

Erectile Dysfunction: A Marker of Early Coronary Heart Disease

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Erectile dysfunction (ED) is an increasingly recognised common condition that affects quality of life.^{1,2} ED is defined as the inability to achieve and/or maintain an erection sufficient to permit satisfactory sexual intercourse.³

Men with coronary heart disease (CHD) have a high prevalence of ED.⁴ This association may be related to the fact that the same risk factors—i.e. hypertension, hyperlipidaemia, smoking and diabetes mellitus (DM)—predict both ED and CHD.⁴⁻¹⁰ Endothelial dysfunction appears to be a common mechanism of disease progression for CHD and ED.¹¹

Epidemiology, risk factors and other associations

The relationship between ED and the risk factors for CHD was noted in the Massachusetts Male Aging Study (MMAS).⁴ MMAS included 1,290 men (aged 40-70 years) and reported a 52% incidence of some degree of ED. In men aged between 40 and 55 years the incidence of moderate impotence increased from 6.7% to 25% as high-density lipoprotein cholesterol (HDL-C) decreased from 90 to 30 mg/dl (2.3 to 0.8 mmol/l).⁴ In a recent study of 154 men with ED, 44% had hypertension, 23% had DM, 16% used tobacco, 79% had a body mass index >26 kg/m² and 74% had a low-densi-

ty lipoprotein cholesterol (LDL-C) level >120 mg/dl (3.1 mmol/l).⁸

The Men's Attitudes to Life Events and Sexuality (MALES) study was an extensive survey (27,839 patients) spanning 8 countries.¹² The overall prevalence of self-reported ED in men aged 20-75 years was 16%. The MALES study confirmed the association between ED and increasing age, hypertension, DM, CHD and hypercholesterolaemia. Furthermore, these co-morbidities acted synergistically to increase the prevalence and severity of ED.¹²

In the MMAS study, there was an adjusted odds ratio of 1.97 for incident ED in smokers compared with non-smokers. Passive smoking also had a significant adverse effect on ED.⁴ Smoking may cause ED by several mechanisms, including impairing intrapenile blood flow.^{13,14} The link between smoking and ED is important since it may motivate some smokers to quit.^{13,15} It is of interest that smoking adversely affects the lipid profile, including lowering serum HDL-C levels.¹⁶ Smoking also produces acute morphological alterations in the vascular endothelium and enhances platelet and leukocyte adhesion to the blood vessel wall.^{14,17} Cigarette smoking results in a transient increase in circulating levels of adrenaline and noradrenaline,¹³ which may have a detumescent effect. Smoking is atherogenic; this in turn leads to ED through

atheroma formation in the pudendal arteries. Moreover, cigarette smoke extracts inhibit prostacyclin (PGI₂) synthesis, a potent vasodilator of penile arterial flow.¹⁸

DM is one of the major organic causes of ED.¹⁹ Men with DM are approximately twice as likely to experience ED compared with those without.^{19,20} The prevalence of ED among diabetic patients is high and increases with age and poor glycaemic control.⁴ Pathophysiological mechanisms underlying DM-associated ED are in large part due to endothelial dysfunction.²¹

The prevalence of metabolic syndrome (MetS) is higher in men with ED.²²⁻²⁵ MetS seems to be a potential risk factor for ED.^{26,27} Moreover, raised abnormal fasting glucose levels (FBG) are a risk factor for ED.^{10,28} Both MetS and a raised FBG are predictors of vascular risk.²⁹

Hypertension is associated with both CHD and ED.⁴ Among men with vascular complications associated with hypertension, 71% also had ED.³⁰ Impaired endothelial nitric oxide (NO) bioavailability could be one explanation why hypertension is a risk factor for vasculogenic ED.³¹ Another cause could be the side effects of antihypertensive medication itself.³²

Hypercholesterolaemia is a recognised risk factor for both vasculogenic ED and CHD.^{4,33} This may explain why there is some evidence that cholesterol lowering with a statin may improve responses to sildenafil.³⁴ The role of lipid lowering drugs is discussed below.

