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Review

Endothelial dysfunction following drug-eluting stent implantation: A systematic review of the literature

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ABSTRACT

Background: While several studies have reported endothelial dysfunction after drug-eluting stent (DES) implantation, their study methods differed and the results were varied.
Methods and results: A literature search was performed using PubMed where 14 clinical studies (537 patients) including two randomized trials were identified. All studies assessed endothelial dysfunction 3–14 months after stent implantation. In the acetylcholine (ACh) loading studies, significant vasoconstrictions were observed in proximal and distal segments after implantation of sirolimus-eluting (SES) and paclitaxel-eluting stents (PES) and a milder diameter change was observed after zotarolimus-eluting stent (ZES) implantation. Coronary diameter changes were greater in distal segments. Significant diameter change was not detected after bare metal stent (BMS) implantation. In the exercise examinations, vasoconstriction was observed in distal and proximal segments following SES and PES implantation, whereas vasodilation was observed in BMS. In the pacing examinations, vasoconstriction was observed in both SES and PES implantations in distal and proximal segments, whereas vasodilation was observed in not only BMS but ZES and biolimus-eluting stents (BES) as well.
Conclusion: In the chronic phase following stent implantation, marked abnormal vasoconstriction distally in the stent was observed in SES and PES implantation but not in ZES or BES, compared with BMS. To clarify the clinical implications and possible mechanisms of these findings, longer-term evaluation with larger patients is needed.

1. Introduction

With the advent of the drug-eluting stent (DES), restenosis, which had been a major problem after bare metal stent (BMS) implantation, has dramatically decreased [1–3]. Although DES is frequently used all over the world, concern of stent thrombosis in the chronic stage remains [4–6]. Several potential mechanisms of stent thrombosis have been suggested, as pathological and angioscopic studies demonstrated several factors including delayed reendothelialization. In addition to anatomical factors, Togni et al. recently reported, endothelial dysfunction (ED) after sirolimus-eluting stent (SES, Cypher™, Cordis, Johnson & Johnson, Miami Lakes, Florida) implantation [7]. Subsequently, several studies have reported ED after SES and other types of DES implantation (Fig. 1). However, their study methods differed and their results were varied.

Therefore, we conducted a systematic literature review about ED following DES implantation to abstract similarities and differences between studies and to discuss possible mechanisms and future issues.

2. Methods

Using PubMed, a search for clinical research papers on ED following DES implantation was conducted using the following keywords: 'endothelial dysfunction' and 'drug-eluting stent' or 'drug eluting stent' or 'sirolimus eluting stent' or 'sirolimus-eluting stent' or 'Cypher' or 'paclitaxel eluting stent' or 'paclitaxel-eluting stent' or 'TAXUS' or 'zotarolimus eluting stent' or 'zotarolimus-eluting stent' or 'Endeavor' or 'everolimus eluting stent' or 'everolimus-eluting stent' or 'Xience V' or 'PROMUS' or 'biolimus A9 eluting stent' or 'biolimus A9-eluting stent' or 'Nobori'. The search was limited to clinical studies published in the English language through November 2011. Cited literatures from the retrieved papers were also included.

Abbreviations: ACh, acetylcholine; BES, biolimus-eluting stent; BMS, bare metal stent; DES, drug-eluting stent; ED, endothelial dysfunction; IVUS, intravascular ultrasound; NO, nitric oxide; OCT, optical coherence tomography; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent; VEGF, vascular endothelial growth factor; ZES, zotarolimus-eluting stent.

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3. Results

3.1. Study characteristics

After screening of titles, abstracts, and evaluation of the full text, 14 clinical studies (15 papers) including two randomized trials were identified (Table 1). From these studies, a total of 537 patients were examined (38 ± 21 per study, range 12–85). All but two studies examined SES, 5 paclitaxel-eluting stent (PES, Taxus™, Boston Scientific Corp, Natick, Massachusetts), 4 zotarolimus-eluting stent (ZES, Endeavor™, Medtronic Vascular, Inc., Santa Rosa, California), and 2 biolimus A9-eluting stent (BES, Nobori™, Terumo corporation, Tokyo, Japan). In 9 studies, BMS was used for the control group. A comparison was made exclusively between DES (N = 3) or between DES including a comparison with BMS (N = 4). Only one study assessed endothelial function at 2 weeks and 6 months after primary DES implantation for acute myocardial infarction (AMI), while most other studies assessed patients who presented with stable angina at DES implantation (mostly a single de novo lesion). All but one study assessed ED 6–14 months after stent implantation in patients without restenosis. One study assessed ED 3 months after ZES implantation. The effect of pharmacological intervention on the reduction of ED was evaluated in one randomized study. Endothelial dysfunction was detected by acetylcholine (ACh) loading (10 studies), exercise (2), or pacing (2) after discontinuation of vasodilators or vasoconstrictors. Quantitative coronary angiography (QCA) analysis was performed in all studies to evaluate the coronary diameter change.

3.2. Pharmacological stress examination

In a normal coronary artery, ACh facilitates nitric oxide (NO) production and release along with dilating the coronary artery. However, in a coronary artery with impaired endothelium, both reduced NO production and release result in vasoconstriction.

