Sexual function in hypertensive patients receiving treatment

Thorsten Reffelmann
Robert A Kloner

University of Southern California, The Heart Institute, Good Samaritan Hospital, Division of Cardiovascular Medicine, Keck School of Medicine, Los Angeles, CA, USA

Abstract: In many forms of erectile dysfunction (ED), cardiovascular risk factors, in particular arterial hypertension, seem to be extremely common. While causes for ED are related to a broad spectrum of diseases, a generalized vascular process seems to be the underlying mechanism in many patients, which in a large portion of clinical cases involves endothelial dysfunction, ie, inadequate vasodilation in response to endothelium-dependent stimuli, both in the systemic vasculature and the penile arteries. Due to this close association of cardiovascular disease and ED, patients with ED should be evaluated as to whether they may suffer from cardiovascular risk factors including hypertension, cardiovascular disease or silent myocardial ischemia. On the other hand, cardiovascular patients, seeking treatment of ED, must be evaluated in order to decide whether treatment of ED or sexual activity can be recommended without significantly increased cardiac risk. The guideline from the first and second Princeton Consensus Conference may be applied in this context. While consequent treatment of cardiovascular risk factors should be accomplished in these patients, many antihypertensive drugs may worsen sexual function as a drug specific side-effect. Importantly, effective treatment for arterial hypertension should not be discontinued as hypertension itself may contribute to altered sexual functioning; to the contrary, alternative antihypertensive regimes should be administered with individually tailored drug regimes with minimal side-effects on sexual function. When phosphodiesterase-5 inhibitors, such as sildenafil, tadalafil and vardenafil, are prescribed to hypertensive patients on antihypertensive drugs, these combinations of antihypertensive drugs and phosphodiesterase 5 are usually well tolerated, provided there is a baseline blood pressure of at least 90/60 mmHg. However, there are two exceptions: nitric oxide donors and α-adrenoceptor blockers. Any drug serving as a nitric oxide donor (nitrates) is absolutely contraindicated in combination with phosphodiesterase 5 inhibitors, due to significant, potentially life threatening hypotension. Also, α-adrenoceptor blockers, such as doxazosin, terazosin and tamsulosin, should only be combined with phosphodiesterase 5 inhibitors with special caution and close monitoring of blood pressure.

Keywords: Sexual function, erectile dysfunction, hypertension, antihypertensive therapy, phosphodiesterase 5 inhibitors

Introduction

Arterial hypertension is a systemic disorder characterized by altered regulation of cardiovascular hemodynamics including arterial vascular resistance and cardiac index leading in effect to increase in arterial blood pressure. Whether the hypertension is of the essential type, without obvious underlying disease, or secondary arterial hypertension due to primary causes, such as renal, vascular, metabolic, endocrine, or other disorders, chronically elevated blood pressure is regarded as an established risk factor for the development of cardiovascular disease, such as stroke, chronic ischemic heart disease, myocardial infarction and heart failure. Therefore, arterial hypertension should be the target of vigorous treatment attempts both in primary and secondary preventive medicine (MacMahon et al 1990).

Correspondence: Robert A Kloner
The Heart Institute, Good Samaritan Hospital, Division of Cardiovascular Medicine, Keck School of Medicine, 1225 Wilshire Boulevard, Los Angeles, CA 90017-2395, USA
Tel +1 213 977 4050
Fax +1 213 977 4107
Email rkloner@goodsam.org

At first sight, erectile dysfunction (ED) seems to be a field quite different from cardiovascular medicine. However, a closer look demonstrates that it is strongly associated with arterial hypertension and also several other cardiovascular risk factors. Many cases of ED are characterized as "vascular", referring to their strong statistical association with cardiovascular risk factors and cardiovascular events (Virag et al 1995; Schwarz et al 2005). Among others, hypertension is a cardiovascular risk factor which is significantly associated with ED (Bansal 1988; Kloner 2000). In the Massachusetts Male Aging Study the annual incidence of ED in a population of 40–69 year old men amounted to 26 new cases per 1000 men. While the incidence in absolute numbers progressively increased with age, hypertension and also diabetes mellitus and heart disease were significantly associated with ED in every age group (Feldman et al 1994; Johannes et al 2000). A systematic evaluation of atherogenic risk factors among men with ED reported a prevalence of 44% for hypertension, 79% for obesity, 74% for elevated low-density lipoprotein cholesterol (above 120 mg/dL), 23% for diabetes mellitus, and 16% for smoking (Walzak et al 2002). As recently demonstrated, this strong association between the presence of ED and cardiovascular risk factors results in a significantly increased incidence of cardiovascular events among patients with ED (Blumentals et al 2004). A retrospective analysis of the placebo group from the Prostate Cancer Prevention Trial estimated an 11% 5-year risk of cardiovascular events in patients suffering from ED, which in current terminology of preventive medicine means that ED can be regarded as a "coronary risk equivalent" (Thompson et al 2005).

The following paragraphs will discuss some basic aspects of this interrelation between hypertension and ED with respect to similarities in pathophysiology and potential interaction of medical treatment options of the two diseases.

Erectile dysfunction: warning for cardiovascular risk factors and cardiovascular disease

Endothelial dysfunction: common denominator of atherogenic risk factors and erectile dysfunction

Table 1 presents a list of potential causes and factors associated with ED, which should be considered in the patient's work-up. Some of them are related to underlying urological, psychosocial or endocrine disorders. However, it is clear that factors associated with the cardiovascular system appear to play a predominant role (Table 1).

