

## REVIEW

# Assessment of endothelial function in the patient with erectile dysfunction: an opportunity for the urologist

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**Although there is now ample evidence that men with manifest coronary, cerebral and peripheral vascular disease and their risk factors are at highest risk for suffering from erectile dysfunction, recent findings demonstrate a strong connection between erectile dysfunction and endothelial dysfunction. This review explores how urologists and other providers may utilize the link between these conditions in clinical practice, compares methods of assessing endothelial dysfunction and finally speculates on how this additional information might impact treatment plans.**

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## Introduction

With 52% of all men age 40–70 suffering from erectile dysfunction (ED) to some degree,<sup>1</sup> urologists are more than twice as likely to screen for ED as general practitioners<sup>2</sup> and have thus become the physicians who are most actively engaged in identifying and treating this condition. A growing body of research is connecting ED to the premier cause of mortality, cardiovascular disease (coronary artery disease, CAD)<sup>3</sup> in men. Gazzaruso *et al.*<sup>4,5</sup> showed high rates of ED in men with diabetes and angiographically documented overt and silent CAD. The prevalence of ED was about eight times higher in patients with CAD. Montorsi *et al.*<sup>6</sup> discovered an ED prevalence of 49% in men with symptomatic CAD, and patients stated that they noticed ED on average 39 months before the onset of angina. According to a pooled analysis, normal penile duplex results virtually excluded CAD;<sup>7</sup> conversely, a high proportion of men with ED<sup>8</sup> had silent CAD on coronary angiography and impaired coronary

flow reserve.<sup>9,10</sup> Salomon *et al.*<sup>11</sup> demonstrated a strong correlation between ED and burden of disease in 132 men with CAD and Nurkalem *et al.*<sup>12</sup> showed slow coronary blood flow in men with ED. Pritzker<sup>13</sup> showed that among 50 men with vasculogenic ED and no cardiac symptoms 28 had abnormal exercise tolerance testing (ETT) results. In a large group of patients of more than 9000 men enrolled in the Prostate Cancer Prevention Trial, ED was found to independently predict cardiovascular disease at a rate similar or even greater to that found in smokers, patients with strong cardiovascular family history or hypercholesterolemia.<sup>14</sup> ED and CAD are both worsened by the components of the metabolic syndrome:<sup>15</sup> dyslipidemia,<sup>16</sup> impaired glycemic control,<sup>17</sup> central obesity<sup>18</sup> and hypertension,<sup>19</sup> in addition to smoking<sup>20</sup> and physical inactivity.<sup>21,22</sup> However, we now know that that the underlying mechanism of pathophysiology for both ED and CAD is endothelial dysfunction.<sup>23,24</sup> In both cases, a deficiency of the vasorelaxing factor nitric oxide (NO) is brought about by impaired production or increased degradation by reactive oxidant species. NO is synthesized by nitric oxide synthase (NOS) from the amino acid L-arginine. It is vital in vasodilation, modulation of smooth muscle cells and the inhibition of cellular adhesion, making the endothelium a highly sensitive and reactive response element.<sup>25</sup> Endothelial dysfunction is seen as the first step toward the generation of atherosclerotic plaques,<sup>26</sup> and can be demonstrated in patients with the cardiovascular risk factors

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mentioned above.<sup>27,28</sup> It is therefore not surprising that Kaiser *et al.*<sup>29</sup> found endothelial dysfunction in men with ED and no CAD.

## Assessing endothelial function

However, the multitude of methods and locations in which endothelial function can be measured can easily cause confusion. We have compiled a list of common options found in the literature (Table 1):

### Serum markers

- Endothelin-1 (ET-1) is a potent vasoconstrictor and proinflammatory peptide<sup>30,31</sup> normally secreted in a paracrine fashion from endothelial cells,<sup>32</sup> but can also be synthesized by macrophages.<sup>33</sup> In an excellent review, Boehm and Pernow<sup>34</sup> enumerate dozens of studies in which ET-1 is associated with endothelial dysfunction, inflammation and vasoconstriction, whereas blockade of ET-1 receptors leads to improved

endothelial function with increased availability of NO. Of the serum markers studied, ET-1 is probably the one that is closest to achieving clinical relevance.

