ENDOTHELIAL DYSFUNCTION AFTER DRUG-ELUTING STENT IMPLANTATION

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ABSTRACT

Introduction: Percutaneous transluminal coronary angioplasty with stent implantation is a very efficient method of revascularization. The major problem after stent implantation is in-stent restenosis. The in-stent restenosis rate has been significantly reduced along with the introduction of drug-eluting stents. However, even these drug-eluting stents can cause endothelial dysfunction in the adjacent stented area, but the severity of the endothelial lesions is much lower in DES implant than in BMS implant. Objective: The aim of this article is to present in a succinct way various recent studies about endothelial dysfunction produced by implantation of drug-eluting stents. Conclusions: First generation drug-eluting stents (paclitaxel and sirolimus) appears to have a lesser risk of stenosis compared to bare-metal stent. Recent researches showed that there are also differences between drug-eluting stents types regarding vascular endothelial damage. Key Words: drug-eluting stent, endothelial dysfunction, coronary artery

INTRODUCTION

Treatment with antiproliferative drugs via coated stents appears to be a promising approach to both mechanically remodel target lesions and biologically reduce neointimal hyperplasia. Drug-eluting stents can maximize local drug effects and minimize the potential for systemic toxic effects.

Drug-eluting stents (DES), coated with vehicles that slowly elute antiproliferative agents, like paclitaxel, sirolimus, tacrolimus, zotarolimus or everolimus were developed to hamper the hyperplastic response that follows the application of bare metal stents.¹

The major limitation of stent implantation effectiveness has been, until the introduction of drug-eluting stents (DES), in-stent restenosis (ISR). DES use however, has led to a significant reduction of ISR, however it was found that DES can cause delayed endothelial healing and endothelial dysfunction in the stented vessels.²

This issue has raised safety concerns because delayed endothelialisation of the stent struts can contribute to in-stent thrombosis in certain patients. The impaired vasomotor endothelial function after DES implantation has recently been described. In addition, the degree of endothelial healing and vasomotor dysfunction seems to depend on whether the old or new generation of DES is used.¹
PRESENTATION

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, 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.4

There are several mechanisms which may contribute to endothelial dysfunction after implantation of DES: reduced bioavailability of vaso-relaxants (nitric oxide, NO), relative increase of vasoconstrictive factor, inflammatory response, impaired maturation of endothelial progenitor cells (EPCs) to endothelial cells (EC), impaired mobilisation of EPCs and endothelialisation of the stent struts, direct toxicity of the drug eluted from stent, polymer toxicity, hypersensitivity, increased production of free radicals.4,16

Proper reendothelialisation of the stented segment is a prerequisite for the formation of functionally mature endothelium which serves as a source of vasoactive, anti-inflammatory and antithrombotic substances. Several studies demonstrated that circulating bone marrow-derived EPCs contribute to the repair of the endothelium after injury, most likely by repopulating the site of stent implantation. Stent expansion causes significant injury to the artery wall.4

The endothelial lining is disrupted and the local inflammatory response is activated. The vessel wall injury also leads to the recruitment of circulating monocytes, EPCs and platelet deposition on the site of endothelial disruption. The ultimate goal of this reaction is to restitute the endothelial integrity over the area of dilated segment (reendothelialisation). The time between the initial endothelial injury caused by stent struts and full endothelialisation is significantly shorter after implantation of bare metal stents (approximately 30 days) than DES (>6 months).5 The reparatory mechanism is in part dependent on the recruitment of circulating EPCs, with their subsequent adherence to the struts surface as well as areas of arterial wall located between the struts. This mechanism is altered after implantation of drug-eluting stents.4

Shiroto et al. showed that paclitaxel activated the expression and activity of Rho-kinase, which is involved in the coronary vasospasm in vascular smooth muscle cells. The use of a Rho-kinase antagonist abolished the endothelium-dependent vasoconstriction after implantation of SES and PES in porcine coronary arteries.7 Pendyala et al. showed that function of not only the conduit, but also the resistance vessels is negatively affected by implantation of PES.8 This effect coexists with local inflammatory reaction, increased production of reactive oxygen species and increased sensitivity to vasoconstrictors such as endothelin-1.9 Murine and rat studies have shown decreased activity of eNOS and increased production of free radicals after implantation of SES.10

Sirolimus was shown to reduce the production of angiogenic vascular endothelial growth factor (VEGF) and responsiveness of the endothelial cells to VEGF.7 Obata et al. showed that in patients with acute MI sirolimus 2 weeks after implantation SES can be detected in arterial blood and coronary sinus.11 Importantly, several studies showed that segments proximal to the stent show abnormal endothelial-dependent vasoreactivity.12 The presence of endothelial dysfunction in non-stented segments of the vessel can also be explained by the propagation of drug through vasa vasorum.11 Therefore the endothelial healing and functional recovery can also be suppressed in segments located proximally and distally to the stent.9 Long term influence of sirolimus and paclixtal cannot be explained solely based on their release kinetics, because most of sirolimus (80%) is eluted from the stent surface within 28 days after implantation. Additionally, PES platforms show biphasic kinetics of drug elution, with rapid release in the first 48 h after implantation and subsequent slow release over 14 days.13

