



## Editorial and Rebuttal from Authors

referring to the article published on pp. 979–985 of this issue

# Is ED Still Only Equal to ED?

Andrea Salonia\*

Department of Urology, University Vita-Salute San Raffaele, Via Olgettina 60, 20132 Milan, Italy

Personally, I believe that the history of sexual medicine is connected with the development of the concept that sexual health is closely related with men's overall cardiovascular well being. In this context, the significant connections which have been demonstrated between cardiovascular disorders (CVD) and erectile dysfunction (ED) have significantly contributed to “dignify” the field of sexual medicine, at least throughout the last decade.

Step by step, researchers have learned (1) that ED is clearly a more frequent complaint in patients with concomitant CVD and medical comorbidities such as hypertension, hypercholesterolemia, coronary artery disease (CAD), and diabetes mellitus (DM) [1]; (2) that the co-presence of ED and CVD is mostly causal, since risk factors for both conditions are often exactly the same (above all, cigarette smoking) [2]; (3) that endothelial dysfunction is the potential pathophysiological link between ED and CVD, since an inadequate endothelial-dependent vasodilatation seems to occur in those cases of vascular erectile function impairment and anginal syndrome [3,4]; and (4) that ED might be considered as an early marker for latent CAD and ischemic heart disease [5,6]. The latter aspect concludes the formal “ennobling of a quality of life” parameter, thus prompting ED towards a so-called “quoad vitam” condition as a potential predictor of cardiovascular health. Even more, ED severity might be associated with poor cardiovascular prognosis in adult diabetic men with no CAD [3,7,8].

Several prominent disease states, including hypertension, heart failure, and atherosclerosis,

may actually present different manifestations of endothelial dysfunction. While a plethora of different studies have confirmed a close association between ED and any subsequent peripheral vascular disease [9], Vardi et al [10] suggest the new concept that an impaired penile endothelial function may predict the subsequent onset of a systemic endothelial disorder and a potentially consequential CVD. Likewise, these findings highlight the point that there could be an impaired “locally confined” penile endothelial dysfunction with a concomitant preserved systemic counterpart [10].

This study provides numerous points with an interesting link to different aspects in both the basic science and the sexual medicine fields.

### 1. What does endothelial dysfunction really mean?

Normally, the endothelium performs several homeostatic functions; for instance, it has an important regulatory role in the maintenance of vascular homeostasis, vascular tone (including vasodilatation and an adequate blood flow) and preserving a nonthrombogenic blood–tissue interface, since it prevents platelets and inflammatory cells from adhering to the vascular surface [11]. Injury to the vascular wall with subsequent endothelial dysfunction alters these important regulatory functions, leading to a state of abnormal endothelial function. In this context, endothelial dysfunction can be an indicator of the susceptibility to develop

cardiovascular disease, since it may be considered as an early marker for the presence of subclinical atherosclerosis. Indeed, individuals with manifest CAD as well as subclinical cardiovascular disease show evidence of depressed endothelial function in the coronary artery as well as in the other arterial beds [11–14]. Moreover, the endothelium releases a number of different vasorelaxant products, such as adenosine; prostaglandins; and, even more important, nitric oxide (NO). The past 2 decades have seen an explosion in the understanding of the role of NO biology; in the field of sexual medicine, NO “prosaically” acts as the major “subject” of penile vasorelaxation, eventually promoting the erection. In their elegant study, Vardi et al [10] supported the well-established theory that an endothelial dysfunction may causally reduce the ability of the endothelial cells to release vasorelaxant products, including endothelial-derived NO, which is produced by endothelial NO synthase (eNOS) in response to increased blood flow, to maintain the tumescence phase of the erection [10]. Understanding of the mechanisms leading to endothelial dysfunction has improved, including the notion that dysfunctional eNOS, at least partially due to the deficiency of the eNOS cofactor tetrahydrobiopterin, likely plays an important role [15]. Our interest in this latter volatile molecule is also supported by the fact that endothelial dysfunction shares with ED a dependence on a common pathway through the release of NO, thus leading to a significant pathophysiologic network [16].

## 2. Why is a locally confined endothelial dysfunction good news?

Flow-mediated dilatation (FMD) and other modalities [17,18] that rely on postischemic reactive hyperemia to indirectly and noninterventionally assess the endothelial function in the peripheral vasculature are usually considered to study any eventual impairment as a marker of systemic endothelial function. An impaired FMD, for instance, has been closely, although controversially, related to the morphologically and clinically angiographic extent of CAD [19–23]. The findings of Vardi et al [10] concerning the existence of a selective local penile vasculopathy in ED patients, regardless of the systemic haemodynamics, actually highlight the idea of an organ-specific endothelial damage. They also strongly support the real “advantage” of a relatively non-health-threatening and peripherally focused condition (ED, ndr) as a potent predictor of real life-threatening disorders

such as CAD and ischemic heart disease [5]. We could be allowed to apply a so-called preventive medicine in those patients complaining only of ED; this is mighty prospective information! Cardiac and systemic vascular prevention could be achieved by the detection and treatment of peripheral endothelial dysfunction with relatively noninvasive methods [18].