- Asymmetrical dimethylarginine (ADMA) is an endogenous analogue of L-arginine and competitively inhibits NOS.<sup>35</sup> Elevated plasma ADMA levels are not only associated with impaired physiologic measures of endothelial dysfunction, such as flow-mediated dilation (FMD),<sup>36,37</sup> but have also been shown to predict cardiovascular events.<sup>37–40</sup> A link to CAD and ED has been firmly established.<sup>41,42</sup> However, one study found that ADMA production was not correlated to decline of endothelial function with aging.<sup>43</sup>
- Inflammatory markers, such as interleukin-6 (IL-6),<sup>44–46</sup> Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ )<sup>45</sup> or C-reactive protein (CRP)<sup>46</sup> have all been associated with impaired endothelial function, cardiovascular events and with ED.<sup>47,48</sup> Elevated CRP levels have also been found to significantly correlate with vascular ED as measured by penile Doppler.<sup>49</sup>
- Finally, markers of cellular adhesion, such as E-selectin,<sup>50</sup> intercellular adhesion molecule-1

**Table 1** Methods of assessing endothelial function

Method	Characteristic	Advantages	Disadvantages
<b>Serum markers</b>			
ET-1	Proinflammatory peptide	Blood draw	Not widely available
ADMA	Competitive inhibitor of NOS	Some prospective clinical data	Not widely available
CRP	Inflammatory marker	Plenty of data in cardiovascular disease and ED, widely available	May be false, high in inflammation/infection
IL-6, TNF- $\alpha$	Inflammatory markers		Not widely available
ICAM-1, VCAM-1, E-selectin	Cellular adhesion markers		Expensive, not widely available
vWF, PAI-1	Thromboembolic markers	vWF is widely available	Not a lot of data in ED
<b>Cellular markers</b>			
cEPCs	Circulating endothelial progenitor cells promoting vasculogenesis	Increasingly good clinical data on correlation with CAD and ED	Expensive, not yet widely available
<b>Imaging</b>			
IMT	Depicts pre-atherosclerotic intimal hyperplasia	Good longitudinal clinical data from large studies	Operator dependent, needs referral to radiologist or vascular lab
<b>Physiologic</b>			
LDF	Describes small-vessel endothelial function	Noninvasive	Susceptible to changes in autonomic nervous function and vasomotor tone
FMD	Reactive hyperemia of brachial artery	Gold standard of measuring endothelial function, large clinical studies correlating results with CAD risk, noninvasive	Not a lot of clinical data with ED, not widely available
PAT	Reactive hyperemia of arterioles	Very easy to perform in office, less operator dependent, mounting clinical data with ED and CAD	Operator dependent, usually needs referral to vascular lab or radiologist

Abbreviations: ADMA, asymmetrical dimethylarginine; CAD, coronary artery disease; CRP, C-reactive protein; cEPCs; circulating endothelial progenitor cells; ED, erectile dysfunction; ET-1, endothelin-1; FMD, flow-mediated dilation; ICAM-1, intercellular adhesion molecule-1; IL-6, interleukin-6; IMT, intima-media thickness; LDF, laser Doppler fluximetry; NOS, nitric oxide synthase; PAI-1, plasminogen-activator inhibitor type-1; PAT, peripheral arterial tonometry; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; vWF, von Willebrand factor.

