European Heart Journal (2006) **27**, 125–126
doi:10.1093/eurheartj/ehi641

Editorial

Coronary endothelial dysfunction following sirolimus-eluting stent placement: should we worry about it?

Amir Lerman[1] and Eric Eeckhout[2]*

[1] *Division of Cardiovascular Diseases, Department of Internal Medicine, Mayo College of Medicine, 200 First Street, SW Rochester, MN 55902, USA; and* [2] *Cardiology Service, Centre Hospitalier Universitaire Vaudois, 1011 Lausanne, Switzerland*

Online publish-ahead-of-print 8 November 2005

This editorial refers to 'Indication of long-term endothelial dysfunction after sirolimus-eluting stent implantation'† by S.H. Hofma *et al.*, on page 166

Hofma *et al.*[1] report the presence of abnormal coronary vasoconstriction to the endothelium-dependent vasodilator acetylcholine distally to the site of sirolimus-eluting stent (SES) implantation. The investigators prospectively studied 15 patients undergoing stenting for a single *de novo* lesion: nine with a SES and six with a bare metal stent (BMS). Coronary endothelial function was assessed at baseline and 6 months follow-up. The presence of abnormal coronary flow reserve or anatomical differences between the groups was ruled out by the coronary flow response to adenosine using intracoronary Doppler and by intravascular ultrasound, respectively. There was significantly more distal epicardial vasoconstriction to acetylcholine in the SES when compared with the BMS group. The authors concluded that SES might have an adverse effect on local coronary endothelial function. The current study compliments a recent report from Togni *et al.*[2] which demonstrated that exercise-induced coronary vasomotion is abnormal in segments distal to SES.

Thus, recently two reports in the literature demonstrated the presence of coronary endothelial dysfunction related to SES when compared with BMS. However, both studies assessed coronary endothelial function by a different methodology: the current study testing the receptor-dependent response to the endothelial-dependent vasodilator acetylcholine and, Togni *et al.*[2] using exercise-induced shear stress and endothelial-dependent vasodilatation.[1] Taken together, these studies imply that the phenomenon of coronary endothelial dysfunction following SES is more generalized and not depending on a specific pathway.

The endothelium is a monolayer of endothelial cells lining up the lumen of the vascular bed, strategically located from a mechanical and metabolic point of view, separating the vascular wall from the circulation and its blood components.[3] A healthy endothelium regulates vascular tone and sustains an anti-thrombotic milieu by the secretion of various substances. They mediate vasodilatation (nitric oxide), exert anti-inflammatory and anti-aggregatory effects on platelets (prostaglandins) or have anti-coagulant or fibrinolytic properties (tissue plasminogen activator). Endothelial dysfunction is characterized by a reduced secretion of the earlier substances and can be identified as paradoxical vasoconstriction to acetylcholine or in response to exercise. Furthermore, endothelial dysfunction favours a thrombogenic vascular environment.

There is a growing body of evidence demonstrating that endothelial dysfunction can be regarded as the most early stage of the atherosclerosis process and that its presence is independently associated with future adverse cardiovascular events.[3] Bearing this in mind, the studies by Hofma *et al.*[1] and Togni *et al.*[2] raise two questions. First, what is the clinical relevance of endothelial dysfunction after SES implantation? Secondly, what can be done to address this issue?

To answer these questions, one needs to identify the potential procedural or drug related mechanisms by which SES may induce coronary endothelial dysfunction.

First, the regulation of distal vascular tone is depending on the integrity of the endothelium. Therefore, using multiple stents covering long segments of the epicardial vessel may decrease the release of nitric oxide and other endothelial derived vasodilators downstream resulting in distal endothelial dysfunction. In the present studies, this procedural issue cannot be addressed because of the small number of patients studied.

Secondly, a direct toxic effect of sirolimus on the distal endothelium cannot be excluded. To address this potential mechanism, two issues need to be discussed: (1) the way by which the drug reaches the distal segment and (2) the drug–endothelium interaction.

The amount of drug on the stent polymer is relatively small and the majority of the drug is released locally within a month. Thus, taking into account the washout by the coronary blood flow, it is unlikely to assume that sirolimus is reaching and affecting the endothelium distal to the stent site directly by the main lumen of the coronary artery. However, as was raised by the authors, an alternative

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

* Corresponding author. Tel: +41 21 3140010; fax: +41 21 3140067.
E-mail address: eric.eeckhout@chuv.ch

† doi:10.1093/eurheartj/ehi571

pathway may be entertained.[1] sirolimus may diffuse locally into the vessel wall and reach the vasa vasorum. These can be regarded as a vascular bed running circumstantially and parallel to the epicardial structure from the ostium of the vessel to the microcirculation. In the early stages of atherosclerosis, a significant increase in the density of the vasa vasorum can be observed.[4] A further stepwise increase of the neovascularization of the vasa vasorum occurs after the barotrauma of percutaneous intervention.[4] It may be speculated that sirolimus (or potentially any other eluting drug) diffuses from the vascular wall into the vasa vasorum and migrates afterwards, reaching the endothelium beyond the distal stent border. At this stage, the drug may have a direct or indirect effect on the endothelium. Endothelial dysfunction is characterized by an imbalance between endothelial derived vasodilators and vasoconstrictors. sirolimus mediates endothelium-dependent vasodilatation *in vitro*.[5] However, sirolimus may also have a direct effect on the release of potent vasoconstrictors such as endothelin, tilting the balance in favour of vasoconstriction.[5] Moreover, sirolimus directly induces vascular endothelium damage and thrombosis.[6]

Another mechanism by which sirolimus may cause endothelial dysfunction is by impairing vascular repair. The vascular wall and the endothelium in particular undergo a constant process of injury and repair in response to mechanical and chemical injuries. Emerging evidence suggests that bone marrow-derived endothelial stem and progenitor cells contribute to the repair of vascular injury.[7] Sirolimus attenuates the recruitment of leukocytes and progenitor cells after vascular injury.[8] This mechanism partially explains its effectiveness in reducing restenosis but may inversely contribute to an impaired vascular repair distal.

