JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 9, NO. 3, 2016

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcin.2015.09.041

TRANSLATIONAL

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

Kensuke Nishimiya, MD, PhD, Yasuharu Matsumoto, MD, PhD, Hironori Uzuka, MD, Tsuyoshi Ogata, MD, Michinori Hirano, MD, Tomohiko Shindo, MD, Yuhi Hasebe, MD, PhD, Ryuji Tsuburaya, MD, PhD, Takashi Shiroto, MD, PhD, Jun Takahashi, MD, PhD, Kenta Ito, MD, PhD, Hiroaki Shimokawa, MD, PhD

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.

From the Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan. This work was supported in part by grants-in-aid for Scientific Research (18890018); the Global COE Project (F02); grants-in-aid (H22-Shinkin-004) from the Japanese Ministry of Education, Culture, Sports, Science, and Technology, Tokyo, Japan (to Dr. Shimokawa); and a grant for young investigators of translational research from Tohoku University Hospital (Dr. Matsumoto). The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received August 10, 2015; accepted September 24, 2015.

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).

SEE PAGE 292

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.

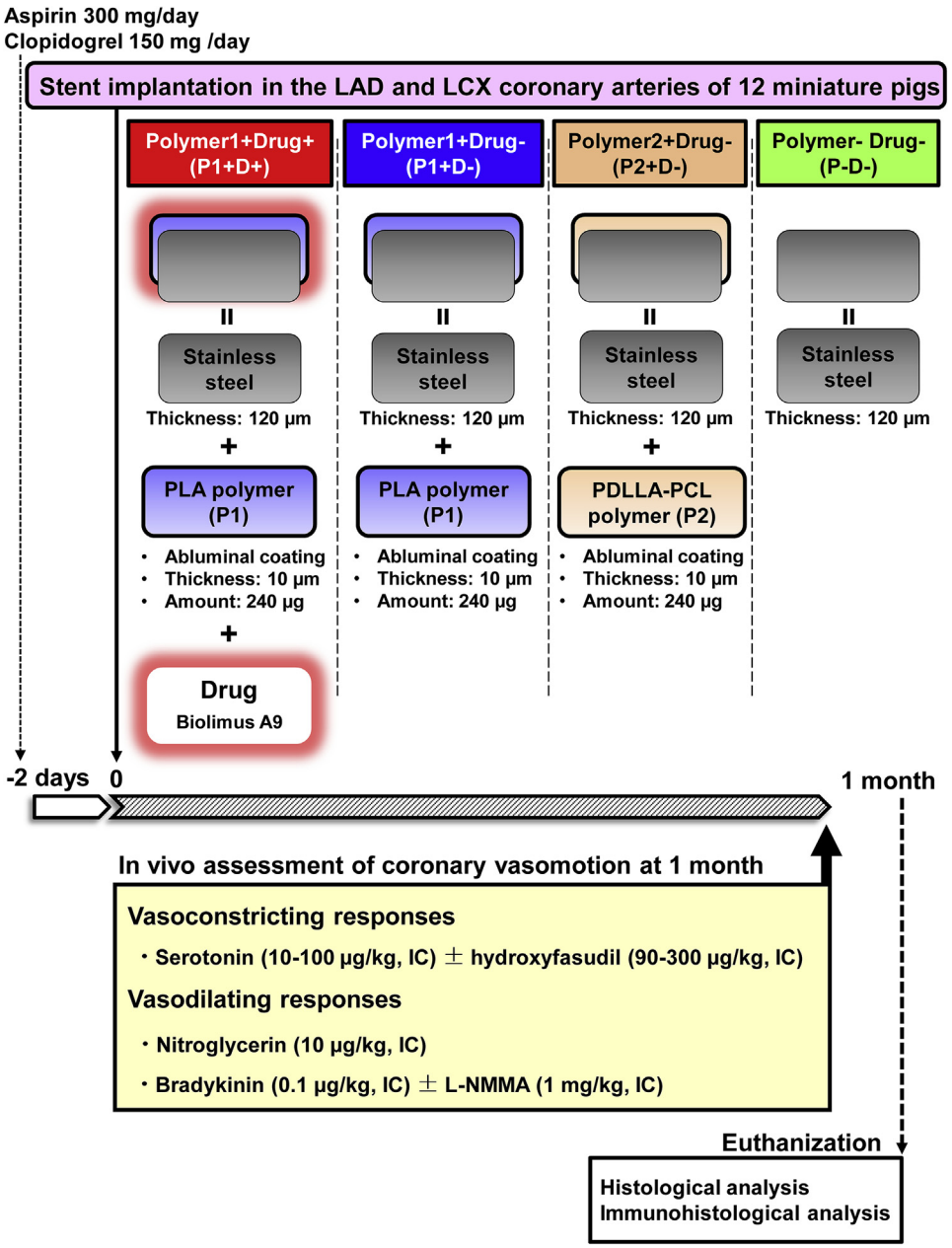
RESULTS