Intracoronary administration of ACh was most frequently used in 10 studies from 8 institutes to investigate ED following DES implantation (Table 1). In these studies, significant diameter changes were observed in a dose–response relationship (0.14 to 100 μg/min, estimated concentration: 10^{-8} mol/L to $10^{-5.36}$ mol/L; Table 2) in proximal and distal segments after DES implantation (Fig. 2-A), despite drug infusion and evaluation methods being different between studies. Coronary diameter change was greater and the dose–response relationship was more apparent in the distal segment. Significant diameter change was not detected in proximal or distal segment after BMS implantation (Fig. 2-B). Moreover, there was no difference in endothelium-independent vasodilatory response after nitrate infusion between DES and BMS groups across all studies.

Hofma et al. [8] reported that a 32% reduction in lumen diameter from baseline was observed in the distal segment of SES with ACh 10^{-6} M administration although no significant change was observed in BMS. Furthermore, there was no difference in coronary flow reserve between both groups using a Doppler tipped guide wire and no residual dissection at the stent edge was detected by intravascular ultrasound (IVUS) analysis.

Fuke et al. [9] conducted an evaluation using ACh in Japanese patients. They reported marked coronary vasoconstriction were observed proximal (−11.3 ± 10.3%, −14.1 ± 11.3%) and distal (−13.7 ± 9.3%, −17.5 ± 12.5%) to the SES after ACh 10^{-8} mol/L and 10^{-7} mol/L infusion though no significant lumen reduction was observed at either concentration in BMS.

Shin [10] and Kim et al. reported ED following PES, SES [10,11], and ZES [12] in Koreans. Kim et al. reported that in the SES and PES groups, the reduction rate in the vascular lumen was significantly higher in the proximal and distal segments of the stent compared to the BMS group. Particularly in the distal segment, lumen diameter

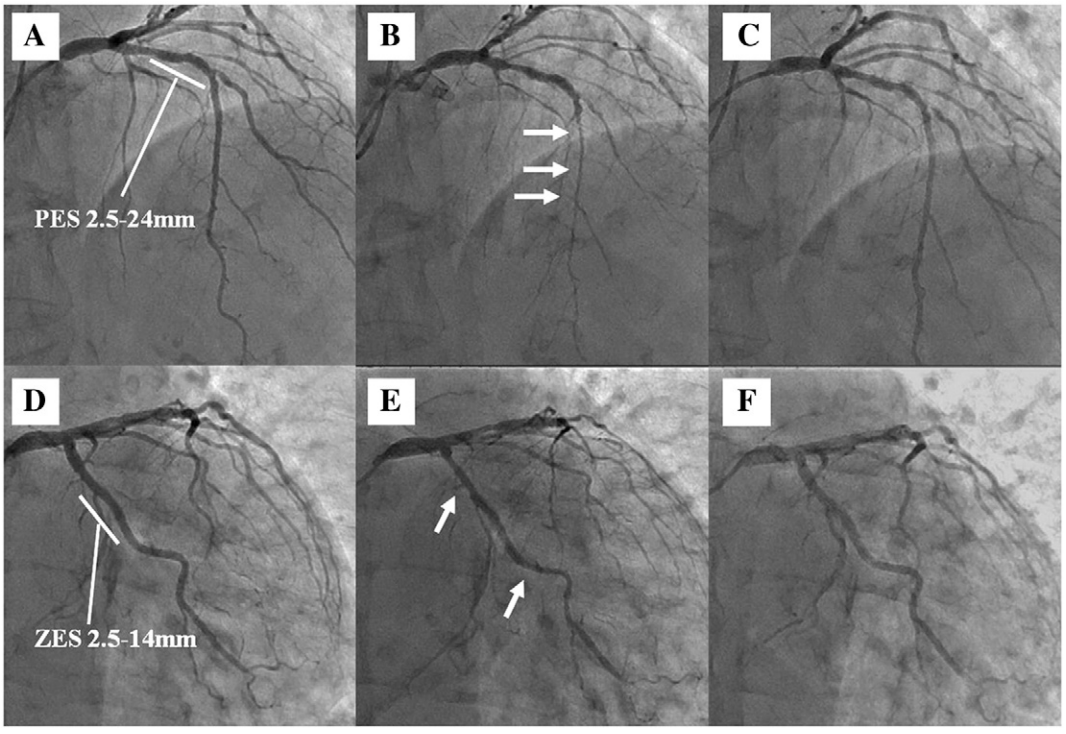

Fig. 1. Representative images of endothelial dysfunction following DES implantation. (A) No significant restenosis of PES was observed at 6 months follow-up angiography. (B) Marked vasoconstriction was observed mainly in distal to the PES (white arrow) after 50 μg/min ACh infusion. (C, F) Endothelium-independent vasodilatory response after nitrate infusion was maintained. (D) No significant restenosis of ZES was observed at 6 months follow-up angiography. (E) Mild vasoconstriction was observed both proximal and distal to the ZES (white arrow) after 100 μg/min ACh infusion. These images and their procedural data were extracted from medical records after obtaining written informed consent from the patient. PES: paclitaxel-eluting stent, ZES: zotarolimus-eluting stent.