(ICAM-1)<sup>44,51</sup> or vascular cell adhesion molecule-1 (VCAM-1)<sup>46</sup> and thrombogenesis, such as von Willebrand factor (vWF)<sup>52</sup> or plasminogen-activator inhibitor type-1 (PAI-1)<sup>53</sup> have also been associated with endothelial dysfunction and increased risk of CAD.<sup>54</sup>

This underlines the importance of inflammation and cellular adhesion in early atherosclerosis,<sup>55</sup> but—with the exception of CRP—so far has not resulted in increased clinical usability. In addition, there is doubt exactly how soluble these cell adhesion molecules are.<sup>56</sup> Serum markers are easily obtained by blood draw. However, with the exception of CRP, most markers are not commonly run in commercial labs, and they can also be elevated in a multitude of other inflammatory processes.

#### Cellular markers

When the endothelium is damaged, circulating endothelial progenitor cells (cEPCs) from the bone marrow<sup>57,58</sup> are activated in the bloodstream<sup>59</sup> and mature into endothelial cells that help repair the site of injury.<sup>60–62</sup> This process, called vasculogenesis,<sup>61</sup> is impaired as documented by low levels of cEPCs in ED<sup>63</sup> and CAD.<sup>64</sup> In fact, Hill *et al.*<sup>65</sup> found that decreased cEPC levels correlated with endothelial dysfunction even better than the subjects' Framingham risk scores. In sharp contrast, mature circulating endothelial cells after detachment from the intima are associated with endothelial disruption.<sup>66</sup> Determination of cEPC levels is performed with flow cytometry, targeting CD34, AC 133 and VEGFR2.<sup>59</sup> This is not a test that is widely commercially available.

#### Imaging

Intima-media thickness (IMT) of the common carotid artery is measured after visualization by ultrasonography. IMT has been found to correlate with other measures of endothelial function, such as FMD,<sup>67–69</sup> ET-1<sup>70</sup> or E-selectin.<sup>71</sup> Data from the Framingham Heart Study show significant correlation with inflammatory markers, such as CRP or IL-6, particularly in smokers.<sup>72</sup> It has also been firmly correlated with ED.<sup>73</sup> Despite its noninvasiveness and reasonably good reproduction of data in longitudinal settings, interpretation is hampered by discordant measurements hailing from operator variability.<sup>74</sup>

#### Physiological measurements

As the endothelium gleams its remarkable properties from its adaptation to various stimuli *in vivo*, the most valid measurements of its function should be of a physiological nature. One can discern between

determination of central and peripheral endothelial function or between invasive and noninvasive techniques.

*Flow-mediated dilation of the brachial artery.* All physiologic assessments incorporate a stimulus that activates NO-dependent vasodilation mediated by the endothelium. Although studies exist with laser Doppler fluximetry (LDF),<sup>75,76</sup> FMD of the brachial artery with ultrasonographic assessment has become the most widely published standard in the assessment of endothelial dysfunction.<sup>77</sup> Briefly, arterial occlusion with a blood pressure cuff for 5 min and subsequent release leads to reactive hyperemia and local endothelial activation. When this is performed on the patient's arm, increased shear stress leads to endothelium-dependent dilation of the brachial artery, which can be measured and quantified by ultrasound. The results can then be contrasted to endothelium-independent dilation provoked by administration of nitroglycerin.

Endothelial function of the brachial artery as measured by FMD has long been firmly linked to coronary endothelial function<sup>78</sup> and predicts CAD.<sup>79</sup> Numerous recent studies have solidly connected impaired FMD with ED. Kaiser *et al.*<sup>29</sup> were able to demonstrate worsened FMD in 30 men with ED without manifest CAD. Chiurla *et al.*<sup>80</sup> had similar findings in 70 men with ED, as opposed to better endothelial function in 73 men without ED, again in patients without manifest CAD (although results also correlated with higher calcium scores). In addition, Yavuzgil *et al.*<sup>81</sup> found vasculogenic ED to be associated with impaired FMD. Kaya *et al.*<sup>82</sup> also showed worse FMD in 32 men with diagnosed vasculogenic ED and no CAD or diabetes, compared to 25 controls.

