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EDITORIAL COMMENT

Endothelial Dysfunction After Sirolimus-Eluting Stent Placement*

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In this issue of the *Journal*, Togni et al. (1) report that exercise-induced coronary vasomotion is abnormal in segments proximal and distal to sirolimus-eluting stents (SES) when evaluated six months after deployment. While subjects who had received bare-metal stents demonstrated normal exercise-induced vasodilation, subjects with SES clearly demonstrated paradoxical vasoconstriction in peri-stent segments, although the vasodilator response to nitroglycerin was maintained.

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The normal response to increased flow in coronary conductance vessels is vasodilation, which is due to stimulation of endothelial nitric oxide (NO) synthesis and release (2,3) in response to shear stress. During exercise, areas of the coronary arteries with damaged endothelium or abnormal endothelial function fail to exert this NO response onto the vascular smooth muscle. Subsequently, normal vasodilation fails to occur and can be replaced by paradoxical vasoconstriction, possibly attributable to the effect of circulating catecholamines (4).

Abnormal endothelial responses have been demonstrated early after balloon percutaneous transluminal coronary angioplasty but are normalized at follow-up months later (5,6). Evaluation of endothelial function within coronary stents has not been possible with current catheterization-based techniques because they rely on the assessment of vasomotion, which is prevented by the stent apparatus. However, coronary segments on the edges of bare-metal stents have been shown to demonstrate a normal vasodilator response to exercise when evaluated at 4 to 8 months after stent deployment in this current work and at 7 to 13 months after stent deployment in a previous publication by Maier et al. (7).

The evidence of peri-stent endothelial dysfunction after SES is in sharp contrast to its consistent absence after bare-metal stenting in this study, but the mechanism by which this abnormality is conferred remains unclear. The Cypher stents (Cordis Corp., Miami Lakes, Florida) used here contain a 5-μm thick coating of the drug sirolimus mixed with non-erodable polymers, topped with a layer of drug-free polymer to allow the release of approximately 80% of the drug within 30 days after implantation (8). Sirolimus (rapamycin) is a macrolide antibiotic that binds to its cytosolic receptor, FKBP12, and inhibits down-regulation of the cyclin-dependent kinase inhibitor $p27^{kip1}$, blocking transition from G_1 to S phase in the cell cycle (9) and inhibiting vascular smooth muscle cell proliferation and migration.

Rapamycin has been shown to impair endothelium-dependent relaxation in an in vitro model using porcine epicardial coronary arteries (10), but it has not been established that this is of consequence with clinical use of SES. Because most of the drug sirolimus is eluted from the polymer coating the stent by 28 days (11) and is reportedly fully eluted by 60 days (12), the abnormal vasomotion observed at six months in the current study should not be the result of a direct effect of sirolimus itself. However, the induction of a persistent abnormality in intact or regenerating endothelium occurring while sirolimus was present cannot be excluded. Alternatively, the polymer from which the drug elutes, which may have contributed to a case of a marked hypersensitivity reaction (12), could be involved in the abnormal vasomotion observed, but this also remains speculative.

As the authors note, the finding of paradoxical constriction could be the result of delayed endothelialization, with inadequate endothelial coverage leading to insufficient NO release to promote normal vasodilation with exercise. Although this could explain the finding of endothelial dysfunction within the stent and at the immediate edges, the angiograms in Figure 1 of the paper (1) show vasoconstriction well beyond the distal margin of the stent. Although the authors did not specify their deployment technique and use of predilation, none of the subjects in the current study had evidence of restenosis, and it seems unlikely that this dysfunctional distal segment (as much as 10 mm distal to the stent) had been subject to balloon dilation and de-endothelialization during stent placement. As noted previously, diffusion of sirolimus well beyond the stent margins with induction of a sustained functional impairment of nontraumatized endothelium may play a role in this finding. Togni et al. (13) also have recently reported a similar observation of abnormal peri-stent vasomotor responsiveness in subjects studied 8 to 10 months after brachytherapy for in-stent restenosis. As in the present study, it is not clear that the abnormal segments were de-endothelialized via balloon trauma, but the beta radiation was applied well beyond the stent margins, raising the possibility of a functional incapacitation of intact endothelium.

