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TRANSLATIONAL

Beneficial Effects of a Novel Bioabsorbable Polymer Coating on Enhanced Coronary Vasoconstricting Responses After Drug-Eluting Stent Implantation in Pigs in Vivo

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ABSTRACT

OBJECTIVES The aim of this study was to examine which component of drug-eluting stents (DES) plays a major role in enhanced coronary vasoconstricting responses after DES implantation in pigs.

BACKGROUND Recent studies have reported unremitting angina due to vasomotion abnormalities even after successful DES implantation. However, it remains to be elucidated which component of DES (metal stent, polymer coating, or antiproliferative drug) is responsible for DES-induced coronary hyperconstricting responses.

METHODS We developed poly-DL-lactic acid and polycaprolactone (PDLLA-PCL) copolymer technology with higher biocompatibility that is resorbed within 3 months. Four types of coronary stents were made: 1) a stent with polylactic acid (PLA) polymer coating containing antiproliferative drug (P1+D+); 2) a stent with PLA polymer coating alone without any drug (P1+D–); 3) a stent with novel PDLLA-PCL polymer coating alone (P2+D–); and 4) a bare metal stent (P–D–). The 4 stents were randomly deployed in the left anterior descending and left circumflex coronary arteries in 12 pigs.

RESULTS After 1 month, coronary vasoconstriction by intracoronary serotonin was enhanced at P1+D+ and P1+D– stent edges compared with P2+D– and P–D– stent edges and was prevented by a specific Rho-kinase (a central molecule of coronary spasm) inhibitor, hydroxyfasudil. Immunostainings showed that inflammatory changes and Rho-kinase activation were significantly enhanced at P1+D+ and P1+D– sites compared with P2+D– and P–D– sites. There were significant positive correlations between the extent of inflammation or Rho-kinase expression/activation and that of coronary vasoconstriction.

CONCLUSIONS These results indicate the important roles of PLA polymer coating in DES-induced coronary vasoconstricting responses through inflammatory changes and Rho-kinase activation in pigs in vivo, which are ameliorated by PDLLA-PCL copolymers. (J Am Coll Cardiol Intv 2016;9:281–91) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

DES = drug-eluting stent(s)

EES = everolimus-eluting stent(s)

PCI = percutaneous coronary intervention

PDLLA-PCL = poly-DL-lactic acid and polycaprolactone

PLA = polylactic acid

P1+D+ stent = stent with a polylactic acid polymer and a drug

P1+D− stent = stent with a polylactic acid polymer but without a drug

P2+D− stent = stent with a poly-DL-lactic acid and polycaprolactone copolymer but without a drug

P−D− stent = stent without a polymer or a drug

VSMC = vascular smooth muscle cell

Drug-eluting stents (DES) have been used most frequently in the field of interventional cardiology worldwide (1). Antiproliferative drug-elution of DES, which is controlled for a fixed period by a polymer coating, has dramatically inhibited neointimal formation and consequent risk of in-stent restenosis (2). Despite these beneficial aspects, DES show no beneficial prognostic effect compared with conventional bare metal stents (3). Notably, several large-scale trials demonstrated that 30% of patients with stable angina were still symptomatic 1 year after successful percutaneous coronary intervention (PCI) (4) and that an initial improvement of angina immediately after revascularization was minimized at 3-year follow-up compared with medical treatment (5). Surprisingly, new or worsening angina was also documented in patients who underwent successful PCI with the most promising product, everolimus-eluting stents (EES) (6).

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Recently, impaired coronary vasomotion after DES implantation has been reported (7–16) as a cause of new or unremitting angina and a predictor of poor vascular healing and subsequent stent thrombosis. Indeed, we have demonstrated that DES-induced coronary hyper-reactivity causes sudden cardiac arrest even after coronary revascularization (15). Thus, DES-induced coronary hyperconstricting responses are an emerging concern in the long-term safety of DES implantation.

We previously demonstrated that activation of a Rho-kinase pathway, which we have identified as the central molecular mechanism of coronary spasm (16–19), is involved in the pathogenesis of DES-induced coronary hyperconstricting responses in animals (11–13) and humans (14) and that inflammatory changes from DES subsequently cause Rho-kinase activation (12–14). A DES consists of 3 major components: a metal stent, a polymer coating, and an antiproliferative drug (1). Although a polymer coating could promote inflammatory changes (20,21), it remains to be fully elucidated which component of a DES plays a major role in DES-induced coronary hyperconstricting responses.

To eliminate the unfavorable effects of DES, a sophisticated biocompatible device is warranted. A poly-DL-lactic acid and polycaprolactone (PDLLA-PCL) copolymer matrix has been recently developed as an innovative polymer technology with higher biocompatibility and is resorbed within 3 months (22,23), whereas the current polylactic acid (PLA) biocompatible polymers are resorbed for up to 6 months (24).

In the present study, we thus examined whether a polymer coating is responsible for DES-induced coronary hyperconstricting responses through Rho-kinase activation in pigs in vivo and, if so, whether novel PDLLA-PCL copolymer technology ameliorates coronary hyperconstricting responses.

METHODS

All procedures were performed according to the protocols approved by the Institutional Committee for Use of Laboratory Animals of Tohoku University (2013MdA-059).

Detailed methods are provided in the Online Methods and Online Figure 1.

RESULTS

STENT IMPLANTATION. The 4 different stents (P1+D+, P1+D−, P2+D−, and P−D− stents) were randomly implanted in a total of 24 coronary segments (left anterior descending and left circumflex arteries) of 12 miniature pigs (**Figure 1**). There was no significant difference in the stenting procedure, including the number of major branch points at the stent implantation sites, in the 4 groups (Online Table 1).

CORONARY VASOMOTION AT 1 MONTH AFTER STENT IMPLANTATION. At 1 month after stent implantation, no significant in-stent restenosis was observed in the 4 groups (**Figures 2A, 2D, 2G, and 2J**). Notably, coronary vasoconstricting responses to intracoronary serotonin were enhanced at the proximal and distal stent edges of the P1+D+ and P1+D− sites compared with the P2+D− and P−D− stent edges (**Figures 2B, 2E, 2H, and 2K**), and all of them were abolished by pre-treatment with intracoronary hydroxyfasudil, a selective Rho-kinase inhibitor (**Figures 2C, 2F, 2I, and 2L**). Quantitative coronary angiography showed that serotonin-induced coronary vasoconstriction was significantly enhanced at the P1+D+ and P1+D− stent edges compared with the P2+D− and P−D− stent edges (**Figure 3**). In contrast, endothelium-dependent and -independent coronary vasodilating responses to nitroglycerin and bradykinin, regardless of the presence or absence of N^G-monomethyl-L-arginine, respectively, were all comparable in the 4 groups (Online Figure 2).

HISTOMORPHOMETRY AT THE STENT IMPLANTATION SITES AND THE STENT EDGES. At the stent implantation sites, the percentage of area stenosis tended