Impaired Coronary Vasomotion After Coronary Intervention With Drug-Eluting Stents

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Drug-eluting stents (DES) were first approved for the European market in 2002, then for the USA in 2003 and since 2004, DES have been commercially available in Japan. Currently, 4 types of DES [sirolimus-eluting stent (SES), paclitaxel-eluting stent (PES), zotarolimus-eluting stent (ZES) and everolimus-eluting stent] are available in Japan. DES are now used in the majority of patients undergoing percutaneous coronary intervention (PCI).¹ Previous randomized controlled trials, large registry studies and meta-analyses have shown that the use of DES is associated with lower rates of late lumen loss, in-stent restenosis and target vessel failure, as compared with bare metal stents (BMS). However, despite these advantages, the rates of death and myocardial infarction are similar between DES and BMS,² caused, at least in part, by the increased risk of late stent thrombosis, which may offset the benefits of DES.³

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By 3–6 months after BMS implantation, neointima covers almost all of the stent struts, and dual antiplatelet therapy can be ceased without fear of late stent thrombosis.⁴ When this neointimal proliferation becomes excessive, it may cause in-stent restenosis, which the DES prevent by inhibiting neointimal hyperplasia. On the other hand, they may interrupt the physiological healing process after PCI. Using recent imaging modalities, it has been demonstrated that the appearance of the delayed healing process is not same among the types of DES. Coronary angioscopic studies have shown that neointimal proliferation is more suppressed with SES than with PES, but thrombus is more frequently observed with PES.⁵ Another angioscopic study reported that ZES is associated with homogeneous neointimal coverage;⁶ however, most clinical studies do not support that ZES are safer than other DES.⁷ One possible explanation for this discrepancy is coronary functional abnormality after DES implantation.

Recent studies have reported that coronary endothelial function is impaired after DES implantation.⁸ The subjects of Togni et al's study underwent quantitative coronary angiography at rest and during supine bicycle exercise and coronary flow-mediated endothelial function was assessed.⁹ In patients with BMS, the proximal and distal segment of the stented vessel showed exercise-induced vasodilation. In contrast, there was exercise-induced vasoconstriction of the proximal and distal vessels segments adjacent to SES. The reference vessel showed exercise-induced vasodilation in both

groups. Fuke et al assessed coronary endothelial function using intracoronary acetylcholine injection 6 months after PCI.¹⁰ Intracoronary acetylcholine injection caused a significant vasoconstriction of the proximal and distal segments of the coronary artery in which the SES had been implanted. In patients with a BMS, however, acetylcholine did not cause vasoconstriction of the coronary artery. Endothelium-independent vasodilation, assessed by intracoronary nitroglycerin injection, was preserved with both the SES and BMS.

Although the acetylcholine-induced vasoreactivity test is commonly used to assess endothelial function, intracoronary injection does not cause severe coronary vasospasm in patients with endothelial dysfunction. It is caused by hypercontraction of vascular smooth muscle cells. Hiasa et al¹¹ reported an interesting case. A woman who had no previous history of chest pain was admitted to hospital because of new onset chest pain. Coronary angiography found severe stenosis in the left descending coronary artery, and the lesion was successfully dilated using 2 SES. Exercise stress test just after PCI was negative, but 6 months later, effort angina occurred and the exercise stress test was positive. Coronary angiography did not reveal restenosis or new lesions. Intracoronary acetylcholine injection caused severe coronary vasospasm in the distal segment adjacent to the SES. After intensive medical therapy with calcium-channel blockers, effort angina disappeared with negative exercise stress test. Recently, Shiroto et al reported in a porcine model that coronary vasoconstricting responses to serotonin, a potent constrictor of smooth muscle cell, were significantly enhanced at the PES site compared with the BMS site.¹² This finding was duplicated in organ chamber experiments using coronary rings without endothelium. Interestingly, paclitaxel increased Rho-kinase expression. Rho-kinase plays a central role in the molecular mechanism of coronary vasospasm through vascular smooth muscle cell hypercontraction, as well as in inflammation.¹³ PES enhanced the inflammatory response and microthrombus formation at the stent edge, where immunoreactivities for Rho-kinase expression and activity were increased. The coronary vasoconstricting responses to serotonin were abolished by hydroxyfasudil, a selective Rho-kinase inhibitor. These changes may cause deterioration in the long-term outcomes of patients undergoing PCI with DES.

In this issue of the Journal, Merla et al investigate the prognostic value of the early exercise stress test in patients undergoing PCI with either BMS or DES. Exercise stress test was performed 1 month after PCI and clinical follow-up

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was obtained. DES use was associated with a positive exercise stress test. The major finding of this study is that a positive exercise stress test was an independent predictor of adverse cardiac events during a median of 18 months' follow-up. Because this study was designed to investigate the prognostic value of an exercise stress test after PCI, we cannot directly draw a conclusion that impaired coronary vasomotion after DES implantation is associated with adverse long-term outcomes. Nevertheless, it is noteworthy that this study is the first to suggest an association between coronary functional abnormalities and adverse outcomes in patients undergoing PCI with DES. Further studies will be needed to understand the clinical relevance of impaired coronary vasomotion after DES implantation.

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