A prospective study involving 3,250 dyslipidaemic men (aged 26-83 years, mean 51 years) without ED reported that both high levels of total cholesterol and low levels of HDL-C were strongly related to the onset of ED.³³ In a cohort of 1,519 healthy men (age 42.9 ± 7.9 years), those with a higher total cholesterol had an increased risk for moderate to severe ED. In this healthy population elevated serum lipids were the most important risk factor for the development of ED.³⁵

Atherosclerosis and ED are associated with the same risk factors and biomarkers of inflammation – high sensitivity-C-reactive protein (hs-CRP), interleukin-1beta (IL-1beta) and tumor necrosis factor (TNF)-alpha – and endothelial-prothrombotic activation markers/mediators – von Willebrand factor (vWF), tissue plasminogen activator (tPA), plasminogen activator inhibitor of type 1 (PAI-1) and fibrinogen.^{36,37} However, Eaton et al did not find any association between erectile function and lipoprotein (a), homocysteine, IL-6 and TNF-alpha receptor, CRP and fibrino-

gen levels.³⁸ Others have shown a link between plasma fibrinogen levels and ED.³⁹

In a small study (n=39) involving patients with ED, high levels of lipoprotein (a) were considered an indicator of vasculogenic ED.⁴⁰ Some studies also support the concept that homocysteine interferes with cavernosal smooth muscle relaxation via an interaction between NO and super oxide anions.^{41,42}

Some unique organic and psychological factors contributing to ED have been identified in patients with underlying vascular problems.³¹ Psychogenic factors include performance anxiety, depression and psychosocial stress. The term organic includes the following aetiologies: neurogenic, vascular, endocrine, medications, pelvic surgery, trauma, radiation, lower tract urinary symptoms and benign prostatic hypertrophy.^{43,44} It has been estimated that vascular disease and DM are the organic causes of ED in as many as 70% of patients.³¹ Furthermore, several drugs used in patients with CHD can induce this adverse effect (e.g. some antihypertensive drugs and possibly lipid lowering agents).⁴⁵

The endothelium and erectile function

The association between ED and CHD raises the question as to whether vasculogenic ED is yet another manifestation of atherosclerosis. Impaired NO activity may provide a unifying explanation for such an association. It is generally accepted that NO is the principal mediator responsible for relaxation of smooth muscle.⁴⁶ In order to achieve an erection, there must be a decrease in sympathetic smooth muscle tone, an increase in parasympathetic smooth muscle relaxation, an increase in arterial inflow and decreased venous outflow leading to the filling of cavernosal spaces.^{47,48}

There is convincing evidence that during erection the local release of NO and/or related factors relax the *corpus cavernosum*.⁴⁹ Consequently, reduced NO activity will impair erectile function. Several conditions that reduce NO activity are associated with vascular disease and endothelial dysfunction (e.g. age, DM, hypertension, hyperlipidaemia and smoking). All these factors increase the risk of ED.⁵⁰

ED and extent of arterial disease

The small diameter (1 to 2 mm) of the cavernous arteries and the relatively high content of endothelium and smooth muscle per unit volume of tissue compared with other organs may make penile function more susceptible to damage from atherosclerosis.⁵¹ An artery size hy-

pothesis has been proposed; larger vessels can better tolerate the same amount of plaque compared with smaller ones. According to this hypothesis, because penile arteries are smaller in diameter than coronary arteries, patients with ED will seldom have concomitant symptoms of CHD, whereas patients with CHD will frequently complain of ED.⁵² It is likely that ED is not only a secondary complication of CHD but also an early marker for vascular risk and subclinical vascular disease.^{53,54}

Given these findings, it is not surprising that the greater the extent of the heart disease the greater the likelihood of ED. In one study, 42% of the patients who had a myocardial infarction (MI) reported ED.⁵⁵ Another survey found an 18% ED prevalence in patients who had a recent acute MI and single-vessel disease, compared with 67% in those who had chronic angina pectoris with multivessel disease.⁵⁶ Thus, it is likely that in patients with CHD the prevalence of ED varies according to angiographic data.⁵² This interpretation is supported by a significant correlation between ED and the number of coronary vessels involved.^{57,58} Furthermore, the degree of ED correlates with the severity of atherosclerotic disease,⁵⁹ even in patients with type 2 DM.²⁰