Concerns that drug-eluting stents (DES) may be associated with increased risk of subacute and later thrombosis have not been substantiated by clinical trial and registry data (14,15) and the U.S. Food and Drug Administration has

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continued to regard these therapies as safe (16), but case reports have described DES thrombosis occurring beyond one year after deployment (17). Although the number of such patients appears to be small based on current data, the ability to identify specific factors placing a patient at greater risk of thrombosis after DES or to identify those patients who may need extended antiplatelet therapy without interruption would be of great value. Whether evidence of persistent peri-SES endothelial dysfunction will be a risk factor for adverse late events, however, will require further study. While the occurrence of late stent thrombosis remains low, the authors have demonstrated that endothelial dysfunction occurs in the majority of patients after SES placement, suggesting it may not be a finding specifically portending adverse outcomes. In fact, the subjects chosen for this current study were included because of an uneventful six-month poststent clinical course and no evidence of restenosis.

The many questions raised by this work underscore the need for additional investigation. Further insight into the mechanism by which paradoxical constriction is associated with SES placement is required, and the duration of this abnormal vasomotor response remains to be defined. Whether endothelial dysfunction in this setting will adversely affect prognosis, as has been shown in other clinical contexts (18), and the effects of approaches manipulating endothelial response (19) are to be determined. Characterization of coronary vasomotion after the use of paclitaxel-eluting stents also is needed. Future studies in this area will help clarify the clinical implications of this stimulating seminal observation of endothelial dysfunction after DES placement.

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REFERENCES

1. Togni M, Windecker A, Cocchia R, et al. Sirolimus-eluting stents associated with paradoxic coronary vasoconstriction. J Am Coll Cardiol 2005;46:231–6.
2. Cooke JP, Rossitch E Jr., Andon NA, Loscalzo J, Dzau VJ. Flow activates an endothelial potassium channel to release an endogenous nitrovasodilator. J Clin Invest 1991;88:1663–71.
3. Nadaud S, Philippe M, Arnal JF, et al. Sustained increase in aortic endothelial nitric oxide synthase expression in vivo in a model of chronic high blood flow. Circ Res 1996;79:857–63.
4. Gordon JB, Ganz P, Nabel EG, et al. Atherosclerosis influences the vasomotor response of epicardial coronary arteries to exercise. J Clin Invest 1989;83:1946–52.
5. Lazzam C, Forster C, Gotlieb A, Dawood F, Schwartz L, Liu P. Impaired vascular reactivity following angioplasty is mainly due to endothelial injury. Exp Mol Pathol 1992;56:153–62.
6. Suter TM, Hess OM, Bortone A, Nonogi H, Grimm J, Krayenbuehl HP. Coronary stenosis vasomotion during dynamic exercise before and after PTCA. Eur Heart J 1989;10 Suppl G:58–63.
7. Maier W, Windecker S, Küng A, et al. Exercise-induced coronary artery vasodilation is not impaired by stent placement. Circulation 2002;105:2373–7.
8. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002;346:1773–80.
9. Marx SO, Marks AR. Bench to bedside: the development of rapamycin and its application to stent restenosis. Circulation 2001;104:852–5.
10. Jeanmart H, Malo O, Carrier M, Nickner C, Desjardins N, Perrault LP. Comparative study of cyclosporine and tacrolimus vs newer immunosuppressants mycophenolate mofetil and rapamycin on coronary endothelial function. J Heart Lung Transplant 2002;21:990–8.
11. Klugherz BD, Llanos G, Lieuallen W, et al. Twenty-eight-day efficacy and phamacokinetics of the sirolimus-eluting stent. Coron Artery Dis 2002;13:183–8.
12. Virmani R, Guagliumi G, Farb A, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent should we be cautious? Circulation 2004;109:701–5.
13. Togni M, Windecker S, Wenaweser P, et al. Deleterious effect of coronary brachytherapy on vasomotor response to exercise. Circulation 2004;110:135–40.
14. Jeremias A, Sylvia B, Bridges J, et al. Stent thrombosis after successful sirolimus-eluting stent implantation. Circulation 2004;109:1930–2.
15. Holmes DR Jr., Leon MB, Moses JW, et al. Analysis of 1-year clinical outcomes in the SIRIUS trial: a randomized trial of a sirolimus-eluting stent versus a standard stent in patients at high risk for coronary restenosis. Circulation 2004;109:634–40.
16. Muni NI, Gross TP. Problems with drug-eluting coronary stents—the FDA perspective. N Engl J Med 2004;351;1593–5.
17. McFadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. Lancet 2004;364:1519–21.
18. Suwaidi JA, Hamasaki S, Higano ST, Nishimura RA, Holmes DR Jr., Lerman A. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. Circulation 2000;101:948–54.
19. Kipshidze N, Dangas G, Tsapenko M, et al. Role of the endothelium in modulating neointimal formation: vasculoprotective approaches to attenuate restenosis after percutaneous coronary interventions. J Am Coll Cardiol 2004;44:733–9.