The endothelium, ie, the inner layer of cells that line the vascular network, contributes significantly to vasomotor regulation, via release of nitric oxide (NO), which is a potent vasodilator. Endothelial dysfunction is defined as a reduced vasodilation or even paradoxic vasoconstriction in response to endothelium-dependent vasodilatory stimuli. In many circumstances endothelial dysfunction precedes morphological changes of the vessel wall or the formation of atherosclerotic plaques. In particular, hypertension might be associated with endothelial dysfunction as shear stress within the vessel wall, hypertension, and associated conditions seem to affect endothelial function significantly (Ludmer et al 1986; Nabel et al 1988; Taddei et al 1993; Nava et al 1995; Cardillo et al 1998).

In many patients with ED, inadequate release of NO from nerve endings and endothelial cells or altered response of penile

Table 1 Risk factors, conditions, and diseases associated with erectile dysfunction

Risk factor associated with atherosclerosis:
• Smoking
• Diabetes mellitus
• Hypertension
• low levels of HDL cholesterol/high levels of LDL cholesterol/ high level of total cholesterol
• sedentary lifestyle
• family history of atherosclerosis
• obesity
Neurological factors
• neuropathy (diabetic, etc)
• spinal cord injury, cerebrovascular insult, multiple sclerosis, nerve damage due to prostate surgery etc.
Medical diseases
• renal failure,
• dialysis,
• abnormal liver function,
• endocrine disorders (hypogonadism, hyperprolactenemia, hypo- and hyperthyroidism),
• sickle cell anemia
Drugs
antihypertensives, thiazide diuretics, spironolactone, digoxin, antidepressants, β-blockers, centrally acting antihypertensives, phenothiazines, carbamazepin, phenytoin, risperidone, fibrates, statins, Histamine-2-receptor antagonists, allopurinol, indomethacin, tranquilizer, disulfiram, levodopa, chemotherapeutics, etc.
alcohol, others
Others
Peyroni's disease, priapism, trauma
Psychosocial causes
depression, anxiety disorder, problems or changes in relationship

Compiled according to Brock et al. 1993; NIH Consensus Development Panel on Impotence 1993; Benet et al. 1995; Greiner et al. 1996; Keene et al. 1999; Kloner et al. 1999; Kloner et al. 2002; Levine 2000; McVary et al. 2001; Nusbaum et al. 2002; Moulik et al. 2003; Nicolosi et al. 2003; Nurnberg et al. 2003, and Roth et al. 2003.

vascular smooth muscle cells to NO appears to be an important step in the pathophysiology of ED (Billups 2004). ED, in this context, can be regarded as one manifestation of a generalized process of vascular deterioration. A recent study examined endothelium-dependent and endothelium-independent vasodilation of the brachial artery in men with ED, but without other clinically overt cardiovascular disease (Kaiser et al 2004). Vasodilation of the brachial artery by both mechanisms was significantly compromised in the group suffering from ED, which illustrates that vascular alterations involved in ED are a generalized process.

Phosphodiesterase 5 inhibitors, namely sildenafil, vardenafil, and tadalafil, which are currently considered to be the most effective medical treatment options for ED, intervene in this pathway of vascular dysfunction (Reffelmann et al 2003): When NO stimulation increases activity of the enzyme guanylate cyclase, intracellular cGMP levels are increased. This mechanism might be further amplified and prolonged in duration by inhibition of the enzyme phosphodiesterase 5, which is responsible for the breakdown of cGMP. Thereby, inadequate vasodilation of the penile arteries in ED as a result of insufficient release of NO can be compensated for by phosphodiesterase 5 inhibition (Gresser and Gleiter 2002; Gross 2005; Reffelmann and Kloner 2005a, b).

Cardiovascular work-up for the patient presenting with erectile dysfunction

Patients without obvious causes for ED, such as anatomical disorders, neurological disease or endocrine causes should be evaluated for cardiovascular risk factors, arterial hypertension, and vascular or arterial disease (Kloner and Jarow 1999; Kim et al 2001; Sairam et al 2001; Solomon et al 2003). The relatively high probability of detecting potentially serious diseases warrants further investigations (Gazzaruso et al 2004; Reffelmann and Kloner 2005a, b).

In addition, the strong association between cardiovascular risk factors and ED should be brought to the patient's attention, as this, in some patients, might be a more convincing motivation to modify these risk factors, change lifestyle, effectively treat hypertension, quit smoking, and others, than the sometimes more abstract statistical association between cardiovascular disease and risk factors.

In general, we propose the following medical work-up for a patient presenting with ED with reasonable modification depending on the individual condition. The patient needs to supply a detailed medical history including sexual and psychosocial history along with a complete list of current and previous medication. A cardiovascular examination including peripheral pulses, signs of peripheral ischemia, and others is necessary. To assess the individual risk for cardiovascular diseases, repeated measurement of blood pressure, a fasting blood glucose level, analysis of cholesterol (total, low-density lipoproteins and high-density lipoproteins), body-mass index (according to weight and height), assessment of lifestyle, actual level of physical activity, and potential genetic predisposition should be obtained. A resting electrocardiogram should also be documented. If a patient has three or more atherogenic risk factors an exercise electrocardiogram should be considered as per the Princeton Consensus Panel. In some high risk patients a Doppler-sonographic examination of the carotid arteries and lower extremity arteries might also be included into the work-up.