## 3. Endothelial function represents a valuable surrogate end point to assess the impact of therapeutic interventions

It is in this context that the potential usefulness of the endothelial circulating progenitor cells (EPCs) as a therapeutic tool could be considered. EPCs are a population of pluripotent cells which originate from the haematopoietic stem cells in the bone marrow and that migrate into the peripheral circulation with the specific capacity to differentiate themselves into formal endothelial cells [24]; EPCs have been demonstrated to restore endothelial function, enhance angiogenesis, promote vascular repair, and diminish atherosclerosis [25–27]. Overall, EPCs may reach sites of neovascularisation and endothelial damage and then differentiate into mature endothelial cells, thus contributing to endothelial repair [28,29]. What is important for ED? Reduced levels of circulating EPCs have been suggested as an independent risk factor for ED [30]. Vardi et al [10] have demonstrated that in patients with ED, there can be a localised impairment of the endothelium without any concomitant systemic involvement. This is great, since this finding supports the idea of causally treating ED patients. A number of reports have described the potential usefulness of the phosphodiesterase type 5 inhibitors (PDE5-Is) as a continuous treatment for restoring ideal or adequate peripheral endothelial function [31–37]. Although criticism exists, I would quote in this context a few studies dealing with the use of PDE5-Is to increase the overall amount of EPCs [29,38,39] for their potential long-term clinical applicability. Of particular interest are a number of animal studies regarding the use of the PDE5-Is. Behr-Roussel et al [37], with their usual great scientific elegance and faultless methodological rigour, recently showed that endothelial dysfunction and oxidative stress associated with insulin resistance can be reversed by daily sildenafil in the animal [36]. In addition, the recent development of methods to deliver both stem and endothelial cells to the penis has kindled a keen interest in treating ED with gene- and cell-based therapies [40–43]. Although there are significant differences

between the two, I consider of major importance the observation that mesenchymal stem cells (MSCs) are pluripotent stromal cells that have the potential to give rise to cells of diverse lineages. Interestingly, MSCs can be found in virtually all postnatal tissues [42]. What is even more appealing to me is that MSCs have also been noted to possess the ability to impart profound immunomodulatory effects *in vivo* [44].

Can we suppose that a focal and discrete impairment of the endothelial function might be locally treated in the future by means of targeted drugs, EPCs, or MSCs? The future will tell us!

