

Erectile Dysfunction, a Sentinel of Cardiovascular Disease... A symptom Not to Be Neglected

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Introduction

Penile erection depends on a complex interaction between neurological stimuli and smooth muscle fibre relaxation within the penis. These neurovascular events are influenced by hormonal and psychological status.

Penile erection is initiated when neurological stimulation results in a decrease in orthosympathic tonus, responsible for penile flaccidity. This stimulation leads to an activation of both the parasympathic system and a nonadrenergic noncholinergic system. The main mechanism controlling for corporal smooth muscle fibre relaxation is the nitric oxide pathway, which, via an increase in cyclic guanosine monophosphate (cGMP) and a drop in intracellular calcium within smooth muscle fibres, causes the opening of the small penile arteries and lacunar spaces of the cavernous body. It is noteworthy that smooth muscle cells are the true agents controlling penile erection. Nitric oxide (NO), produced by nitric oxide synthase (NOS) within an oxygenated medium, is released by afferent nerve terminals subserving the cavernous body, as well as by endothelial cells, under the action of erectogenic stimuli. NO has been shown to play a significant role in regulating both vascular tone and vascular reactivity. As a result, a several-fold increase in penile arterial blood flow occurs. Certain studies have revealed androgens to play a significant role in improving NO-synthase activity.

This increase in penile blood flow alone does not produce a rigid penile erection but allows for the development of penile tumescence. To achieve erection, an additional veno-occlusive phenomenon is required, which largely suppresses venous outflow from the cavernous bodies.

Under normal circumstances, compression of albugineal venules allows the intracavernous compartment to function as a closed system, a real active sponge.

The penis becomes very rigid and at this stage, arterial blood flow significantly decreases until reaching equilibrium with the minor physiological blood escape from the cavernous bodies, which is instrumental in maintaining the erection. The bulbocavernous reflex is

triggered causing ischiocavernous muscles, surrounding the "dead space" on the posterior part of the cavernous bodies, to forcefully contract, resulting in further intracavernous pressure rise.

Ejaculation, along with its orthosympathic activation, inverts the process and causes detumescence. During the return to the flaccid state, cGMP is hydrolysed to guanosine monophosphate by phosphodiesterase type 5 (PDE5) within smooth muscle fibres, with a return of arterial luminae and cavernous body tonus to resting values.

Erectile dysfunction as a barometer of vascular health

Erectile dysfunction (ED) is defined as the persistent inability to achieve and/or maintain an appropriate erection, enabling satisfactory and successful intercourse. The prevalence of erectile dysfunction is high and, according to MMAS study (1), a major American trial in this field of research, ED affects 22% of men aged 22 to 29 years, increasing to 49% among those aged 70 to 79 years. These American findings have been confirmed by more recent European study results. ED is highly age-dependent but also relates to a variety of cardiovascular, urological, neurological, and hormonal risk factors, including penile traumatism.

Lipid anomalies, hypertension, diabetes, smoking, obesity, and lack of exercise are shared risk factors for both cardiovascular diseases and ED. In addition, a variety of medical and social conditions have been shown to increase the risk of developing ED (2, 3) (Table I).

ED is an isolated or combined failure of different psychological, hormonal, neurological, vascular and cavernous body systems that are implicated in causing penile erection.

ED may additionally be caused by various drugs, such as centrally acting antihypertensive drugs, antidepressants, antihistaminics, and antiandrogens. Moreover, its occurrence may be facilitated by misuse of legal or illegal substances, such as tobacco, alcohol, cocaine, heroine, and methadone.

Table I

Clinical and social conditions shown to increase risk of developing erectile dysfunction in comparison with age-matched men

Cardiac disease	2-fold
Hypertension	1.5–2-fold
Diabetes	3–4-fold
Depression	2–3.5-fold
Urinary problems	1.5–2-fold
Low HDL cholesterol	4-fold
Unemployment	2-fold

Table II

Prevalence of ED in the presence of cardiovascular risk factors in the MALES study

Risk factor (RF)	RF prevalence	ED prevalence
No diabetes or other RF	64%	11%
Diabetes	6%	39%
Hypertension	22%	26%
Angina	9%	31%
Hypercholesterolemia	18%	26%
Diabetes and one RF	4%	42%
Diabetes and hypertension	3%	42%
Diabetes and angina	2%	46%
Diabetes and hypercholesterolemia	2%	45%

According to both clinical experience and epidemiological studies, the risk of developing ED is significantly increased in patients presenting concomitant cardiovascular risk factors (MALES study – Table II).