Patients with diabetes suffering from ED are at special risk for silent cardiovascular disease (Gazzaruso et al 2004). Therefore, some authors recommend an exercise test for every diabetic patient presenting with ED, as a significant number of patients with silent ischemic heart disease will be detected (Stern 2005).

If the results suggest an increased risk for cardiovascular disease, a referral to a cardiologist is reasonable for detailed diagnostic testing and initiation of therapy. Importantly, the cardiac situation should be carefully clarified before initiation of medical treatment, as phosphodiesterase 5 inhibitors must not be used in certain cardiovascular conditions or at least require special precaution (see below). In addition, detailed recommendations for cardiovascular patients, concerned about a potential risk of sexual intercourse in the light of their underlying cardiovascular condition, are available both for further diagnostic work up and therapeutic interventions according to the first and second Princeton Consensus Conference (DeBusk 2000; Kostis et al 2005). Patients are categorized as low-risk, high risk, or, if stabilization or further diagnostics are necessary, as indeterminate or intermediate risk (Table 2). In the high-risk group, sexual activity should be deferred until a patient's cardiac condition has been stabilized by medical treatment, revascularization procedures or by simply waiting until stabilization has occurred. In the intermediate group, further work-up is required, which in many circumstances needs referral to a cardiologist.

Patients whose blood pressure is well controlled with one or more antihypertensive drugs are categorized as belonging to the "low-risk group", meaning that sexual activity and also treatment for ED could be safely recommended. However, patients with poorly controlled hypertension, or hypertension

Table 2 Three risk groups of patients with cardiovascular disease according to the "Second Princeton Consensus Panel" (Kostis 2005; see also DeBusk 2000)

1. Low risk group
Patients with • Two or less atherogenic risk factors, asymtomatic • Medically controlled hypertension with ≥1 antihypertensive drug • mild, stable angina (consider exercise test in some cases) • after successful coronary revascularization (without remaining ischemia) • after uncomplicated myocardial infarction (>6–8 weeks) • mild valvular disease • Left ventricular dysfunction: New York Heart Association I
2. Intermediate or indetermined risk group
Patients with • Three or more atherogenic risk factors, asymptomatic • moderate, stable angina • myocardial infarction (2–6 weeks after the acute event) • congestive heart failure: New York Heart Association II • non-cardiac sequelae of atherosclerotic disease (stroke, transient ischemic attack, peripheral vascular disease)
3. High risk group
Patients with • unstable angina /refractory angina • untreated, poorly controlled, accelerated, or malignant hypertension • congestive heart failure (New York Heart Association III–IV) • myocardial infarction (within the last 2 weeks) • recent stroke • moderate to severe valvular heart disease, particularly aortic stenosis or hypertrophic obstructive cardiomyopathy • high risk arrhythmia

before initiation of adequate treatment or malignant hypertension are categorized as "high-risk" for cardiac or vascular events, especially also for stroke (Kostis et al 2005). As a consequence these patients first require medical treatment of hypertension and also a diagnostic work-up of accompanying medical disorders.

Sex: a risk for a cardiovascular patient?

Among patients and doctors there is substantial uncertainty as to whether sexual activity in different cardiovascular conditions and stages of heart disease can be safely recommended. A cardiovascular patient asking for treatment options for ED, who might have not been sexually active for a certain period of time, needs a realistic, individual estimate of a potential risk of a cardiac event related to sexual intercourse preferentially based on recommendations of the (first and second) Princeton Consensus Conference (DeBusk 2000; Kostis et al 2005).

Statistically, available data suggest that the risk of myocardial infarction and sudden cardiac death during sexual intercourse, the so-called coition-induced death, is very low. Fewer than 1% of myocardial infarctions occur during sexual intercourse, and only about 0.6% of sudden cardiac deaths may be related to sexual activity (Muller et al 1996; DeBusk 2000; Jackson 2000; Ueno 2000). Nonetheless, sexual activity, even if associated with a very low absolute risk, is an established trigger of myocardial infarction (DeBusk 2000). A 50-year-old man in the US is considered to have a baseline risk of myocardial infarction of 1.00% per year. This risk increases to 1.01% as a consequence of sexual activity. For patients with prior myocardial infarction, the risk may increase to 1.10%. Using cross-over statistics, Muller et al (1996) estimated the relative risk of myocardial infarction occurring during and within a 2-hour period after sexual intercourse as being 2.5 in comparison with non-sexual activities. Importantly, the relative risk in patients with known cardiac disease was 2.1. Interestingly, regular physical activity and cardiovascular risk factor modification might further reduce the risk (Stein 1977; DeBusk 1996). Patients with ischemic heart disease who have undergone successful revascularization (percutaneous transluminal angioplasty or coronary artery bypass surgery) are not at increased risk of myocardial infarction during sexual intercourse compared with the general population (Jackson 1999).

In general, physical activity is regarded as a trigger of cardiac events in susceptible patients (Muller et al 1997). With respect to the cardiovascular system, sexual intercourse can be regarded as physical activity resulting in increased blood pressure and heart rate, which is not decisively different from other physical exercise in daily life.