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

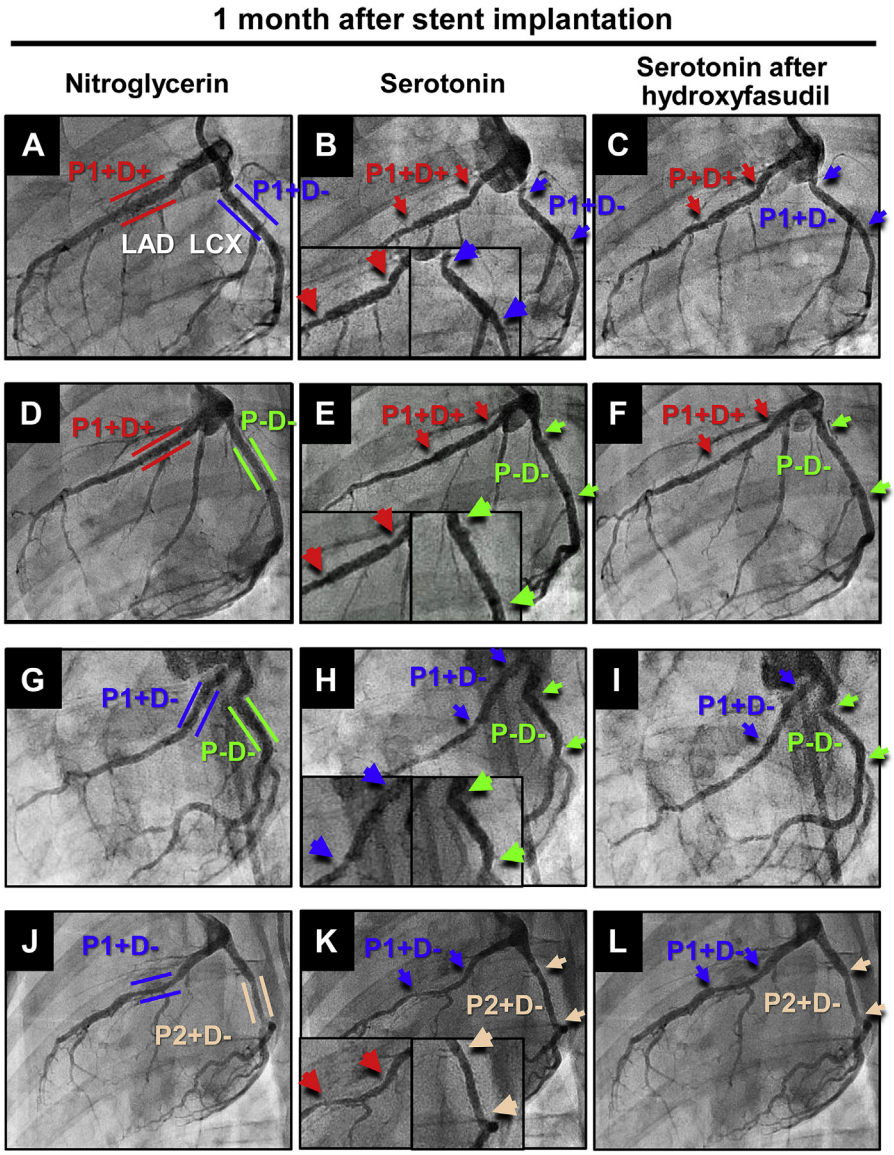
FIGURE 1 Study Protocol



The 4 different stents, P1+D+, P1+D−, P2+D−, and P−D− (6 each), were randomly implanted in the LAD and LCX in 12 miniature pigs. At 1 month after stent implantation, animals underwent follow-up coronary angiography to assess coronary vasomotion in vivo and were then euthanized for histological and immunohistological analyses of the inflammation and expression/activity of Rho-kinase. IC = intracoronary; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; P−D− = stent without a polymer or a drug; P1+D+ = stent with a polylactic acid polymer and a drug; P1+D− = stent with a polylactic acid polymer but without a drug; P2+D− stent with a poly-DL-lactic acid and polycaprolactone copolymer but without a drug; PDLLA-PCL = poly-DL-lactic acid and polycaprolactone; PLA = polylactic acid.

to be lower at the P1+D+ sites compared with other 3 groups (**Figures 4A to 4D**, Online Table 2). Endothelialization was almost complete at the 4 sites, although slightly less at the P1+D+ sites compared with the other 3 sites (Online Table 2). At the stent edges, no significant difference in the histomorphometry was noted at the 4 stent sites (Online Table 3).