Cardiovascular disease is thus recognised to be the most frequent cause of ED.

In addition, the metabolic syndrome which associates abdominal obesity, insulin resistance, hypertension, and dyslipidemia, is frequently associated with ED. Current evidence strongly suggests that this condition of multifactorial origin is often accompanied by hypogonadism. Currently, due to the accumulation of risk factors, metabolic syndrome is considered to be an important predictor of ED.

In the case of diabetes, atherogenic dyslipidemia (low HDL cholesterol, elevated triglycerides, and increased small and dense LDL particles), hypertension, obesity, smoking, and ED, common shared features of these conditions are vascular corporal endothelial damage and decreased penile blood supply. More precisely, the endothelial lesion resulting from cardiovascular risk factors is associated with inflammatory reactions, vasoconstriction, thrombosis, and atherosclerosis (Fig. 1).

Endothelial injury is also caused by increased oxidative stress with excessive free radical formation, altered NO production, or decreased expression of VEGF (4). Thus, within the endothelial penile system, the loss of functional endothelial integrity and drop in NO bio-

activity induce alterations in smooth muscle reactivity and relaxation, which eventually leads to ED.

Moreover, by altering corporal fibroelastic structures, hypercholesterolemia and diabetes decrease tissue compliance and result in veno-occlusive dysfunction. The penis thus becomes sclerotic, diminishing in size and elasticity.

ED might be a clinical predictor of cardiovascular diseases that have not yet become apparent (5). In fact, while similar mechanisms of tissue ischemia appear to underlie both ED and cardiovascular diseases, the symptoms related to vascular obstruction occur at an earlier time in organs presenting a fine vascular structure such as the penis, as compared to those receiving blood supply from big arteries (myocardial infarct) (6) (Fig. 2).

Percentages of luminal obstruction are presented at the bottom.

An angiographic obstruction exceeding 50% of the vessels' lumen is required for symptoms to occur. The blue part of the figure represents the plaque mass in a patient with isolated ED, whereas the yellow part of the figure illustrates a subsequent stage of atherosclerotic disease, with a more significant plaque mass in a patient with clinically manifest coronary artery disease.

AMI : acute myocardial infarction ; CAD : coronary artery disease ; CVD : cerebrovascular disease ; ED : erectile dysfunction ; PAD : peripheral arterial disease ; TIA : transient ischemic attack (Montorsi 2003).

Several studies have shown that patients with ED present a significantly increased long-term risk for myocardial infarction and cerebrovascular accidents (7, 8). If routine anamnesis would include a questions such as “do you still have good-quality erections”, the patients' answers would enable us to direct complementary explorations towards coronary and carotid arteries, thereby facilitating earlier detection of common and morbid cardiovascular diseases.

According to an exhaustive literature review covering papers published from 2002 to 2008, there was substantial clinical evidence that ED was independently related to subsequent cardiovascular events (mean time interval : 3 years, ESSM 2009), and that 60% of men admitted to hospital for myocardial infarction presented ED of variable intensity (9). This study, as well as other studies support the concept that *ED constituted a unique opportunity for detecting at an early stage a clinically non-apparent cardiovascular disease*. According to this concept, failure of the NO pathway would be the common denominator in the pathophysiology underlying both ischemic heart disease and ED (10).

Treating erectile dysfunction with astonishing efficacy... is the clinician aware of all of the therapeutic benefits ?

Since the launch of sildenafil (Viagra) in 1998, inhibitors of phosphodiesterase type 5 (PDE5i) have been available