While energy expenditures during sexual intercourse may vary depending on many individual factors, estimates were obtained in a laboratory setting by Bohlen et al (1984) using the metabolic equivalent of energy expenditure (MET) in the resting state (equal to 3.5 mL/kg/min oxygen consumption) as a quantitative parameter. Healthy males attained 2.5–3.3 METs during sexual stimulation and orgasm with some variability (2.0–5.4 METs). For comparison with daily life activities, one might say that 3 METs equals briskly climbing two flights of stairs, and 5 METs may be compared with digging in the garden. Peak heart rate during sexual intercourse ranged between 110 and 127 beats/minutes in

these individuals (Bohlen 1984). In these investigations, heart rate rarely increased to more than 130/min and systolic blood pressure rarely exceeded 170 mmHg in healthy individuals (Bohlen et al 1984; DeBusk 2000).

A possible conclusion derived from these measurements might be that a patient, who is able to achieve 5–6 METs on exercise testing without signs of ischemia, major arrhythmia or inadequate increase of blood pressure, may not be at excess risk for a cardiac event during sexual activity. In addition, effort-induced triggering of myocardial infarction is, in general, believed to be reduced by revascularization and optimized medical treatment using aspirin, β-blockers and lipid-lowering strategies (Jackson 1997, 2000).

Antihypertensive interventions: cause or cure of erectile dysfunction?

The close association between hypertension and other cardiovascular risk factors and the presence of ED respectively and also the similarities in pathophysiology might suggest that adequate treatment of hypertension and other risk factors could favorably influence the severity or progression of ED or even result in reversal of symptoms. To the contrary, however, many antihypertensive drugs might even worsen sexual function as a drug specific side-effect, which could significantly decrease patient adherence to anti-hypertensive treatment, further increasing risk of cardiovascular morbidity. This might be true, in particular, if the question of sexual health is not openly addressed between the patient and the clinician.

Epidemiological data suggest that cessation of tobacco use can in part reverse ED (McVary et al 2001). For diabetes mellitus, better glycemic control, measured as lower levels of glycosylated hemoglobin is associated with less severity and lower incidence of ED (Romeo et al 2000). But for hypertension, such clear data is not consistently available: Possibly two confounding factors, drug-specific side effects and beneficial effects of effective blood pressure control may make it difficult or impossible to tell whether treatment of hypertension can attenuate ED.

In general, one might consider lifestyle changes and/or medical treatment as a potential therapeutic strategy. It is quite well established that lifestyle changes associated with reduced arterial blood pressure, such as initiation of physical activity and weight loss, favorably influence sexual function. These lifestyle changes seem to be most effective at younger age compared with older patients (Derby et al 2000).

There are experimental animal investigations, suggesting that medical treatment of hypertension may have the potential to reduce the incidence of ED (Hale et al 2001). However, most medical antihypertensive interventions, such as thiazides, β-blocking agents etc, were reported to potentially worsen sexual function.

An exception to this rule is the experience with angiotensin II receptor type-1 blockers (Llisterri et al 2001), which seem to slightly improve sexual function along with effective blood pressure control. For losartan and valsartan, clinical studies demonstrated a reduction in the incidence of ED and a slight, but consistent improvement in common parameters of erectile function (Ferrario et al 2002; Dusing 2003). Moreover, animal studies supported the concept of improved sexual function along with effective blood pressure control under the influence of losartan (Tobbli et al 2004; Park et al 2005).

When choosing the appropriate antihypertensive regime, one should also bear in mind that, for example, thiazide diuretics are reported to have a higher incidence of ED than β-blocking agents, the most commonly mentioned drugs in this context (Table 3). In addition, a simple weight loss diet may reverse sexual dysfunction induced by thiazide diuretics (Langford et al 1989). Loop diuretics might be a better choice than thiazides and angiotensin II receptor type-1 blocker may have some benefit compared with angiotensin converting enzyme inhibitors (Carvajal et al 1995). Calcium channel antagonists do not appear to have a high incidence of ED albeit in some cases prolactin levels increase which could interfere with sexual function. In Table 3 a summary of some alternatives is shown when choosing the appropriate drug regime in cardiovascular, particularly hypertensive patients.

Interaction between treatment of erectile dysfunction and treatment of hypertension

Phosphodiesterase 5 inhibitors and arterial blood pressure

As mentioned above, phosphodiesterase 5 inhibitors, such as sildenafil, vardenafil and tadalafil, inhibit the breakdown of cGMP in tissues with significant phosphodiesterase 5 activity, eg, the penile vasculature, resulting in enhanced erections.

Phosphodiesterase 5 is also expressed in systemic vascular smooth muscle cells including the arterial, venous, pulmonary and coronary network; bronchial smooth muscle cells; platelets and the central nervous system (Wallis et al 1999).