FIGURE 2 Coronary Vasoconstricting Responses at the Stent Edges 1 Month After Stent Implantation in Pigs In Vivo



Representative left coronary angiograms after nitroglycerin (10 μg/kg, IC) **(A, D, G, J)**, serotonin alone (100 μg/kg, IC) **(B, E, H, K)**, and serotonin after pre-treatment with hydroxyfasudil (a selective Rho-kinase inhibitor, 300 μg/kg IC) **(C, F, I, L)** 1 month after stent implantation. No in-stent restenosis was noted in the 4 groups **(A, D, G, J)**. Serotonin-induced coronary vasoconstriction was enhanced at the P1+D+ and P1+D− stent edges compared with the P2+D− and P−D− stent edges **(B, E, H, K)** and was prevented with hydroxyfasudil **(C, F, I, L)**. Each **bar** indicates stent implantation sites; each **arrow**, stent edges. Abbreviations as in Figure 1.

INFLAMMATORY CHANGES IN THE STENT SITES AND STENT EDGES. At the stent implantation sites, the extent of inflammation was significantly greater at the P1+D+ and P1+D− sites compared with the P2+D− and P−D− sites (Figures 4E to 4H, and 4M). At the stent edges, more intense inflammatory changes were noted in the coronary adventitia compared with the intima or media (Figures 4I to 4L). The extent of adventitial inflammation of the stent edges was significantly greater at the P1+D+ and P1+D− stent edges compared with the P2+D− and P−D− stent edges (Figure 4N).

There were significant positive correlations between the extent of the inflammation at the stent implantation sites and the stent edges and that of serotonin-induced coronary vasoconstriction (Figures 4O and 4P).

RHO-KINASE ACTIVITY AT THE STENT EDGE. Immunoreactivity of Rho-kinase expression (Rho-kinase isoform β) and Rho-kinase activation (phosphorylated myosin phosphatase target subunit 1) was enhanced at the coronary media of the P1+D+ and P1+D− stent edges compared with P2+D− and P−D− stent edges (Figures 5A to 5O). Importantly, there were significant positive correlations between the extent of Rho-kinase expression/activation and that of serotonin-induced coronary vasoconstriction (Figures 5P to 5R). All parameters including vasoconstriction to intracoronary serotonin, inflammation, and Rho-kinase expression/activation were not affected by the measurement position (left anterior descending artery vs. left circumflex artery, proximal site vs. distal site) (Online Tables 4 and 5).

