Editorial

Erectile Dysfunction and Coronary Artery Disease: A Relationship for Disclosure

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Penile erection is a vascular process, and flow through the small vessels of the penis is very sensitive to their functional and structural changes. Rather than being thought of as a late consequence of a localized vascular disease, vasculogenic erectile dysfunction (ED) is now beginning to be considered an early manifestation of generalized vascular disease. The diagnosis of ED and the subsequent evaluation of underlying cardiovascular risk could enhance overall preventive measures of vascular health in men.

Epidemiology and risk factors

It is estimated that nearly one half of men older than 40 years report some degree of ED.[1] Epidemiological evidence suggests a clear link between ED and risk factors for cardiovascular disease.[1-4] Hypertension, smoking, dyslipidemia, diabetes and obesity stand out, being present in approximately 90% of ED cases, and they are considered predictors of this dysfunction.[3] Conversely, men with ED are more likely to have risk factors such as hypertension than are men without ED[5] and the prevalence of ED is also positively associated with undiagnosed hyperglycemia.[6] Such evidence suggests that ED should be used as an alerting signal to detect and treat undiagnosed hypertension and diabetes.[6]

Pathophysiological considerations

Vasculogenic ED may result from impairment of endothelial dependent and/or independent smooth muscle relaxation (i.e. functional vascular ED, early stages), occlusion of the penile arteries by atherosclerosis (i.e. structural vascular ED, late stages), or a combination of these processes.[7-8] The small diameter of the cavernosal arteries and the relatively high content of endothelium and smooth muscle on a per-unit-volume tissue basis compared to other organs suggests that the penile vascular bed may be a sensitive indicator of systemic vascular disease.[9] From the pathophysiological standpoint, endothelial dysfunction, inflammatory and thrombotic activation, as well as oxidative stress, are common denominators between ED and generalized vascular disease.

Reduced nitric oxide (NO) bioavailability is a cornerstone of the pathophysiology of ED. Dysfunctional endothelial cells lining the penile arterial system and the *corpus cavernosum* produce less NO. As a consequence, phosphodiesterase type 5, abundant in perivascular smooth muscle cells, degrades faster the reduced quantities of cyclic-3',5'-guanosine monophosphate, thus limiting the duration of vasodilation and having a negative impact on obtaining and sustaining an erection.[10] Endothelial dysfunction is not confined to

penile tissue, but is widespread in other vascular beds. Indeed, men with ED exhibit significantly lower brachial artery flow-mediated (endothelium dependent) and endothelium-independent vasodilation.[11] Widespread endothelial dysfunction is further supported by additional findings. Circulating biochemical markers of endothelial cell activation, such as adhesion molecules, are found to be elevated in ED patients without risk factors and without overt vascular damage.[12] Recent studies show that levels of asymmetric dimethylarginine, an endogenous competitive inhibitor of NO synthase, are increased in men with ED.[13] Furthermore, decreased numbers of circulating endothelial progenitor cells have been shown to be an independent predictor for ED.[14]

The role of oxidative stress has been highlighted in *in vitro* studies showing that increased production of reactive oxygen species is associated with decreased normal erectile response, primarily because of inactivation of NO.[10,15]

Inflammation also links ED to generalized vascular disease. Several studies show that the presence and the severity of ED are associated with markers and mediators of subclinical inflammation in men with ED and vascular risk factors, but without clinical evidence of coronary artery disease (CAD).[16] We recently investigated the association of ED with inflammatory and endothelial-prothrombotic activation in men with or without CAD.[17] ED was related to significantly increased circulating levels of such variables, in patients either with or without CAD, suggesting that ED adds an incremental inflammatory and endothelial-prothrombotic activation on top of CAD. Interestingly enough, no significant difference was observed for many inflammatory and endothelial-prothrombotic substances between men with ED only and men with CAD but normal erectile function. This could be interpreted as equivalence between ED and CAD in terms of endothelial or inflammatory activation.

CAD and ED: a close relationship

Once the Massachusetts Male Aging Study[1] established that ED and cardiovascular disease share common risk factors, the question emerged whether ED could be a marker or sentinel for the development of cardiovascular disease.[18] Among patients with *established* CAD, prevalence reports of ED have ranged from 42% to 75%.[19-22] Furthermore, ED is more frequent in diabetic patients with silent CAD than in those without CAD.[23] ED severity but not ED prevalence has also been correlated with coronary plaque burden and extent of CAD.[24] Furthermore, Montorsi et al[24] reported that ED rate differs significantly across patients with established CAD according to coronary clinical presentation and atherosclerosis burden: it is low in acute coronary symptoms and one-vessel disease and high in chronic coronary syndrome.