Table 3 Medical therapy, incidence of erectile dysfunction, and potential alternatives

Drug	Potential alternative	Comment
thiazide diuretics	loop diuretics	thiazide diuretics: higher incidence of erectile dysfunction than β-blockers
β-blockers	angiotensin converting enzyme inhibitors, angiotensin II receptor type-1 blockers, calcium channel blockers	prognostic benefit after myocardial infarction or in heart failure needs to be weighed against side effects
aldosterone receptor antagonists (spironolactone)	potassium sparing diuretics or eplerenone in the treatment of congestive heart failure	limited information
fibrates	statins	-
angiotensin-converting enzyme inhibitors	angiotensin II type-1 receptor blockers	angiotensin II receptor type-1 blockers may even improve sexual function

Notes: Some of the alternatives may not be applicable in individual patients
Compiled according to Langford et al. (1989), Carvajal et al. (1995), Llisterri et al. (2001), Ralph (2000), Rizvi et al. (2002), Schachter et al. (2000), and Bruckert et al. (1996).

Looking at the mechanism of action, one could imagine that administration of phosphodiesterase 5 inhibitors, intended to treat ED, could also alter vascular hemodynamics, lower blood pressure or affect the coronary circulation. This might be of special interest in hypertensive patients or patients on various antihypertensive drugs. However, in general, blood pressure lowering effects of the three phosphodiesterase 5 inhibitors do not appear to be a major problem. Oral administration of sildenafil reduced systolic and diastolic blood pressure by 7–10 mmHg in a non-dose dependent manner (Zusman et al 1999) without any evidence of significant reflex tachycardia. Similarly, effects of sildenafil on blood pressure in hypertensive patients on multiple antihypertensive drugs (angiotensin converting enzyme inhibitors, β-adrenoceptor blockers, calcium channel antagonists) were minimal and well-tolerated (Webb et al 1999; Kloner et al 2001; Vardi et al 2002). Comparable results were obtained with newer phosphodiesterase 5 inhibitors vardenafil and tadalafil (Kloner et al 2003a, b; Pomara et al 2004; Kloner et al 2004). A statistical evaluation of side-effects of sildenfil after its approval did not demonstrate an increased cardiovascular risk as compared with an adequate reference population (Wysowski et al 2002). However, there are a few, but important exceptions to mention: NO donors, which have a marked blood pressure lowering effect, even if most of them are not used as antihypertensive agents, and α-adrenoceptor blocker, used as antihypertensives and in the treatment of prostate hyperplasia. Patients treated with phosphodiesterase 5 inhibitors must be informed about these interactions.

Interaction of phosphodiesterase 5 inhibitor with antihypertensive treatment

Nitric oxide donors

Looking at the mechanism of vasodilation induced by phosphodiesterase 5 inhibitors, it becomes clear that the amount of preactivation of the guanylate cyclase— NO system may determine the degree of blood pressure lowering in response to phosphodiesterase 5 inhibitors (Cheitlin et al 1999; Webb et al 1999). Therefore, phosphodiesterase 5 inhibitors in combination with any drug serving as a NO donor can lead to life-threatening hypotension, as uncontrolled accumulation of cGMP within the vascular smooth muscle cells can occur. 24 hours, equal to 6 half-lives of sildenafil, should elapse between administration of a nitrate and sildenfil or vice-versa (Cheitlin et al 1999). For vardenafil, with a similar half-life as sildenafil, also 24 hours are required until nitrate oxide donors can be used safely. For tadalafil, however, with a half-life of 17.5 hours, recent studies suggest that at least 48 hours should elapse after the intake of 20 mg tadalafil before nitrates can be administerd (Brock et al 2002; Corbin et al 2002; Emmick et al 2002; Kloner 2002; Kloner et al 2002; Nichols et al 2002). If a patient, who has taken phosphodiesterase 5 inhibitors inadvertently receives nitrates and a marked drop in blood pressure occurs, emergency measures may range from Trendelenburg-position, aggressive fluid resuscitation to intravenous application of adrenergic drugs, or even intra-aortic balloon counterpulsation (Cheitlin et al 1999).

Alpha-adrenoceptor blockers

Another class of drugs used for treatment of hypertension requires special attention: α-adrenoceptor blockers, such as doxazosin and terazosin (used for both arterial hypertension and benign prostatic hypertrophy) and tamsulosin (an α_{1a}-adrenoceptor blocker used in the treatment of prostatic hyperplasia). When vardenafil was first released to the market, it was contraindicated in combination with any α-adrenoceptor blocker as significant hypotension had been observed in some of the initial studies. This appeared also to be the case for tadalafil in combination with non-selective α_1-adrenoceptor blockers (not for tamsulosin). Analysis of subsequent studies, however, suggested that hypotension with these combinations is less significant than initially assumed; and therefore the label "precaution" is now officially used for the combined use of PDE 5 inhibitors and α-adrenoceptor blockers (Auerbach et al 2004; Kloner et al 2004).

As a rule of thumb, a baseline blood pressure of more than 90/60 mmHg is a prerequisite for any PDE 5 inhibitor to be administered. Furthermore, α-adrenoceptor blockers should only be used in combination with PDE 5 inhibitors if other alternatives do not appear to be applicable and only under close medical monitoring.

Summary

In many forms of ED, cardiovascular risk factors, in particular arterial hypertension, seem to be extremely common. While causes for ED are related to a broad spectrum of diseases, a generalized vascular process seems to be the underlying mechanism in many patients, which frequently involves endothelial dysfunction, ie, inadequate vasodilation in response to endothelium-dependent stimuli, both in the systemic vasculature and the penile arteries. Due to this close association of cardiovascular disease and ED, patients with ED should be evaluated for cardiovascular risk factors including hypertension, cardiovascular disease or silent myocardial ischemia. Cardiovascular patients, seeking treatment of ED must be closely examined to determine whether treatment of ED or sexual activity can be recommended without significantly increased cardiac risk according to the guidelines issued from the Princeton Consensus Conference.