Although FMD is noninvasive and the most widely published method to evaluate endothelial function, problems with reproducibility persist. Corretti *et al.*<sup>77</sup> have sought to establish guidelines for FMD, but a variety of factors continue to influence the quality of the study. Timing of the measurement of dilation is crucial and will yield altered results if missed by as much as 15 s. There is still no consensus whether the blood pressure cuff for induction of hyperemia should be placed on the upper or lower arm. Results are highly operator dependent and can be confounded by changes in baseline diameter of the brachial artery.<sup>77</sup>

*Peripheral arterial tonometry measuring reactive hyperemia.* A more recent method of assessing endothelial function is peripheral arterial tonometry measuring reactive hyperemia (RH-PAT). This Food and Drug Administration (FDA)-approved office-based technique uses a finger probe to assess digital volume changes accompanying pulse waves after inducing reactive hyperemia with a blood pressure

cuff on the upper arm<sup>83,84</sup> (Endo-PAT 2000, Itamar Medical Ltd, Caesarea, Israel). RH-PAT has been extensively correlated to early and clinically relevant CAD.<sup>84–89</sup> For instance, RH-PAT results were significantly impaired in patients with exercise-induced myocardial ischemia.<sup>87</sup> More importantly, it is similar to FMD in representing a true physiological reflection of peripheral endothelial function,<sup>90–92</sup> and is particularly useful in conditions such as diabetes<sup>93–95</sup> or the metabolic syndrome<sup>96,97</sup> that impair endothelial function. RH-PAT results have also been found to correlate well with coronary endothelial function. RH-PAT is a 15 min noninvasive assessment that can be performed in an office setting. Furthermore RH-PAT, when compared to FMD, requires less specialized training, and the results are not operator dependent.<sup>83,84,98</sup>

## Relevance to the clinical urologist

The equivalence of ED and endothelial dysfunction in pathophysiology and screening has important implications for the forward-thinking urologist on three levels:

First, assessment of endothelial dysfunction may be used in the future to replace the more invasive penile Doppler to help determine ED etiology. Very recently, several groups<sup>99,100</sup> have demonstrated that the severity of the endothelial dysfunction correlated with ED etiology. Endothelial function was significantly worse in subjects with arteriogenic ED as demonstrated by penile Doppler than in patients with other forms of ED (psychogenic, venous occlusive dysfunction). Several urology practices and men's health centers in the United States and Europe have therefore incorporated assessment of endothelial function in their diagnostic algorithms. At the last annual meeting of the Sexual Medicine Society of North America, Khera *et al.*<sup>101</sup> presented data obtained by RH-PAT (Endo-PAT 2000, Itamar Medical Ltd) indicating that screening for endothelial dysfunction in ED population is useful in establishing cardiovascular risk in the urology office setting and can help differentiate vasculogenic ED from other etiologies. Prospective scientific as well as epidemiological studies using this technology are ongoing at numerous medical facilities.

This connection illustrates the second implication of the connection between endothelial function and ED for the practicing urologist: Once the diagnosis is established, vasculogenic ED should be regarded as the harbinger of future cardiovascular disease,<sup>102</sup> particularly because patients report the onset of ED years before CAD.<sup>6,11</sup> The Princeton II consensus guidelines therefore highlighted this role, invoking common risk factors and pathophysiology mediated through endothelial dysfunction.<sup>103,104</sup>

Recommendations include that all men with ED should undergo a full medical assessment. Otherwise unexplained ED should be treated as a cardiovascular derivative until proven otherwise. These patients should therefore undergo standard screening for vascular disease, including elective ETT for risk stratification.<sup>103</sup> Similarly, the Minority Health Institute issued an algorithm that demands aggressive assessment for overt or occult cardiovascular disease in all men with ED.<sup>24</sup> Montorsi *et al.*<sup>7</sup> recommend additional noninvasive tests for men with intermediate cardiac risk. Going by the standardized Framingham risk score, this risk category represents almost 40% of the male US population. It is defined by 10–20% risk of experiencing a cardiovascular event over the subsequent 10 years.