Some studies evaluated angiographically the incidence of asymptomatic CHD in men with ED of vascular origin. There was a strong and independent association between ED and silent CHD in apparently uncomplicated type 2 diabetic patients. Thus, ED may be a potential marker to identify diabetic patients with silent CHD.²⁰ In another study, 19% of patients with ED of vascular origin had angiographically documented silent CHD. These findings support the strategy that patients with ED should undergo further cardiovascular evaluation.⁵⁴

Sexual activity and CHD

Of concern to patients and clinicians is the risk that sexual activity may trigger an acute cardiac event (e.g. MI, sudden death, or unstable angina). In one study, 1,774 MI patients were interviewed. This study showed that sexual activity can trigger the onset of MI, but the relative risk (RR) is low and the absolute hourly risk of MI is extremely low. The absolute risk increase caused by sexual activity is also extremely low (1 chance in a million for a healthy individual). Moreover, the relative risk is not increased in patients with a prior history of cardiac disease, while regular exercise appears to prevent triggering of MI.⁶⁰

In a study involving 88 outpatients with stable CHD (age range from 36 to 66 years, mean 52 years) an arrhythmia was detected during intercourse in 56% of patients compared with 38% on exercise. The ventricular ectopic activity that occurred in intercourse was most often simple and essentially similar to disturbances seen during daily activity.⁶¹ A small proportion (about 1%) of cases of acute coronary syndromes occur during or after sexual activity.⁶² The risk of MI in a patient with a history of MI has been found to be 10 per million in the first hour, and the doubling of this risk in the two hours following coitus has a negligible impact on annual risk.¹¹

A small but definite risk of a cardiac event exists for patients with a history of CHD who resume sexual activity. Thus, the Princeton Consensus Panel produced specific guidelines for the management of ED in the cardiovascular patient.⁶³ They stratified patients into groups according to cardiovascular symptoms and physiological reserve.⁶³ These guidelines incorporate clinically useful assessments of cardiac risk associated with sexual activity and the management of sexual dysfunction among patients with known cardiovascular risk factors or disease.

Treatment of ED and CHD

The management of ED may include a combination of pharmacological measures and counselling. Lifestyle change is associated with improved sexual function in about one third of obese men with ED.⁶⁴

Phosphodiesterase type 5 (PDE 5) inhibitors are commonly used to treat ED. PDE 5 hydrolyses cyclic guanosine monophosphate in cavernosal tissue, rendering it inactive.^{65,66} The early use of PDE 5 inhibitors in patients with hypertension, hyperlipidaemia or DM with concomitant ED may improve corporeal blood flow and lead to long-term preservation of cavernosal function.^{67,63}

One of the earliest recognisable benefits of treatment with statins is the normalisation of endothelium-dependent relaxation in hypercholesterolaemia.⁶⁸ This effect occurs before significant lowering of serum cholesterol levels.⁶⁸ Therefore, it would be expected that statins improve ED. As discussed above, there is some evidence that adding a statin improves responses to sildenafil.³⁴ However, these drugs also seem to include ED as a side effect.

A recent case-control study suggested that lipid-lowering medication could itself increase the prevalence of ED.⁶⁹ The mechanism by which statins may

cause ED remains uncertain. Statins have become widely used but are not generally accepted as a cause of ED. Surprisingly, most publications describing major randomised statin trials have not reported the incidence of ED.⁷⁰⁻⁸² However, in the 4S study, 37 of 1,814 patients on simvastatin developed ED, as did 28 of 1,803 on placebo; this difference was not significant.⁸³

Antihypertensive drugs may be detrimental to ED; this potential side effect depends on the class of agent used.³¹ Thiazide diuretics and beta-blockers seem to cause ED more often than other antihypertensives,³² while calcium channel antagonists and angiotensin converting enzyme inhibitors (ACE-I) may be neutral with respect to this side effect.⁸⁴ There is evidence showing that alpha (1)-adrenoceptor antagonists (doxazosin) and angiotensin II type 1-receptor blockers (ARBs) have a positive effect on erectile function.⁸⁵