**Conflicts of interest:** The author has nothing to disclose.

## References

- [1] Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol* 1994;151:54–61.
- [2] Mannino DM, Klevens RM, Flanders WD. Cigarette smoking: an independent risk factor for impotence? *Am J Epidemiol* 1994;140:1003–8.
- [3] Vlachopoulos C, Rokkas K, Ioakeimidis N, et al. Prevalence of asymptomatic coronary artery disease in men with vasculogenic erectile dysfunction: a prospective angiographic study. *Eur Urol* 2005;48:996–1003.
- [4] Ma RC, So WY, Yang X, et al. Erectile dysfunction predicts coronary heart disease in type 2 diabetes. *J Am Coll Cardiol* 2008;51:2045–50.
- [5] Montorsi F, Briganti A, Salonia A, et al. Erectile dysfunction prevalence, time of onset and association with risk factors in 300 consecutive patients with acute chest pain and angiographically documented coronary artery disease. *Eur Urol* 2003;44:360–5.
- [6] Stuckey BG, Walsh JP, Ching HL, et al. Erectile dysfunction predicts generalised cardiovascular disease: evidence from a case-control study. *Atherosclerosis* 2007;194:458–64.
- [7] Heruti RJ, Uri I, Arbel Y, Swartzon M, Galor S, Justo D. Erectile dysfunction severity might be associated with poor cardiovascular prognosis in diabetic men. *J Sex Med* 2007;4:465–71.
- [8] Brocq ML, Leslie SJ, Milliken P, Megson IL. Endothelial dysfunction: from molecular mechanisms to measurement, clinical implications, and therapeutic opportunities. *Antioxid Redox Signal* 2008;10:1631–74.
- [9] Kovács I, Császár A, Toth J, et al. Correlation between flow-mediated dilation and erectile dysfunction. *J Cardiovasc Pharmacol* 2008;51:148–53.
- [10] Vardi Y, Dayan L, Apple B, Gruenwald I, Ofer Y, Jacob G. Penile and systemic endothelial function in men with and without erectile dysfunction. *Eur Urol* 2009;55:979–85.
- [11] Eaton CB, Liu YL, Mittleman MA, Miner M, Glasser DB, Rimm EB. A retrospective study of the relationship between biomarkers of atherosclerosis and erectile dysfunction in 988 men. *Int J Impot Res* 2007;19:218–25.
- [12] Kugiyama K, Ohgushi M, Motoyama T, et al. Nitric oxide-mediated flow-dependent dilation is impaired in coronary arteries in patients with coronary spastic angina. *J Am Coll Cardiol* 1997;30:920–6.
- [13] Solomon H, Man JW, Jackson G. Erectile dysfunction and the cardiovascular patient: endothelial dysfunction is the common denominator. *Heart* 2003;89:251–3.
- [14] Maas R, Schwedhelm E, Albsmeier J, Böger RH. The pathophysiology of erectile dysfunction related to endothelial dysfunction and mediators of vascular function. *Vasc Med* 2002;7:213–25.
- [15] Landmesser U, Drexler H. The clinical significance of endothelial dysfunction. *Curr Opin Cardiol* 2005;20:547–51.
- [16] Widlansky ME, Gokce N, Keaney Jr JF, Vita JA. The clinical implications of endothelial dysfunction. *J Am Coll Cardiol* 2003;42:1149–60.
- [17] Tamler R, Bar-Chama N. Assessment of endothelial function in the patient with erectile dysfunction: an opportunity for the urologist. *Int J Impot Res* 2008;20:370–7.
- [18] Korkmaz H, Onalan O. Evaluation of endothelial dysfunction: flow-mediated dilation. *Endothelium* 2008;15:157–63.
- [19] Neunteufl T, Katzenschlager R, Hassan A, et al. Systemic endothelial dysfunction is related to the extent and severity of coronary artery disease. *Atherosclerosis* 1997;129:111–8.
- [20] Kirma C, Akcakoyun M, Esen AM, et al. Relationship between endothelial function and coronary risk factors in patients with stable coronary artery disease. *Circ J* 2007;71:698–702.
- [21] Perrone-Filardi P, Cuocolo A, Brevetti G, et al. Relation of brachial artery flow-mediated vasodilation to significant coronary artery disease in patients with peripheral arterial disease. *Am J Cardiol* 2005;96:1337–41.
- [22] Jambrik Z, Venneri L, Varga A, Rigo F, Borges A, Picano E. Peripheral vascular endothelial function testing for the diagnosis of coronary artery disease. *Am Heart J* 2004;148:684–9.
- [23] Celermajer DS. Reliable endothelial function testing: at our fingertips? *Circulation* 2008;117:2428–30.
- [24] Asahara T, Murohara T, Sullivan A, et al. Isolation of putative progenitor endothelial cells for angiogenesis. *Science* 1997;275:964–7.
- [25] Rafii S, Lyden D. Therapeutic stem and progenitor cell transplantation for organ vascularisation and regeneration. *Nat Med* 2003;9:702–12.
- [26] Asahara T, Kawamoto A. Endothelial progenitor cells for postnatal vasculogenesis. *Am J Physiol Cell Physiol* 2004;287:C572–9.
- [27] Aicher A, Zeiher AM, Dimmeler S. Mobilizing endothelial progenitor cells. *Hypertension* 2005;45:321–5.
- [28] Dimmeler S, Zeiher AM. Vascular repair by circulating endothelial progenitor cells: the missing link in atherosclerosis? *J Mol Med* 2004;82:671–7.
- [29] Foresta C, Caretta N, Lana A, et al. Reduced number of circulating endothelial progenitor cells in hypogonadal men. *J Clin Endocrinol Metab* 2006;91:4599–602.
- [30] Baumhäkel M, Werner N, Böhm M, Nickenig G. Circulating endothelial progenitor cells correlate with erectile func-