Just how important the role of the urologist can be in helping discover cardiovascular disease was demonstrated by a study by Smith *et al.*,<sup>105</sup> in which 40% of patients presenting with ED to the urologist's office were diagnosed with new dyslipidemia. Although the cardiovascular benefits of diagnosis and treatment of dyslipidemia are undoubted, one would not define the prescription of statin therapy as a core task for a urologist. However, if urologists are the first physicians to detect ED, one can make a solid argument that they should be the first providers to diagnose and treat endothelial dysfunction.

This leads us to the third and final important implication of endothelial dysfunction for the practicing urologist: treatment. The role of the urologist is particularly evident as both conditions, ED and endothelial dysfunction, respond to the same agents. Phosphodiesterase-5 (PDE-5) inhibitors decrease breakdown of cyclic guanosine monophosphate in the smooth muscle cell, thereby enhancing the downstream effects of NO.<sup>106</sup> PDE-5 inhibitors not only favorably affect erections,<sup>107</sup> but also hold significant promise for endothelial function, as PDE-5 is expressed throughout the vasculature.<sup>108</sup> This hope is based on favorable outcomes from trials with daily PDE-5 inhibitors improving endothelial function. Though it is common practice to prescribe episodic PDE-5 inhibitors for ED, chronic activation of the eNOS pathway with daily administration of PDE-5 inhibitors<sup>109,110</sup> can 'salvage' a significant number of patients with ED who have not responded to on-demand dosing.<sup>111,112</sup> It is not at all surprising that although single-dose administration of PDE-5 inhibitor is known to somewhat increase cPEC levels,<sup>113</sup> several trials with chronic administration of tadalafil have uniformly resulted in drastically increased mobilization of cEPCs and improved peripheral endothelial function as measured by FMD<sup>114,115</sup> in men with ED. Chronic administration of tadalafil for 1 month also resulted in pronounced reductions in CRP, VCAM-1 and ET-1, remarkably with sustained effect beyond the treatment period.<sup>116,117</sup> The decrease in ET-1 was confirmed in a small study with men suffering from systemic

sclerosis.<sup>118</sup> Similar results for numerous markers of endothelial function were seen with sildenafil three times daily in men with type 2 diabetes mellitus.<sup>119,120</sup> This brings us back to the role of the practicing urologist: response to treatment of ED with PDE-5 inhibitors is best in patients with vasculogenic ED and, due to the shared pathophysiology, can be predicted based on peripheral endothelial function.<sup>99</sup> It appears that chronic PDE-5 inhibitor therapy is required to achieve sustained improvement in endothelial function. Rosano<sup>117</sup> demonstrated improved endothelial function following chronic tadalafil use persisting for up to 2 weeks after cessation of therapy. In a prospective crossover study, Aversa *et al.*<sup>116</sup> demonstrated that improvement in endothelial function was noted only with chronic tadalafil therapy and not with on-demand dosing for sexual function. Not surprisingly, tadalafil was recently approved by the FDA and in Europe for daily dosing.

We therefore not only support published algorithms that demand a greater involvement of the urology community in screening for cardiovascular disease; but also suggest in-office assessment for endothelial dysfunction in the ED population with possibly more aggressive cardiologic evaluation. Taking this responsibility to the next level, urologists should consider offering their patients treatment of both ED and endothelial dysfunction with daily PDE-5 therapy.

In conclusion, it is now common understanding that vasculogenic ED and endothelial dysfunction are tightly linked if not identical, and that they derive from an impaired NO pathway. Increasingly available options of determining peripheral endothelial function in the office setting can help diagnose the presence of vasculogenic ED and endothelial dysfunction, and thus offer predictive value regarding therapeutic response. With this knowledge in mind, primary care physicians, cardiologists and urologists should work together for the benefit of their patients to diagnose and treat cardiovascular disease (and ED) earlier. Finally, and most importantly, once endothelial dysfunction and ED are determined, endothelial conditioning with chronic PDE-5 inhibitor treatment may be of great benefit to the patient.

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