Kim et al. 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.12 Endothelial-independent function was assessed with nitrate vasodilator 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.12

In another study, Togni et al. reported paradoxical exercise-induced vasoconstriction after SES in both proximal and distal segments.14 Nonetheless, both Kim et al. and Togni et al. 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. 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.3,14

In vitro studies have shown both rapamycin 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.15 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.16

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. Endothelial progenitor cells (EPCs) may be attracted by antibodies coated onto coronary stents. 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 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.17-19

In light of studies linking the exaggerated endothelial dysfunction with an excess of adverse clinical events, we should be especially vigilant in following those patients with the potential problems noted for DES physiology. Kim et al. present us with another downside of DES that must be weighed in the consideration of implantation of this important therapeutic advance for patients with coronary artery disease.20

Finn et al. showed that sirolimus or paclitaxel released from a drug-eluting stent (DES) impaired the normal healing processes of the injured arterial wall, even over a period of 40 months after implantation, and the heterogeneity of healing in the stents was associated with late stent thrombosis.21 In their previous report provided in vivo evidence that both sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) can equally impair endothelial function and that their effects were demonstrable 6 months after implantation, especially in the arterial segments distal to the DES 6 months after stenting.12

A zotarolimus-eluting stent (ZES) has been reported to promote rapid and uniform healing of the endothelium, but little is known about the functional impairment of the endothelium after ZES implantation. Therefore, this study was prospectively designed to compare coronary endothelial dysfunction in patients with a ZES versus a SES or a bare-metal stent (BMS) at pre- and post-intervention 6-month follow-up.20

Longer stents were used in the DES group compared with the BMS group. No differences were observed among the SES, ZES, and BMS groups in terms of reference segment diameter proximal and distal to the stents. The segments proximal to the stents were more strongly constricted to the Ach infusion in the SES group compared with the BMS group. In contrast, between the ZES and BMS group, a significant difference in vasomotor reactivity was observed after the Ach infusion. The magnitude of the estimated differences in vascular changes was mildly attenuated after adjustment for stent length and late loss as potential confounding factors. However, the differences among SES, ZES, and BMS remained significant.20

The segment distal to the stent was more strongly constricted to Ach infusion in the SES group and in the ZES group as compared with the BMS group.20

The diameter changes between the SES and the ZES had significant differences of vasoreactivity in response to the Ach in sites distal to the stents but not the sites proximal to the stents. The diameter changes in response to the Ach infusion were greater at the sites distal to the stent than proximal to the stent in both the SES and ZES.20

When comparing the diameter changes to the Ach infusion between the pre- and post-intervention, there was a more intense vasoconstriction in the SES group than the ZES group. The degree of vasoconstriction was greater at the 6-month post-stenting in the proximal and in the distal segments after the Ach infusion in the SES group as compared with pre-intervention.
However, in the ZES group, the significant changes between the pre-stenting and 6-month post-stenting were observed only in the distal segments after the Ach infusion.  

The ZES, SES, and BMS groups showed no differences of vasodilation in response to nitrate or nitro-GTP between the pre- and post-intervention or between the sites proximal and distal to stents.  

Endothelial vasomotor reactivity at the 6-month post-intervention was significantly impaired in both the ZES and SES groups compared with the BMS group. However, the endothelial function associated with the ZES was more preserved at the 6-month follow-up compared with the SES.  

There is compelling clinical evidence that ZES carries an extremely low risk of late stent thrombosis.  

In humans, the ZES is associated with a greater amount of neointimal hyperplasia by IVUS at 8 months and a homogeneous complete healing by optical coherence tomography (OCT) at 6 months compared with the SES. In the current study, despite a greater degree of endothelial dysfunction compared with the BMS, the ZES was associated with lesser vasoconstriction to Ach compared with the SES.  

The differential effects of DES on endothelial function could be explained by the characteristics of the loaded drug. An in vitro study by Jabs et al. reported continuous sirolimus exposure causes impaired endothelium-dependent vascular relaxation by stimulation of mitochondrial reactive oxygen species release. In the SES, the loaded drug is released from the stent up to 60 days after stent implantation, the ZES maintains effective drug levels through initial 2 weeks of elution from the stent, and thus local toxicity is minimized. A recent study by Hamilos et al. showed that the biolimus A9-eluting stent, on the basis of a bioabsorbable polymer, showed a better-preserved endothelium-dependent vasomotion response at adjacent stent segments compared with the SES.  

**CONCLUSIONS**

Recent data from clinical trials using several types of DES suggest that significant endothelial dysfunction appears limited to first generation DES. Comparison of studies in which endothelium-dependent vasorelaxation was assessed using intracoronary infusion of Ach showed that implantation of PES and SES led to significant impairment of this reaction. On the other hand newer DES [zotarolimus eluting (ZES), everolimus-eluting (EES) and biolimus-eluting (BES) stents] do not produce the endothelial dysfunction.

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