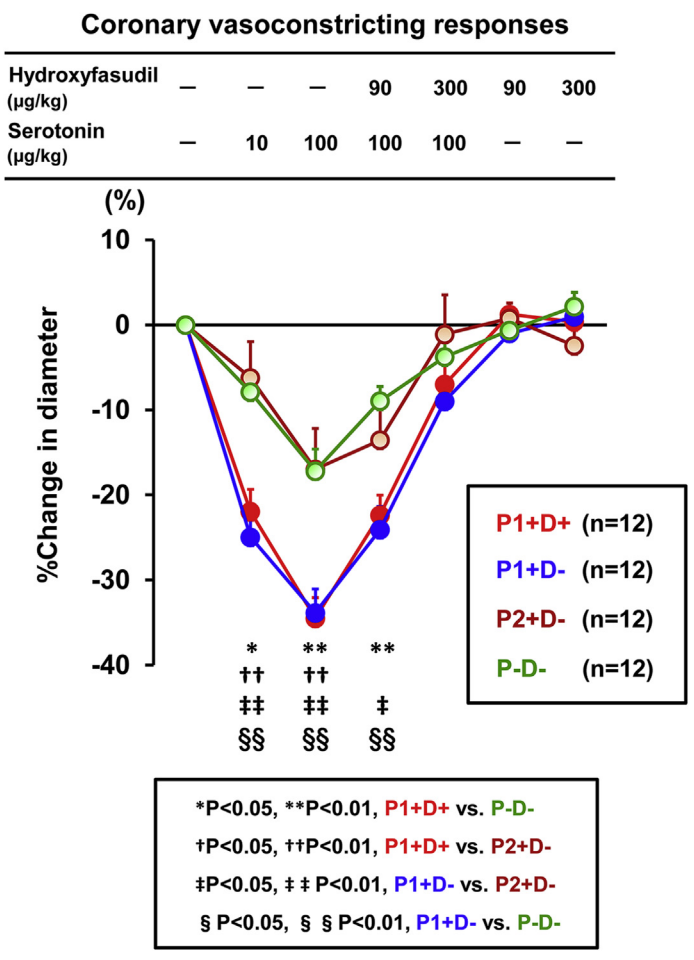
DISCUSSION

The major findings of the present study were that coronary vasoconstricting responses were significantly enhanced at the P1+D+ and P1+D− sites compared with the P−D− site at 1 month after stent implantation in pigs in vivo, which were dramatically attenuated at P2+D− site and those functional alterations were significantly associated with adventitial inflammatory changes and Rho-kinase activation (Figure 6).

ESSENTIAL ROLE OF A POLYMER COATING IN DES-INDUCED CORONARY HYPERREACTIVITY. Widespread use of DES has reduced the late lumen loss and the rate of repeat revascularization (1,2). However, an improvement in symptoms exhibited by successful PCI is still limited. Emphasis should be placed on the fact that 30% of stable angina patients remained symptomatic 1 year after PCI (4). Surprisingly, new or worsening angina was also documented in the patients who underwent PCI with EES (6). DES-induced coronary hyperconstricting responses have currently been raised as an important issue (7–16), resulting in new or unremitting angina after DES implantation. The high prevalence of coronary vasomotor abnormalities after PCI (~50%) was recently reported (25). Impaired coronary vasomotion is associated with increased cardiovascular risks (26). Indeed, we recently reported on a patient who had cardiac arrest associated with DES-induced coronary hyperconstriction (15). Thus, more attention should be paid to coronary hyperconstricting responses and resulting new or worsening angina after successful PCI with DES.

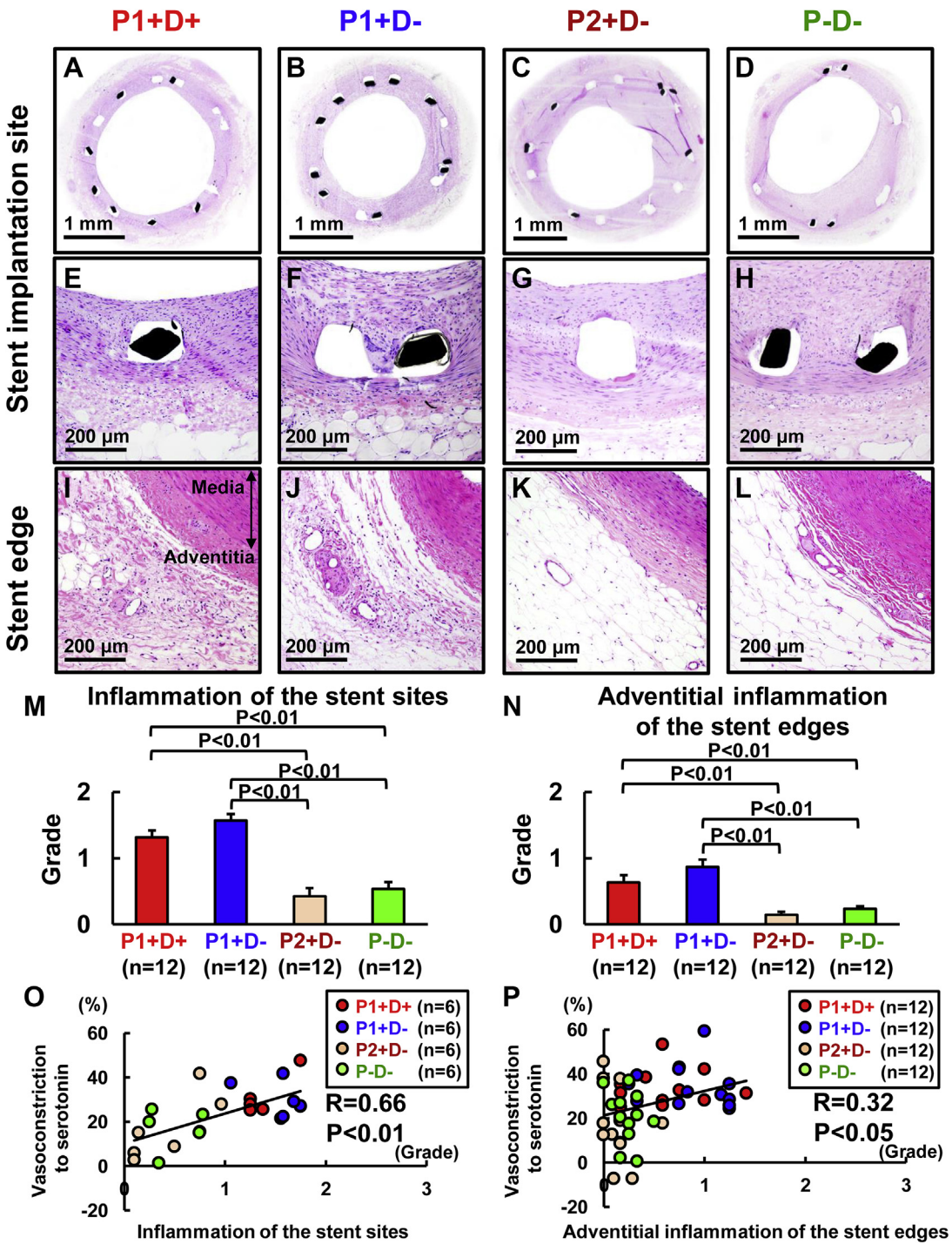
A DES consists of 3 components: a metal stent, a polymer coating, and an antiproliferative drug (1). Although a polymer coating is necessary to permit the drug release kinetics for a fixed period, persistent polymer residues in the coronary arterial wall may be most responsible for the late-phase

