JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 1, NO. 1, 2008

ISSN 1936-8798/08/$34.00
PUBLISHED BY ELSEVIER
DOI: 10.1016/j.jcin.2007.10.003

EDITORIAL COMMENT

Persistent Endothelial Dysfunction After Drug-Eluting Stents

Another Continuing Cost of Reducing Restenosis*

Morton J. Kern, MD, FSCAI, FAHA, FACC

Irvine, California

It has long been known that the newly established endothelium within and adjacent to bare-metal stents (BMS) is not normal. As a response to healing after the barotrauma of balloon angioplasty alone (1,2), the newly seeded endothelial cells are dysfunctional and remain so for variable periods of time. Endothelial dysfunction is even more severe after metal stent implantation. The paradoxical vasoconstrictor effects of neurohumoral stimulation are the measurable gross marker of endothelial dysfunction, the consequences of which can be devastating. Abnormal endothelial cells have a thrombogenic surface, promoting adherence of various circulating monocytes and platelets and facilitating platelet aggregation, leukocyte infiltration, and vascular smooth muscle proliferation. It has been the hope, but not the reality, that the new endothelium covering drug-eluting stents (DES) would be more functional and that restoration of coronary flow would likewise limit endothelial dysfunction. In this issue of *JACC: Cardiovascular Interventions,* Kim et al. (3), as have others (4,5), continue to demonstrate the opposite.

See page 65

Kim et al. (3) examined endothelial function 6 months after the implantation of sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES). In 39 patients with SES, 36 patients with PES, and 10 patients with BMS, left anterior descending coronary artery vasoconstrictor responses after incremental acetylcholine infusions were measured. Endothelial-independent function was assessed with nitrate vasodilatory responses. Quantitative angiographic vessel segment diameter changes demonstrated greater vasoconstriction to acetylcholine in both SES and PES than in BMS patients. There was no difference between SES and PES responses. Interestingly, the DES vasoconstrictor responses were more prominent in the distal than in the proximal vessel segments.

The limitations of the study by Kim et al. (3) were few. The underlying degree of endothelial dysfunction in a noninstrumented artery was similar for the unstented vessel segments remote from the stent site. Kim et al. (3) used a bolus incremental acetylcholine dose administration, whereas others have used continuous infusions and pacing-induced or exercise-induced coronary vasomotor changes. These methods are not identical but should not impact the consistent differences observed for the endothelial functional responses. In addition, only patients from Korea were studied. Although the sensitivity to acetylcholine may differ among well-defined ethnic populations, the endothelial functional response certainly can be generalized to most other patients. Unlike Kim et al. (3), Togni et al. (4) reported paradoxical exercise-induced vasoconstriction after SES in both proximal and distal segments. Nonetheless, both Kim et al. (3) and Togni et al. (4) found endothelial dysfunction was greater in the DES groups than in the BMS groups. Persistent (>6 months) endothelial dysfunction, in addition to its attendant adverse consequences related to paradoxical vasoconstriction (more ischemia), endothelial cell surface activation (late thrombosis), and reduced collateral function (more severe ischemia insult after acute thrombosis), is another of the continuing costs we pay to reduce in-stent restenosis.

As Kim et al. (3) demonstrate, the increased potential for adverse clinical events associated with the ubiquitous pathology of endothelial dysfunction forces us to explore alternatives to the antiproliferative drug approach to restenosis. In vitro studies have shown both rampamycin and paclitaxel are toxic to endothelial cells. Limiting the toxicity would impact distant endothelial cells downstream from the implantation site. Reducing drug penetration into the local vascular wall and vaso vasorum may favorably influence distal regional endothelial cell turnover and function. That the antiproliferative drugs likely play a negative role on distal vasculature is deduced from the response in BMS and angioplasty groups, as well as from studies involving diminished collateral function studied late after DES (6).

The future lies in delivery of new endothelial growth factors, endothelial cell seeding, and the ability to attract endothelial progenitor cells to the injured and adjacent areas to restore endothelial function (7–9). Endothelial progenitor cells (EPCs) may be attracted by antibodies coated onto coronary stents. Current investigation into this process is underway (10). This approach might lead to improved endothelial cell growth and function in the absence of toxins, and the reduction of a thrombotic milieu, vasoconstriction, and acute or subacute stent thrombosis. Exactly

*Editorials published in the *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

From the Division of Cardiology, University of California, Irvine.

how to deliver or attract EPCs or whether EPCs and their offspring will reverse or improve endothelial dysfunction in patients with diffuse atherosclerosis is unknown at this time.

In light of studies linking the exaggerated endothelial dysfunction with an excess of adverse clinical events (11), we should be especially vigilant in following those patients with the potential problems noted for DES physiology. Kim et al. (3) present us with another downside of DES that must be weighed in the consideration of implantation of this important therapeutic advance for our patients with coronary artery disease.

Reprint requests and correspondence: Dr. Morton J. Kern, Division of Cardiology, University of California, Irvine, Building 53, Route 81, Room 100, 101 The City Drive, Orange, California 92868-4080. E-mail: mkern@uci.edu.

REFERENCES

1. Van Beusekom HMM, Whelan DM, Hofma SH, et al. Long-term endothelial dysfunction is more pronounced after stenting than after balloon angioplasty in porcine coronary arteries. J Am Coll Cardiol 1998;32:1109–17.
2. Caramori PRA, Lima VC, Seidelin PH, Newton GE, Parker JD, Adelman AA. Long-term endothelial dysfunction after coronary artery stenting. J Am Coll Cardiol 1999;34:1675–9.
3. Kim JW, Suh SY, Choi CU, et al. Six-month comparison of coronary endothelial dysfunction associated with sirolimus-eluting stent versus paclitaxel-eluting stent. J Am Coll Cardiol Intv 2008;1:65–71.
4. Togni M, Windecker S, Cocchia R, et al. Sirolimus-eluting stents associated with paradoxic coronary vasoconstriction. J Am Coll Cardiol 2005;46:231–6.
5. Obata J, Kitta Y, Takano H, et al. Sirolimus-eluting stent implantation aggravates endothelial vasomotor dysfunction in the infarct-related coronary artery in patients with acute myocardial infarction. J Am Coll Cardiol 2007;50:1305–9.
6. Meier P, Zbinden R, Togni M, et al. Coronary collateral function long after drug-eluting stent implantation. J Am Coll Cardiol 2007;49:15–20.
7. Kipshidze N, Dangas G, Tsapenko M, et al. Role of endothelium in modulating neointimal formation. J Am Coll Cardiol 2004;44:733–9.
8. Roy-Chaudhury P. Endothelial progenitor cells, neointimal hyperplasia, and hemodialysis vascular access dysfunction: novel therapies for a recalcitrant clinical problem. Circulation 2005;112:3–5.
9. Szmitko PE, Fedak PWM, Weisel RD, Stewart DJ, Kutryk MJB, Verma S. Endothelial progenitor cells: new hope for a broken heart. Circulation 2003;107:3093–100.
10. Wojakowski W. Endothelial progenitor cell capture stents—practical use of cell mobilization. ESC Cardio Website e-Journal Article. February 27, 2007. Available at: http://www.escardio.org/knowledge/cardiology_practice/ejournal_vol5/vol5n23.htm. Accessed November 28, 2007.
11. Suwaidi JA, Hamasaki S, Higano ST, Nishimura RA, Holmes DR, Lerman A. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. Circulation 2000;101:948–54.