The tight relationship between ED and established CAD has created enthusiasm about an issue that is possibly more important in clinical terms: could ED be useful as a marker of occult or future CAD? Evidence is continuously expanding (Table 1). Penile peak systolic velocities less than 35 cm/s showed 100% specificity for predicting ischemic heart disease.[28] The incidence of positive exercise stress testing in patients with ED has ranged from 8% to 56%.[25-30] The prevalence and extent of asymptomatic coronary atherosclerosis, as detected by multi-slice computed tomography (calcium score), is significantly higher among patients with ED and cannot be pre-

Table 1. Positive exercise stress test and angiographically documented coronary artery disease in patients with erectile dysfunction and clinically silent coronary artery disease

	Study Population (n)	Age range (yrs)	ED duration (months)	≥2 RF/DM (%)	Positive EST (%)	Significant coronary stenosis
Pritzker MR et al.[25]	50	40-60	NA	80/20	28 (56)	20/42
Kawanishi Y et al.[26]	58	25-78	NA	NA	8 (14)	NA
Kim SW et al.[27]	97	45-75	NA	41/31	8 (8)	NA
Shamloul R et al.[28]	40	>40	>3	NA	12 (30)	NA
Vlachopoulos C et al.[29]	50	41-74	25 ± 21	78/20	12 (24)	9/47
Jackson G et al.[30]	19	39-69	NA	37/none	4 (21)	10/19*

DM – diabetes mellitus; ED: erectile dysfunction; EST – exercise stress test; NA – not available; RF – risk factor. *Assessed by coronary computed tomographic angiography.

dicted by the presence of traditional risk factors for cardiovascular disease.[31] In a recent study, ED was a strong independent predictor of CAD as assessed by nuclear stress testing.[32] Most importantly, as documented in a prospective angiographic study, almost one out of five men without symptoms for CAD, presenting with erectile function abnormalities of vascular origin as their only symptom, have significant coronary artery stenosis.[29] This is a substantially higher proportion than the 4% found in the general population.[33]

An important issue that deserves further investigation is *by how long* the clinical manifestation of ED precedes the clinical manifestation of CAD. According to the "artery size" hypothesis, for a given atherosclerotic burden, the smaller penile arteries suffer obstruction earlier than the larger coronary arteries; hence ED may be symptomatic before a coronary event.[8] Furthermore, in theory, the longer the ED duration, the longer the time of exposure to risk factors and to disease processes, and thus the greater the risk of subclinical or future CAD. In men with ED and CAD, erectile function abnormalities became evident prior to the manifestation (or documentation) of CAD by a mean time interval of 2-3 years.[20,29,34] Based on these reports, this "time window" is of paramount importance, since it provides the opportunity to reveal (any) occult CAD and to aggressively treat cardiovascular risk factors in order to prevent progression of atherosclerosis and development of coronary events, thus ultimately reducing cardiovascular risk.

The relation of ED with coronary events resulting from non-flow-limiting lesions is a challenging issue. The risk of acute coronary syndromes in the overall ED patient population is still poorly quantified, although it seems to be higher than in the population without ED. Due to involvement of inflammation in the rupture of vulnerable plaques, proinflammatory markers/mediators could be integrated in the identification of patients at high risk of acute coronary syndromes in the absence of flow-limiting coronary stenoses.[17]

ED and surrogate markers of cardiovascular risk

Markers of early atherosclerosis, such as intima-media thickness (IMT), and functional arterial indices, such as arterial stiffness, are markers of cardiovascular disease and independent prognosticators of cardiovascular risk.[35-37] Recently, an association between the severity of ED and carotid IMT was demonstrated.[38] In preliminary studies from our laboratory, ED was associated with impaired aortic elastic properties in men with and without CAD.[39] Furthermore, we and others have shown that IMT and aortic stiffness correlate significantly with increasing penile vascular damage assessed by penile color Doppler.[39-40] A combination of penile vascular hemodynamic indexes,[40] markers of early atherosclerosis,[38] arterial stiffness indices,[39] and proinflammatory and endothelial prothrombotic molecules, such as C-reactive protein and fibrinogen,[17] could be of significance for risk stratification of ED patients.

