP has numerous actions as an intracellular signalling molecule, including relaxation

of smooth muscle. The vasodilatory effect of nitric oxide on smooth muscle is mediated by the production of cGMP by guanylyl cyclase.

Phosphodiesterase type-5 (PDE-5) inhibitors

PDE-5 is the enzyme that metabolises cyclic guanosine monophosphate (cGMP). Therefore, PDE-5 inhibitors will prevent the degradation of cGMP and increase tissue levels of cGMP. A well known example of a PDE-5 inhibitor is sildenafil (marketed as Viagra[®]). In addition to its smooth muscle relaxing effects in the penis, sildenafil can also induce pulmonary and coronary vasodilation, precondition the myocardium, reduce platelet activation, and potentially reduce early graft occlusion. As a result, PDE-5 inhibitors have potential in the treatment of both pulmonary hypertension and ischemic heart disease.