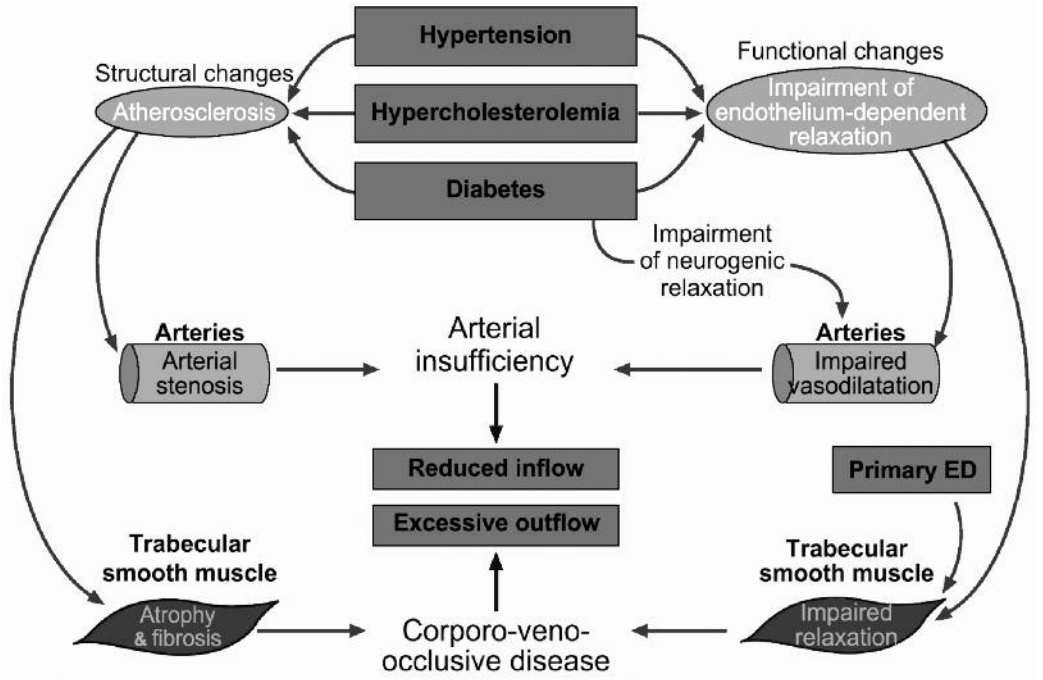


Fig. 1
Erectile dysfunction at the centre of vascular events

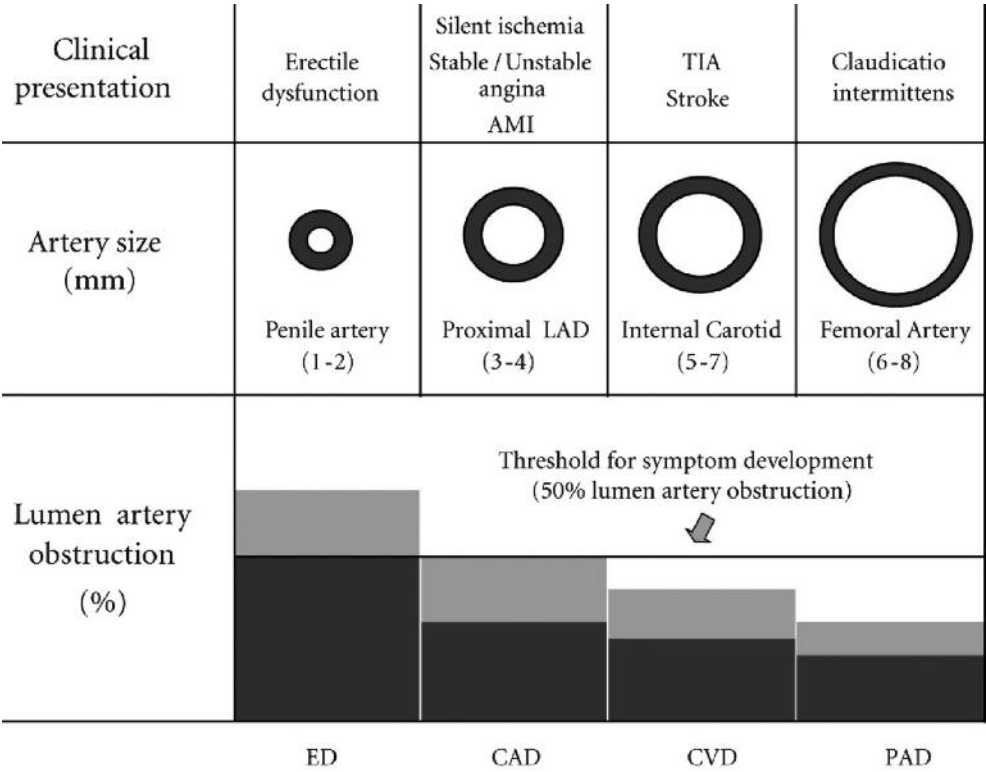


Fig. 2
Arteriosclerotic degradation of different-size arteries : relevance of artery calibre