While consequent treatment of cardiovascular risk factors should be accomplished in these patients, many antihypertensive drugs may worsen sexual function as a drug specific side-effect. Effective treatment for arterial hypertension should not be discontinued as this, in the long term, most likely deteriorates sexual function. Alternative antihypertensive regimes should be administered with individually tailored drug regimes with minimal side effects on sexual function. Angiotensin II receptor type-1 blockers may be associated with little side-effects or even with a slight improvement of sexual function.

Disclosures

Dr Kloner is a speaker, consultant, and researcher for Pfizer, Lilly ICOS, Bayer, and a consultant to Schering/Plough and King/Palatine.

References

Auerbach S, Gittleman M, Mazzu A, et al. 2004. Simultaneous administration of vardenafil and tamsulosin does not induce clinically significant hypotension in patients with benign prostatic hyperplasia. *Urology*, 64:998–1003.

Bansal S. 1988. Sexual dysfunction in hypertensive men: a critical review of the literature. *Hypertension*, 12:1–10.

Benet AE, Melman A. 1995. The epidemiology of erectile dysfunction. *Urol Clin North Am*, 22:699–709.

Billups KL. 2004. Endothelial dysfunction as a common link between erectile dysfunction and cardiovascular disease. *Current Sexual Health Reports*, 1:137–41.

Blumentals WA, Gomez-Caminero A, Joo S, et al. 2004. Should erectile dysfunction be considered as a marker for acute myocardial infarction? Results from a retrospective cohort study. *Int J Impot Res*, 16:350–3.

Bohlen JG, Held JP, Sanderson MO, et al. 1984. Heart rate, rate-pressure product and oxygen uptake during four sexual activities. *Arch Intern Med*, 14:1745–8.

Brock GB, et al. 1993. Drug-induced male sexual dysfunction. An update. *Drug Saf*, 8:414–26.

Brock H, McMahon CG, Chen KK, et al. 2002. Efficacy and safety of tadalafil for the treatment of erectile dysfunction: results of integrated analyses. *J Urol*, 168:1332–6.

Bruckert E, Giral P, Heshmati HM, et al. 1996. Men treated with hypolipidaemic drugs complain more frequently of erectile dysfunction. *J Clin Pharm Ther*, 21:89–94.

Carvajal A, Lerida MT, Sanchez A, et al. 1995. ACE inhibitors and impotence: a case series from Spanish drug monitoring system. *Drug Saf*, 13:130–1.

Cardillo C, Kilcoyne CM, Quyyumi AA, et al. 1998. A selective defect in nitric oxide synthesis may explain the impaired endothelium-dependent vasodilation in patients with essential hypertension. *Circulation*, 97:851–6.

Cheitlin MD, Hutter AM, Brindis RG, et al. 1999. ACC/AHA Expert consensus document. Use of sildenafil (Viagra) in patients with cardiovascular disease. *J Am Coll Cardiol*, 33:273–82.

Corbin JD. 2002. Pharmacology of phosphodiesterase-5 inhibitors. *Int J Clin Prct*, 56:453–9.

DeBusk RF. 1996. Sexual activity triggering myocardial infarction: one less thing to worry about. *JAMA*, 275:1447–8.

DeBusk R, Drory Y, Goldstein I, et al. 2000. Management of sexual dysfunction in patients with cardiovascular disease: recommendations of the Princeton Consensus Panel. *Am J Cardiol*, 86:175–81.

DeBusk RF. 2000. Evaluating the cardiovascular tolerance to sex. *Am J Cardiol*, 86(suppl):51F–56F.

Derby CA, Mohr BA, Goldstein I, et al. 2000. Modifiable risk factors and erectile dysfunction: can lifestyle changes modify risk? *Urology*, 56:302–6.

Dusing R 2003. Effect of the angiotensin II antagonist valsartan on sexual function in hypertensive men. *Blood Press Suppl*, 2:29–34.

Emmick JT, Stuewe SR, Mitchell M. 2002. Overview of the cardiovascular effects of tadalafil. *Eur Heart J*, 4:H32–H47.

Feldman HA, Goldstein I, Hatzichristou DG, et al. 1994. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol*, 151:54–61.

Ferrario CM, Levy P. 2002. Sexual function in patients with hypertension: implications for therapy. *J Clin Hypertens*, 4:424–432.

Gazzaruso C, Giordanetti S, De Amici E, et al. 2004. Relationship between erectile dysfunction and silent myocardial ischemia in apparently uncomplicated type 2 diabetes patients. *Circulation*, 110:22–6.

Greiner KA, Weigel JW. 1996. Erectile dysfunction. *Am Fam Physician*, 54:1675–82.

Gresser U, Gleiter CH. 2002. Erectile dysfunction: comparison of efficacy and side effects of the PDE-5 inhibitors sildenafil, vardenafil and tadalafil. Review of the literature. *Eur J Med Res*, 7:435–46.

Gross GJ. 2005. Sildenafil and endothelial dysfunction in humans. *Circulation*, 111:721–3.