ED as a cardiovascular risk predictor

Overall, the crucial issue to be addressed is whether ED increases the risk of a future cardiovascular event. In a retrospective study, Blumentals et al[41] analyzed 12,825 men with ED and an equal number of men without ED. The cohort of men with ED had a twofold increase in the risk for acute myocardial infarction after adjusting for age at ED diagnosis, smoking and obesity. A large cross-sectional primary care study conducted in Canada assessed the association of cardiovascular disease and ED and found a robust correlation: in men without a diagnosis of cardiovascular disease, the presence of ED was strongly associated with an unfavorable vascular risk profile (odds ratio: 1.31). Particularly among men in their forties, the impact was even greater (relative risk 1.65).[6] Ponholzer et al[42] added to the growing evidence base by evaluating 2495 men in a health-screening project. Compared to subjects without ED, men with moderate/severe ED had a 65% increased relative risk for developing CAD within 10 years, estimated according to Framingham risk profile algorithms (absolute risk: 8.0% for no ED and 13.2% for moderate/severe ED). Finally, Thompson et al[43] made an important step forward. In a large-scale prospective study, ED was independently related to increased cardiovascular events (myocardial infarction, angina, transient ischemic attack, heart failure, non-fatal arrhythmia) with an adjusted hazard ratio of 1.25 over a 5-year follow-up.

Clinical implications

The emerging awareness of ED as a barometer for vascular health and occult or future cardiovascular disease represents a unique opportunity for prevention of vascular disease in all men. ED should be part of a cardiovascular risk assessment. Conversely, a

strict medical surveillance program should be mandatory in ED patients who are asymptomatic for CAD. In this regard, the Second Princeton Consensus Conference guidelines recommend stratification of cardiovascular risk, considering ED in concert with other risk factors.[44] All men with ED and no cardiac symptoms should undergo a detailed assessment of cardiovascular history and clinical examination, as well as blood pressure, fasting lipid profile and glucose measurement. Subsequently, ED patients should be referred for aggressive risk reduction therapy that includes lifestyle advice regarding weight and exercise.[45] Those at increased cardiovascular risk ideally need stress testing with appropriate follow-up.[44]

Type 5 phosphodiesterase inhibitors are the reference class of drugs for ED treatment. Apart from their main mechanism of action to restore vasodilation, they appear to possess pleiotropic properties that include anti-inflammatory, antithrombotic, and vascular protective actions.[46-53] While currently their only additional indication, beyond ED, is idiopathic pulmonary hypertension (exclusively for sildenafil),[54] they show potential to be of benefit in several other conditions, such as CAD, heart failure, pulmonary and systemic hypertension and connective tissue disorders.[55]

On the other side of the coin, risk factor modification, including lifestyle interventions[45,56,57] (such as exercise and weight loss), as well as drugs used in cardiovascular disease prevention and treatment, such as angiotensin converting enzyme inhibitors[58] and statins,[59] apart from reducing cardiovascular risk appear to have a beneficial effect on ED itself.

Conclusions

Available data make a strong argument for the role of ED as an early marker of cardiovascular disease. ED and generalized vascular disease are linked at the pathophysiological level by endothelial dysfunction, activated inflammatory and thrombotic state and increased oxidative stress. Patients with CAD very often have ED, and, importantly, patients presenting with ED as their initial condition have an increased prevalence of silent CAD. ED symptoms appear to precede coronary events by a time window of 2 to 3 years. Most importantly, ED is an independent predictor of future cardiovascular events. While further studies that will address the exact additional risk burden that ED carries are warranted, at present, diagnosis of ED should raise suspicions about early atherosclerosis in the coronary and other vascular beds, even in men who would not otherwise be considered at high risk. A combination of penile vascular hemodynamic indexes, markers of early atherosclerosis, arterial stiffness indices and circulating markers/mediators of inflammatory and thrombotic activation and endothelial dysfunction could further aid risk stratification. Diagnosis of ED calls for engagement of patients in beneficial lifestyle and aggressive risk factor reduction strategies, and should initiate cardiovascular disease assessment in appropriately selected patients.

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