on the market. Two other products have been extensively used since 2003, notably vardenafil (Levitra®) and tadalafil. These drugs are considered first-line therapy for the majority of ED patients, as they are efficacious (over 65% in an unselected patient population) and devoid of significant adverse events (hot flashes, headaches, dyspepsia, and rhinitis). Although these molecules belong to the same pharmacological class, they differ in terms of selectivity, adverse events, and pharmacokinetic properties (11). These drugs should not be administered in association with nitrate therapy and other NO donors, which are contra-indications to their use. Furthermore, cytochrome P450-mediated drug interactions may occur, and dose adjustments are likely to be required in cases of severe renal or hepatic impairment. For men with pre-existing cardiovascular disease, the Princeton consensus recommends investigating exercise tolerance (capability to easily walk up two floors). A cardiologist consultation is recommended in the case of sedentary patients with more than three cardiovascular risk factors and for men with pre-existing coronary disease, especially if treated using nitrite medications (12).

Overall, PDE5i amplify the effects of endogenous NO by blocking cGMP (second messenger for smooth muscle relaxation) inactivation, thereby increasing its concentration, which facilitates massive smooth muscle relaxation in the penis and better erections.

In clinical practice, goal directed first-line therapy is based on a "test prescription" of one of the PDE5i. Patients are then classified into two groups, as "responsive" or "resistant" to PDE5i.

Responsive patients (more than 65% of ED patients) do not require any additional investigation (13, 14), with the exception of young patients with no cardiovascular risk factors. A medical evaluation is conducted, and reversible risk factors must be corrected and treated.

In fact, in certain ED cases, the sole correction of an existing dyslipidemia using atorvastatine has been shown to improve erectile function (15). The therapeutic management of arterial hypertension in a patient with ED appears to be more difficult, as most antihypertensive medications have a deleterious effect on erectile function, potentially leading to ED aggravation during therapy, which diminishes treatment compliance. Nevertheless, using losartan in patients suffering from both arterial hypertension and ED has resulted in erectile function improvements, with ED levels decreasing from 75.3% to 11.8% within a 12-week time period (16).

There are only few data regarding the beneficial effects on ED produced by normalising blood glucose levels in patients with diabetes. Lifestyle modifications, such as smoking cessation and weight loss, have only little effect on erectile function, whereas correcting a sedentary lifestyle by enhancing physical activity appears to be a more promising approach (17).

These findings, along with those of other authors, raise the question as to whether a combination of long-term medication along with a reduction of risk factors may allow ED to be successfully treated in patients who are responsive to PDE5i. The encouraging results achieved with this approach in some patients suffering from ED may be accounted for by a revalidation of the vascular endothelium (18, 19).

Yet, the overall cardiovascular benefits that ED patients at risk of developing cardiovascular events may gain from long-term PDE5i therapy must still be determined. The results of the first phase 3 and 4 trials with these molecules are encouraging, as they seem to suggest a protective effect of PDE5i therapy. However, such a protective effect still needs to be confirmed in men. According to Radovits (20), cardioprotection may be obtained in diabetic patients who present both endothelial and cardiac dysfunctions along with decreased NO production via increased intracellular cGMP levels. Based on studies conducted on rats rendered diabetic, Radovits showed that vardenafil improved cardiovascular dysfunction induced by an up-regulation of NO-cGMP pathways in the vascular wall and myocardium.

Depending on the clinical condition, first-line therapy is completed by uro-sexological recommendations, cardiovascular prevention measures, and lifestyle modifications within a pluridisciplinary medical team.

Patients, who are resistant to PDE5i, should be referred to specialists and receive second-line or third-line therapies, after having undergone additional complementary investigations. When confronted with a heavier therapeutic approach, some patients may resign themselves to dropping therapy, which is mostly approved upon by the clinician, provided that a causal systemic pathology has been excluded or correctly treated.

Second-line therapy consists in *intracavernous injection of vaso-active drugs*, such as prostaglandin E1 (Caverject®) or papaverine. For this procedure, a muscle-relaxing substance aimed at inducing erection is injected in one of the cavernous bodies so as to attain erection. The most common side effects of this procedure include penile pain, prolonged or priapic erections, as well as local fibrosis. This local therapy may be indicated in patients who are taking nitrates.

Another therapeutic option is the use of a *vacuum constriction device*, also referred to as erection pump, which allows the patient to attain an erection via vacuum suctioning of blood that is trapped in the penis with an elastic constriction device placed at the penis base. The side effects of this therapeutic modality include pain, coldness, trapped ejaculate, and petechiae. This type of therapy is limited to older and motivated patients, who are in stable relationships (21).