Hale TM, Okabe H, Heaton JP, et al. 2001. Antihypertensive drugs induce structural remodeling of penile vasculature. *J Urol*, 166:739–45.

Jackson G. 1997. Stable angina: drugs, angioplasty or surgery? *Eur Heart J*, 18:B2–B10.

Jackson G 1999. Erectile dysfunction and cardiovascular disease. *Int J Clin Pract*, 53:363–8.

Jackson G. 2000. Sexual intercourse and stable angina pectoris. *Am J Cardiol*, 86(suppl):35F–37F.

Johannes CB, Araujo AB, Feldman HA, et al. 2000. Incidence of erectile dysfunction in men 40 to 69 years old: longitudinal results from the Massachusetts Male Aging Study. *J Urol*, 163:460–3.

Kaiser DR, Billups K, Mason C, et al. 2004. Impaired brachial artery endothelium-dependent and -independent vasodilation in men with erectile dysfunction and no other clinical cardiovascular disease. *J Am Coll Cardiol*, 43:179–84.

Keene LC, Davies PH. 1999. Drug-related erectile dysfunction. *Adverse Drug React Toxicol Rev*, 18:5–24.

Kim SW, Paick J, Park DW. 2001. Potential predictors of asymptomatic ischemic heart disease in patients with vasculogenic erectile dysfunction. *Urology*, 58:441–5.

Kloner RA, Jarow JP. 1999. Erectile dysfunction and sildenafil citrate and cardiologists. *Am J Cardiol*, 83:576–82.

Kloner RA. 2000. Hypertension as a risk for erectile dysfunction: implications for sildenafil use. *J Clin Hypertens*, 2:33–6.

Kloner RA, Brown M, Prisant LM, et al. 2001. Effect of sildenafil in patients with erectile dysfunction taking antihypertensive therapy. *Am J Hypertens*, 14:515–24.

Kloner RA. 2002. Erectile dysfunction and atherosclerosis. *Curr Atheroscler Rep*, 4:397–401.

Kloner RA, Hutter AH, Emmick JT, et al. 2003a. Time course of the interaction between tadalafil and nitrates. *J Am Coll Cardiol*, 42: 1855–60.

Kloner RA, Mitchell M, Emmick JT. 2003b. Cardiovascular effects of tadalafil in patients on common antihypertensive therapies. *Am J Cardiol*, 92:47M–57M.

Kloner RA, Mohan P, Norenberg C, et al. 2002. Cardiovascular safety of vardenafil, a potent, highly selective PDE-5 inhibitor in patients with erectile dysfunction: an analysis of five placebo controlled trials. *Pharmacol Ther*, 22:1371–6.

Kloner RA. 2004. Cardiovascular effects of 3 phosphodiesterase-5 inhibitors approved for the treatment of erectile dysfunction. *Circulation*, 110:3149–55.

Kloner RA, Jackson G, Emmick JT, et al. 2004. Interaction between the phosphodiesterase 5 inhibitor, tadalafil, and the two α-blockers doxazosin and tamsulosin in healthy normotensive men. *J Urol*, 172:1935–40.

Kostis JB, Jackson G, Rosen R, et al. 2005. Sexual dysfunction and cardiac risk (the second Princeton Consensus Conference). *Am J Cardiol*, 96:313–21.

Langford HG, Rockfold RW, Wassertheil-Smoller S, et al. 1989. Effect of weight loss on thiazide produced erectile problems in men. *Trans Am CLin Climatol Assoc*, 101:190–4.

Levine LA. 2000. Diagnosis and treatment of erectile dysfunction. *Am J Med*, 109**:**3S–12S.

Llisterri JL, Lozano Vidal JV, Aznar Vicente J, et al. 2001. Sexual dysfunction in hypertensive patients treated with lorsatan. *Am J Med Sci*, 321:336–41.

Ludmer PL, Selwyn AP, Shook TL, et al. 1986. Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic coronary arteries. *N Engl J Med*, 315:1046–1051.

MacMahon S, Petro R, Cutler J, et al. 1990. Blood pressure, stroke, and coronary heart disease. Part 1. Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet*, 335:765–74.

McVary KT, Carrier S, Wessells H, et al. 2001. Smoking and erectile dysfunction: evidence based analysis. *J Urol* 166:1624–32.

Moulik PK, et al. 2003. Hypertension, anti-hypertensive drug therapy and erectile dysfunction in diabetes. *Diabet Med*, 20:290–3.

Muller JE, Mittleman MA, Maclure M, et al. 1996. Triggering myocardial infarction by sexual activity. *JAMA*, 275:1405–9.

Muller JE, Kaufmann PG, Luepker RV, et al. 1997. Mechanisms precipitating acute cardiac events. Review and recommendations of an NHLBI Workshop. *Circulation*, 96:3233–9.

Nabel EG, Ganz P, Gordon JB, et al. 1988. Dilation of normal and constriction of atherosclerotic coronary arteries caused by cold pressure test. *Circulation*, 77:43–52.

Nava E, Luscher TF. 1995. Endothelium-derived vasoactive factors in hypertension: nitric oxide and endothelin. *J Hypertens*, 13(suppl 2):S39–S48.

Nichols DJ, Muirhead GJ, Harness JA, et al. 2002. Pharmacokinetics of sildenafil after single oral doses in healthy male subjects: absolute bioavailability, food effects and dose proportionality. *Br J Pharmacol*, 53:5S–12S.