- tion in patients with coronary heart disease. *Eur Heart J* 2006;27:2184–8.
- [31] Rosano GMC, Aversa A, Vitale C, Fabbri A, Fini M, Spera G. Chronic treatment with tadalafil improves endothelial function in men with increased cardiovascular risk. *Eur Urol* 2005;47:214–22.
- [32] Sommer F, Schulze W. Treating erectile dysfunction by endothelial rehabilitation with phosphodiesterase 5 inhibitors. *World J Urol* 2005;23:385–92.
- [33] Aversa A, Greco E, Bruziches R, Pili M, Rosano G, Spera G. Relationship between chronic tadalafil administration and improvement of endothelial function in men with erectile dysfunction: a pilot study. *Int J Impot Res* 2007;19:200–7.
- [34] Sánchez A, Villalba N, Martínez AC, García-Sacristán A, Hernández M, Prieto D. Mechanisms of the relaxant effect of vardenafil in rat penile arteries. *Eur J Pharmacol* 2008;586:283–7.
- [35] Guazzi M, Samaja M, Arena R, Vicenzi M, Guazzi MD. Long-term use of sildenafil in the therapeutic management of heart failure. *Am Coll Cardiol* 2007;50:2136–44.
- [36] Schäfer A, Fraccarollo D, Pfortsch S, et al. Improvement of vascular function by acute and chronic treatment with the PDE-5 inhibitor sildenafil in experimental diabetes mellitus. *Br J Pharmacol* 2008;153:886–93.
- [37] Behr-Roussel D, Oudot A, Caisey S, et al. Daily treatment with sildenafil reverses endothelial dysfunction and oxidative stress in an animal model of insulin resistance. *Eur Urol* 2008;53:1272–81.
- [38] Foresta C, Caretta N, Lana A, Cabrelle A, Palù G, Ferlin A. Circulating endothelial progenitor cells in subjects with erectile dysfunction. *Int J Impot Res* 2005;17:288–90.
- [39] Foresta C, Caretta N, Lana A, et al. Relationship between vascular damage degrees and endothelial progenitor cells in patients with erectile dysfunction: effect of vardenafil administration and PDE5 expression in the bone marrow. *Eur Urol* 2007;51:1411–9.
- [40] Bivalacqua TJ, Deng W, Kendirci M, et al. Mesenchymal stem cells alone or ex vivo gene modified with endothelial nitric oxide synthase reverse age-associated erectile dysfunction. *Am J Physiol Heart Circ Physiol* 2007;292:H1278–90.
- [41] Strong TD, Gebaska MA, Champion HC, Burnett AL, Bivalacqua TJ. Stem and endothelial progenitor cells in erection biology. *Int J Impot Res* 2008;20:243–54.
- [42] Nolzco G, Kovanecz I, Vernet D, et al. Effect of muscle-derived stem cells on the restoration of corpora cavernosa smooth muscle and erectile function in the aged rat. *BJU Int* 2008;101:1156–64.
- [43] Sievert K-D, Amend B, Stenzl A. Tissue engineering for the lower urinary tract: a review of a state of the art approach. *Eur Urol* 2007;52:1580–9.
- [44] Abdi R, Fiorina P, Adra CN, Atkinson M, Sayegh MH. Immunomodulation by mesenchymal stem cells: a potential therapeutic strategy for type 1 diabetes. *Diabetes* 2008;57:1759–67.

doi:10.1016/j.eururo.2008.08.068

## Rebuttal from Authors re: Andrea Salonia. Is ED Still Only Equal to ED? *Eur Urol* 2009;55:794–7

Giris Jacob, Yoram Vardi\*

*J. Recanti Autonomic Dysfunction Center and Neurourology Unit, Rambam Medical Center, and Faculty of Medicine, Technion, Haifa, Israel*

Over the last 2 decades, it has become evident that the vascular endothelium is not merely a dormant cell barrier that covers the inner surface of the blood vessels but is a multifunctional cell layer whose functions are crucial in vascular homeostasis. Alterations in endothelial function (EnF) are pivotal for the development of atherosclerosis, which is the greatest health threat to humans in the modern era.

DOIs of original articles: 10.1016/j.eururo.2008.07.041, 10.1016/j.eururo.2008.08.068

\* Corresponding author. Rambam Medical Center, Neurourology Unit, Haifa 31096, Israel. Tel. +972 4 8542819; Fax: +972 4 8542883. E-mail address: yvardi@rambam.health.gov.il (Y. Vardi).

The morphologic changes in the vasculature that occur in atherosclerosis can appear long after the onset of endothelial dysfunction. Erectile dysfunction (ED) is commonly encountered in men with cardiovascular disease. These patients can present with early endothelial dysfunction that contributes to a decrease in penile vascular responses to sexual stimuli.

### 1. Penile and systemic endothelial dysfunction

Cardiovascular diseases and ED share similar etiology and pathophysiology. Usually, the degree of ED correlates with the severity of cardiovascular disease. It has been demonstrated that erectile dysfunction can even precede coronary symptoms; therefore, impairment in erectile function could be a sentinel for the presence of occult cardiovascular disease [1,2].

Organic ED is generally associated with established systemic atherosclerosis that involves the penile vasculature, but it can also present as an