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Coronary Endothelial Dysfunction Distal to Stent of First-Generation Drug-Eluting Stents

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Objectives This study sought to evaluate the relationship between coronary endothelial function and neointimal coverage after drug-eluting stent (DES) implantation.

Background The mechanisms of endothelial dysfunction after DES implantation remain to be fully elucidated. We hypothesized that poor neointimal coverage after DES implantation may be associated with endothelial dysfunction distal to the stent site.

Methods Sixty-six stable angina patients treated with a first-generation DES were enrolled. At 9-month follow-up, coronary endothelial function was evaluated with intracoronary infusion of incremental doses of acetylcholine (10^{-8}, 10^{-7}, and 10^{-6} mol/l) and nitroglycerin (200 μg). Vascular responses at the segments proximal and distal to the stent site were angiographically and quantitatively measured. At the same time, the degree of neointimal coverage was evaluated using coronary angioscopy and classified into 4 grades: 0 (no coverage) to 3 (full coverage).

Results We divided the subjects into poor-coverage (grades 0 to 1, n = 33) and good-coverage (grades 2 to 3, n = 33) groups. Acetylcholine induced dose-dependent coronary vasoconstrictions in both groups. At the segment distal to the stent, the magnitude of vasoconstriction to acetylcholine in the poor-coverage group was significantly greater than in the good-coverage group ($p < 0.001$), whereas vasomotor responses proximal to the stent and vasodilation by nitroglycerine were similar between the 2 groups.

Conclusions Coronary endothelial dysfunction distal to the stent was associated with poor neointimal coverage after DES implantation. (J Am Coll Cardiol Intv 2012;5:966–73) © 2012 by the American College of Cardiology Foundation

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The penetration of drug-eluting stents (DES), compared with bare-metal stents (BMS), has significantly reduced in-stent restenosis and target lesion revascularization after percutaneous coronary intervention (1,2). Despite these benefits, there is no evidence that DES improve mortality rates when compared with BMS use (1,2). Furthermore, the concerns of late stent thrombosis (LST) and very late stent thrombosis (VLST) after DES implantation have arisen (3,4). Although the incidences of LST and VLST are low, they occur steadily at a constant rate of 0.4% to 0.6% per year up to 3 years after first-generation DES implantation (sirolimus-eluting stents [SES] and paclitaxel-eluting stents [PES]) (5,6) and may be life threatening. The mechanisms of LST and VLST have not been fully elucidated. Several factors may be involved, such as patient-related issues, lesion characteristics, and procedural-related variables, as well as cessation of dual antiplatelet therapy (7). Previous histopathological studies have suggested that poor re-endothelialization may be associated with LST and VLST after DES implantation (8,9). Recently, several clinical studies have revealed coronary endothelial dysfunction at segments adjacent to the first-generation DES implanted site (10–12). Endothelial dysfunction is a well-known factor for thrombosis. Thus, poor re-endothelialization at the stent site and endothelial dysfunction adjacent to the stent site may work together to produce LST and VLST. In this context, we previously reported in the canine model of acute coronary syndrome that endothelium function was impaired distal to the thrombotic site of coronary arteries (13). However, as far as we know, there have been no clinical studies available in which poor re-endothelialization and adjacent endothelial function were investigated simultaneously in humans in vivo.

To evaluate the magnitude of endothelialization in human coronary arteries has been challenging. Imaging modalities such as intravascular ultrasound or coronary angiography are unsatisfactory. In this regard, coronary angioscopy has been used to visually evaluate and inspect the macroscopic pathology at the stent site. Several coronary angioscopic observational data revealed poor neointimal coverage and thrombus formation at the first-generation DES implanted site (14–16). However, endothelial function was not examined in these studies and therefore the association of neointimal coverage with endothelial function has been unknown.

Accordingly, the objective of this study was to clarify the relationship between neointimal coverage and coronary endothelial function in patients treated with first-generation DES.

Methods

Study protocol. From January 2009 to June 2010, 66 patients diagnosed as having stable angina and treated with a single DES for a de novo lesion were enrolled in this study. SES (Cypher, Cordis Corporation, Miami Lakes, Florida) were implanted in 40 patients, and PES (Taxus, Boston Scientific Corporation, Natick, Massachusetts) were implanted in 26 patients. All stents were implanted using standard percutaneous coronary intervention techniques. Follow-up coronary angiography, coronary endothelial function evaluation, and coronary angioscopy were performed 9 months after percutaneous coronary intervention. The following subjects were excluded from this study: acute and old myocardial infarction; clinical or angiographic history of coronary vasospasm; previous coronary bypass graft surgery; left main coronary artery lesion; bifurcation lesion requiring 2 stents; chronic total occlusions; in-stent restenosis lesion; angiographic in-stent restenosis by follow-up angiography; symptomatic congestive heart failure; severe left ventricular dysfunction (ejection fraction <30%); and severe valvular heart disease. This study was approved by the institutional review board of Kurume University, and all patients provided written informed consent.

Abbreviations and Acronyms

Ach = acetylcholine
BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
LST = late stent thrombosis
NTG = nitroglycerin
PES = paclitaxel-eluting stent(s)
rs = Spearman rank correlation coefficient
SES = sirolimus-eluting stent(s)
VLST = very late stent thrombosis

Medication regimen. All patients received aspirin (100 mg/day) and clopidogrel (75 mg/day) during the follow-up period. Statin and renin-angiotensin system inhibitor, including angiotensin-converting enzyme inhibitor and angiotensin receptor blocker were administered daily to all patients. These drugs may have salutary effects on coronary endothelial function (17–19).

Evaluation of coronary endothelial function. Coronary endothelial function was estimated by measuring coronary vasomotion in response to acetylcholine (Ach) at 9-month follow-up. All vasoactive medications, including calcium channel blockers, long-acting nitrates, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta-blockers, were discontinued at least 48 h before the test. After baseline angiography, endothelium-dependent vasomotor response was evaluated by intracoronary infusion of incremental doses of Ach at 10^{-8}, 10^{-7}, and 10^{-6} mol/l for 2 min. At least 3 min was allowed between each infusion. If clinically needed, a temporary pacemaker was inserted through the femoral vein. Subsequently, endothelium-independent vasomotor response was tested after an intracoronary bolus infusion of nitroglycerin (NTG) (200 μg). Angiography was repeated every 30 s for 2 min after each drug infusion. The maximal vasomotor responses to Ach and NTG infusion were determined by quantitative coronary angiography with a