Nicolosi A et al. 2003. Epidemiology of erectile dysfunction in four countries: cross-national study of the prevalence and correlates of erectile dysfunction. *Urology*, 61:201–6.

NIH Consensus Development Panel on Impotence. 1993. Impotence. *JAMA*, 270:83–90.

Nurnberg HG et al. 2003. Treatment of antidepressant-associated sexual dysfunction with sildenafil: a randomized controlled trial. *JAMA*, 289:56–64.

Nusbaum MR. 2002. Erectile dysfunction: prevalence, etiology, and major risk factors. *J Am Osteopath Assoc*, 102:S1–S6.

Park K, Shin JW, Oh JK, et al. 2005. Restoration of erectile capacity in normotensive aged rats by modulation of angiotensin receptor type 1. *J Androl*, 26:123–128.

Pomara G, Morelli G, Pomara S, et al. 2004. Cardiovascular parameter changes in patients with erectile dysfunction using PDE-5 inhibitors: a study with sildenafil and vardenafil. *J Androl*, 25:625–9.

Ralph D, McNicholas T. 2000. UK management guidelines for erectile dysfunction. *BMJ*, 321:499–502.

Reffelmann T, Kloner RA. 2003. Therapeutic potential of phosphodiesterase 5 inhibitors for cardiovascular disease. *Circulation*, 108:239–44.

Reffelmann T, Kloner RA. 2005a. Erectile dysfunction. Assessing risk and managing the cardiac patient. In Broderick GA (ed) Oral pharmacotherapy for male sexual dysfunction. A guide to clinical management. Totowa, New Jersey: Humana Press Inc. pp 199–220.

Reffelmann T, Kloner RA. 2005b. Pharmacotherapy of erectile dysfunction: focus on cardiovascular safety. *Expert Opin Drug Saf*, 4:531–40.

Rizvi K, Hampson JP, Harvey JN. 2002. Do lipid-lowering drugs cause erectile dysfunction? A systemativ review. *Fam Pract*, 19:95–8.

Romeo JH, Seftel AD, Madhum ZT, et al. 2000. Sexual function in men with diabetes type 2: association with glycemic control. *J Urol*, 166:739–45.

Roth A et al. 2003. Prevalence and risk factors for erectile dysfunction in men with diabetes, hypertension, or both diseases: a community survey among 1,412 Israeli men. *Clin Cardiol*, 26:25–30.

Schachter M. 2000. Erectile dysfunction and lipid disorders. *Curr Med Res Opin*, 16:S9–S12.

Schwarz ER, Rodriguez J. 2005. Sex and the heart. *Int J Impot Res*, 17(Suppl 1):S4–6.

Sairam K, Kulinskaya E, Boustead GB, et al. 2001. Prevalence of undiagnosed diabetes mellitus in male erectile dysfunction. *BJU Int*, 88:68–71.

Solomon H, Man J, Wierzbicki AS et al. 2003. Erectile dysfunction: cardiovascular risk and the role of the cardiologist. *Int J Clin Pract*, 57:96–9.

Stein RA. 1977. The effect of exercise training on heart rate during sexual activity in the post-myocardial infarction patient. *Circulation*, 55:738–40.

Stern S. 2005. Symptoms other than chest pain may be important in the diagnosis of "silent ischemia" or "the sound of silence". *Circulation*, 111:e435–e437.

Taddei S, Virdis A, Mattei P, et al. 1993. Vasodilation to acetylcholine in primary and secondary forms of hypertension. *Hypertension*, 21:929–33.

Tobbli JE, Stella I, Mazza ON, et al. 2004. Different effect of losartan and amlodipine on penile structures in male spontaneously hypertensive rats. *Am J Nephrol*, 24:614–623.

Thompson IM, Tangen CM, Goodman PJ, et al. 2005. Erectile dysfunction and subsequent cardiovascular disease. *JAMA*, 294:2996–3002.

Ueno M. 1963. The so-called coition death. *Jpn J Leg Med*, 17:330–335.

Vardi Y, Klerin L, Nassar S, et al. 2002. Effects of sildenafil citrate (Viagra) on blood pressure in normotensive and hypertensive men. *Urology*, 59:747–52.

Walczak MK, Lokhandwala N, Hodge MB, et al. 2002. Prevalence of cardiovascular risk factors in erectile dysfunction. *J Gend Specif Med*, 6:19–21.

Wallis RM, Corbin JD, Francis SH, et al. 1999. Tissue distribution of phosphodiesterase families and the effect of sildenafil on tissue cyclic nucleotides, platelet function and contractile responses of trabeculae carneae and aortic rings. *Am J Cardiol*, 83:3C–12C.

Webb DJ, Freedstone S, Allen MJ, et al. 1999. Sildenafil citrate and blood-pressure lowering drugs: results of drug interaction studies with an organic nitrate and a calcium channel antagonist. *Am J Cardiol*, 83:21C–28C.

Wysowski DK, Farinas E, Swartz L. 2002. Comparison of reported and expected deaths in sildenafil (Viagra) users. *Am J Cardiol*, 89:1331–4.

Zusman RM, Morales A, Glaser DB, et al. 1999. Overall cardiovascular profile of sildenafil citrate. *Am J Cardiol*, 83:35C–44C.