Another pathway by which sirolimus may affect vascular repair is by a decreased production of vascular endothelial growth factor, which is considered as a major and essential stimulus for vascular repair.[9]

This brings us back to the two baseline questions about the clinical implications of these recent observations. There is compelling evidence to suggest that the treatment of *de novo* coronary stenosis with SESs is highly effective and associated with a sustained clinical benefit up to 3 years after device implantation. How can we reconcile the excellent clinical outcomes with the emerging reports demonstrating the association between SES and coronary endothelial dysfunction? At present, from a clinical point of view, only the issue of SES thrombosis, in particular late thrombosis has raised concern with the use of SES. Is early SES thrombosis a potential clinical manifestation of endothelial dysfunction? Clearly, the concept is unlikely but nevertheless appealing, certainly in the context of SES thrombosis occurring during exercise. At present, from large clinical registries or the randomized trials, no detailed information is available on the clinical circumstances of early SES thrombosis. It is indeed not impossible that the mechanisms of SES and BMS thrombosis are totally different.

How to integrate late SES thrombosis in the concept of endothelial dysfunction? Currently, the answer is unknown as endothelial function tests have been performed at 6 months and not beyond, indicating the need for long-term testing.

Patients, treated by SES, who persist with symptoms or who present with documented ischaemia without angiographic restenosis, might be considered as another potential clinical manifestation of SES-induced endothelial dysfunction. However, this phenomenon has not been reported until present.

In the light of current knowledge, what can be done from a practical point of view? The beneficial impact of drugs such as statins or angiotensin-converting enzyme (ACE) inhibitors on endothelial function in coronary patients is known for years.[10] Moreover, the benefit of statins, in particular, has been underscored by the recent observation that their administration preserves coronary endothelial function in association with the inhibition of the vasa vasorum neovascularization in experimental atherosclerosis.[10] It is unclear to which extent statins (and/or ACE-inhibitors) potentially counterbalance SES-induced endothelial dysfunction. Anyway, these drugs are, by recommendation, part of the pharmacological regimen of the coronary patient.

In conclusion, the association between SES and coronary endothelial dysfunction should alert us, even if its clinical relevance remains unclear today. Practically, all patients treated by SES require optimal pharmacological secondary prevention. Further clinical research is warranted to investigate the long-term impact of SES on endothelial function.

Acknowledgement

This work was supported by NIH grants number HL-0391 and Mayo Foundation, Dr Lerman is an established Investigator of the American Heart Association.

Conflict of interest: none declared.

References

1. Hofma SH, van der Giessen WJ, van Dalen BM, Lemos PA, McFadden E, Sianos G, Ligthart JMR, van Essen D, de Feyter PJ, Serruys PW. Indication of long-term endothelial dysfunction after sirolimus-eluting stent implantation. *Eur Heart J* 2006;**27**:166–170. First published on October 25, 2005, doi:10.1093/eurheartj/ehi571.
2. Togni M, Windecker S, Cocchia R, Wenaweser P, Cook S, Billinger M, Meier B, Hess OM. Sirolimus-eluting stents associated with paradoxic coronary vasoconstriction. *J Am Coll Cardiol* 2005;**46**: 231–236.
3. Lerman A, Zeiher AM. Endothelial function: cardiac events. *Circulation* 2005;**111**:363–368.
4. Kwon HM, Sangiorgi G, Ritman EL, Lerman A, McKenna C, Virmani R, Edwards W, Holmes DR, Schwartz RS. Adventitial vasa vasorum in balloon-injured coronary arteries: visualization and quantitation by a microscopic three-dimensional computed tomography technique. *J Am Coll Cardiol* 1998;**32**:2072–2079.
5. Yatscoff RW, Fryer J, Thliveris JA. Comparison of the effect of rapamycin and FK506 on release of prostacyclin and endothelin in vitro. *Clin Biochem* 1993;**26**:409–414.
6. Bruns CJ, Koehl GE, Guba M, Yezhelyev M, Steinbauer M, Seeliger H, Schwend A, Hoehn A, Jauch KW, Geissler EK. Rapamycin-induced endothelial cell death and tumor vessel thrombosis potentiate cytotoxic therapy against pancreatic cancer. *Clin Cancer Res* 2004;**10**:2109–2119.
7. Rafii S, Lyden D. Therapeutic stem and progenitor cell transplantation for organ vascularization and regeneration. *Nat Med* 2003;**9**:702–712.
8. Nuhrenberg TG, Voisard R, Fahlisch F, Rudelius M, Braun J, Gschwend J, Kountides M, Herter T, Baur R, Hombach V, Bauerle P, Zohlnhöfer D. Rapamycin attenuates vascular wall inflammation and progenitor cell promoters after angioplasty. *FASEB J* 2005;**19**:246–248.
9. Guba M, von Breitenbuch P, Steinbauer M, Koehl G, Flegel S, Hornung M, Bruns CJ, Zuelke C, Farkas S, Anthuber M, Jauch KW, Geissler EK. Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: involvement of vascular endothelial growth factor. *Nat Med* 2002;**8**:128–135.
10. Wilson SH, Herrmann J, Lerman LO, Holmes DR, Napoli C, Ritman EL, Lerman A. Simvastatin preserves the structure of coronary adventitial vasa vasorum in experimental hypercholesterolemia independent of lipid lowering. *Circulation* 2002;**105**: 415–418.