Venous surgery has been abandoned, whereas arterial revascularisation surgery is rarely used, mainly in young patients with ED occurring after injuries.

The use of a *penile prosthesis* has proven efficacious in motivated and informed patients, following failure or refusal of all other treatment options (22). These devices are implanted directly within the body and function as substitutes to the erectile apparatus. They are considered third-line therapy.

And testosterone ...

For a good-quality erection, oxygen is chiefly required, as testosterone levels are usually sufficient. Given that the prevalence of both testosterone deficits and ED increases with age, it is tempting to assume that hormonal aging might account for the occurrence of ED in men, as testosterone is involved in both sexual desire and erections (23). However, only few studies have found significant correlations between testosterone levels and sexual parameters in older men. Hypogonadism is observed in only 7.8% of patients with ED, in particular in those older than 50 years (14.7%).

In observational studies involving hypogonadic ED patients, substitutive treatment with testosterone resulted in mitigated effects (36% improvement in non-placebo-controlled studies) (24, 25, 27-29).

Therefore, testosterone deficiency observed in some ED patients does not appear to be the authentic or unique cause of ED. Severe anomalies of penile arteries are found in 42% of patients presenting both ED and testosterone deficiency (30), and an even higher patient percentage is likely to be affected by endothelial dysfunction.

In certain cases, low testosterone levels are the consequence rather than the cause of ED. Interestingly, three studies (25, 31, 32) revealed that successful non-hormonal treatment of ED (intracavernous injections, iPDE5, or penile prostheses) was associated with testosterone level normalisation.

ED-induced sexual hypoactivity, stress, and masked depression are likely to account for the hypogonadism that is associated with a reversible dysfunction of LH activity, under hypothalamic control (31).

The lack of ED improvement following testosterone administration in men presenting both ED and testosterone deficiency might be explained by the fact that androgenic treatment was prescribed too late in the course of ED, at a time when testosterone deficiency had already led to irreversible vascular endothelial dysfunction, partly via the development of insulin resistance and metabolic syndrome (33).

However, despite the poor therapeutic effects of testosterone in this population, hypogonadism should always be sought for in patients with ED, as its

correction improves spontaneous erections (improved cavernous oxygenation), sexual desire (improved partnership based on sexual fulfilment), other hypogonadism-related parameters (mood and lack of energy), as well as the efficacy of PDE5i. Furthermore, correcting hypogonadism might also improve other cardiovascular parameters, such as cardiac compensation and abnormal lipid profiles (22bis, 34-38).

Should other endocrinological problems be detected in the course of the investigations, they must be properly addressed by specific treatments.

Further investigations in view of goal-directed therapy

Complementary examinations are focused on vascular, endocrinological, neurological, or psychosexual aspects. A general laboratory analysis is conducted, depending on anamnesis and physical examination findings. Assessment of testosterone levels is indicated, particularly when suspecting an altered libido.

As primary investigation for vascular assessment, a colour pulsed Doppler ultrasonography of the penis must be performed. To this end, an intracavernous injection of 10 micrograms prostaglandine E1 is carried out, following which cavernous tissue reactivity and appearance, as well as systolic and diastolic flows during the different phases of penile erection phenomenon are assessed.

Dynamic cavernous artery blood-flow studies, along with cavernous ultrasound velocimetry, are considered the gold standard to confirm a cavernous venous escape, suspected on Doppler sonographic findings.

Hypersensitive arteriography of internal iliac arteries and their branches is indicated in selected cases, with eventual stent placement for internal iliac arteries during the procedure.

Conclusions that could be of interest for the surgeons...

Among the causes of ED, endothelial dysfunction is the most common shared physiopathological mechanism. This results in arterial damage, first involving small-calibre blood vessels and erectile tissue prior to affecting coronary and carotid arteries. As the risk factors for ED are identical to those for cardiovascular diseases, the ED symptom should be used as a clinical marker in order to identify patients at risk for subsequent cardiovascular events. Moreover, ED should be part of the recommendations for doctors regarding the prevention of cardiovascular diseases in clinical practice.

The diagnosis of ED is easy, provided that the right question is being asked.

Treatment of ED is simple using PDE5i monotherapy, the potential long-term cardiovascular benefits of which warrant further investigations.

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