A multicentre, prospective, randomised controlled trial (LIFE) showed that a beta-blocker (atenolol) based regimen was associated with significantly ($p=0.009$) more ED compared with losartan, an ARB, in 9,193 participants with essential hypertension and left ventricular hypertrophy.⁸⁶ In another trial (ASCOTT-BPLA), 19,257 patients with hypertension and at least three other cardiovascular risk factors were assigned to either a calcium channel blocker (amlodipine) plus ACE-I (perindopril) or a beta-blocker (atenolol) plus diuretic (bendroflumethiazide). There was significantly ($p<0.0001$) less ED in the amlodipine-perindopril group compared with the atenolol-diuretic group.⁸⁷

In a study that compared the effects of two antihypertensive agents, carvedilol and valsartan, on sexual activity in healthy men, carvedilol induced a worsening of sexual activity. In contrast, valsartan did not significantly worsen sexual activity and may even have improved it.⁸⁸

In contrast to the findings mentioned above, a study from Finland (1,665 men) showed that the risk of ED was higher in men using calcium channel antagonists [RR=1.6, 95% confidence interval (CI) 1.0-2.4], ARBs [RR=2.2, 95% CI 1.0-4.7], non-selective beta-blockers [RR=1.7, 95% CI 0.9-3.2] or diuretic [RR= 1.3, 95% CI 0.7-2.4] compared with non-users. ED was not associated with using organic nitrates, ACE-I, selective beta-blockers or lipid-lowering agents.⁸⁹

Doxazosin appears to have some interaction with PDE 5 inhibitors, which may result in orthostatic hypotension.⁶⁷ In contrast, in another study the combination of sildenafil and doxazosin was a safe and effective option for men with ED who failed on sildenafil alone.⁹⁰

In general, the adverse event profile of PDE 5 inhibitors is not worsened even if the patient is taking multiple antihypertensive agents.⁶⁷ However, caution is advised when co-prescribing these medications.

The cardiac safety of PDE 5 inhibitors has been a subject of great interest. Long-term studies have shown no increase in MI or death rate, although PDE 5 inhibitors are contraindicated in patients in whom sexual activity is inadvisable due to underlying cardiovascular disease, until an appropriate CHD intervention has been performed.⁹¹⁻⁹³

PDE 5 inhibitors do not affect the force of cardiac contraction and cardiac performance, are mildly vasodilating in the coronary circulation, and do not increase the risk of ventricular arrhythmia.⁶³ During exercise and recovery, PDE 5 inhibitors do not cause clinically significant alterations in haemodynamic parameters in men with CHD. Furthermore, PDE 5 inhibitors have no negative effects on coronary oxygen consumption, ischaemia or exercise capacity.⁹⁴ In men with hypertension and CHD, heart rate is not altered to a clinically significant extent by the administration of PDE 5 inhibitors. The minimal effect of these agents on heart rate shows that blood pressure reductions were insufficient to stimulate a reflex increase in heart rate.⁹⁴

All PDE 5 inhibitors potentiate the hypotensive effects of organic nitrates and are therefore contraindicated in patients using nitrates.⁹¹⁻⁹³

Conclusions

ED and CHD have many common features. Firstly, they share the same risk factors. Secondly, similar pathophysiological mechanisms contribute to impaired endothelial function. Thirdly, ED is more frequent in patients with vascular disease (e.g. CHD, cerebrovascular and peripheral arterial disease). ED is also related to the extent of CHD (e.g. as established by angiography). Finally, some of the drugs used to treat CHD can aggravate ED, while some drugs that are used to treat ED (e.g. PDE 5 inhibitors) can influence the blood pressure.

The recognition of ED as a warning sign of silent vascular disease has led to the concept that a man with ED and no cardiac symptoms is a cardiac (or vascular) patient until proven otherwise.^{63,95}

Treating vascular risk factors in patients with ED may increase corporeal blood flow by improving endothelial function with concomitant amelioration of the CHD.

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