FIGURE 3 Quantitative Coronary Angiography for Coronary Vasoconstricting Responses 1 Month After Stent Implantation in Pigs In Vivo



Results of quantitative coronary angiography for coronary vasoconstricting response to serotonin (10 and 100 μg/kg IC) before and after hydroxyfasudil (90 and 300 μg/kg IC) 1 month after stent implantation. Coronary vasoconstricting responses to serotonin were equally enhanced at the P1+D+ and P1+D− stent edges compared with the P2+D− and P−D− stent edges. Those responses were all prevented by pre-treatment with hydroxyfasudil. Results are expressed as mean ± SEM. Abbreviations as in Figure 1.

FIGURE 4 Histological Analysis of Inflammatory Changes



Representative hematoxylin-eosin stainings of P1+D+ **(A, E, I)**, P1+D− **(B, F, J)**, P2+D− **(C, G, K)**, and P−D− sites **(D, H, L)** 1 month after stent implantation. Results of the semiquantitative analysis of the inflammatory changes in the stent implantation sites **(M)** and those in the adventitia of the stent edges **(N)**. The extent of inflammatory changes were significantly greater in P1+D+ and P1+D sites compared with P2+D − and P−D− stent edges **(M, N)**. There were significant positive correlations between the extent of inflammatory changes and that of serotonin-induced coronary vasoconstriction **(O, P)**. Results are expressed as mean ± SEM **(M, N)**. Abbreviations as in Figure 1.

inflammatory changes after DES implantation (20). We have also demonstrated that sirolimus-eluting stents enhance coronary vasoconstricting responses compared with its platform bare metal stents through inflammatory changes and subsequent Rho-kinase activation in pigs and humans (11,14), suggesting that the polymer coating or the eluting drug, but not the metal stent, may be responsible for the DES-induced coronary hyperconstricting responses. In the present study, all of the coronary stents were made of stainless steel with 120-μm-thick strut to precisely evaluate the effects of a polymer coating and an eluting drug (Online Figure 1). Although it has been hypothesized that hyperreactivity to a polymer coating is involved in the impairment of coronary vasoconstriction (7–13), the influence of each stent component remains to be fully elucidated. In the present study, we were able to demonstrate that removal of both a PLA polymer coating and an eluting drug from DES system (P−D−) significantly reduced coronary hyperconstricting responses, whereas drug removal alone (P1+D−) was insufficient. These results thus provide the first direct evidence that polymer coating residues play a major role in the coronary hyperconstricting responses after DES implantation.

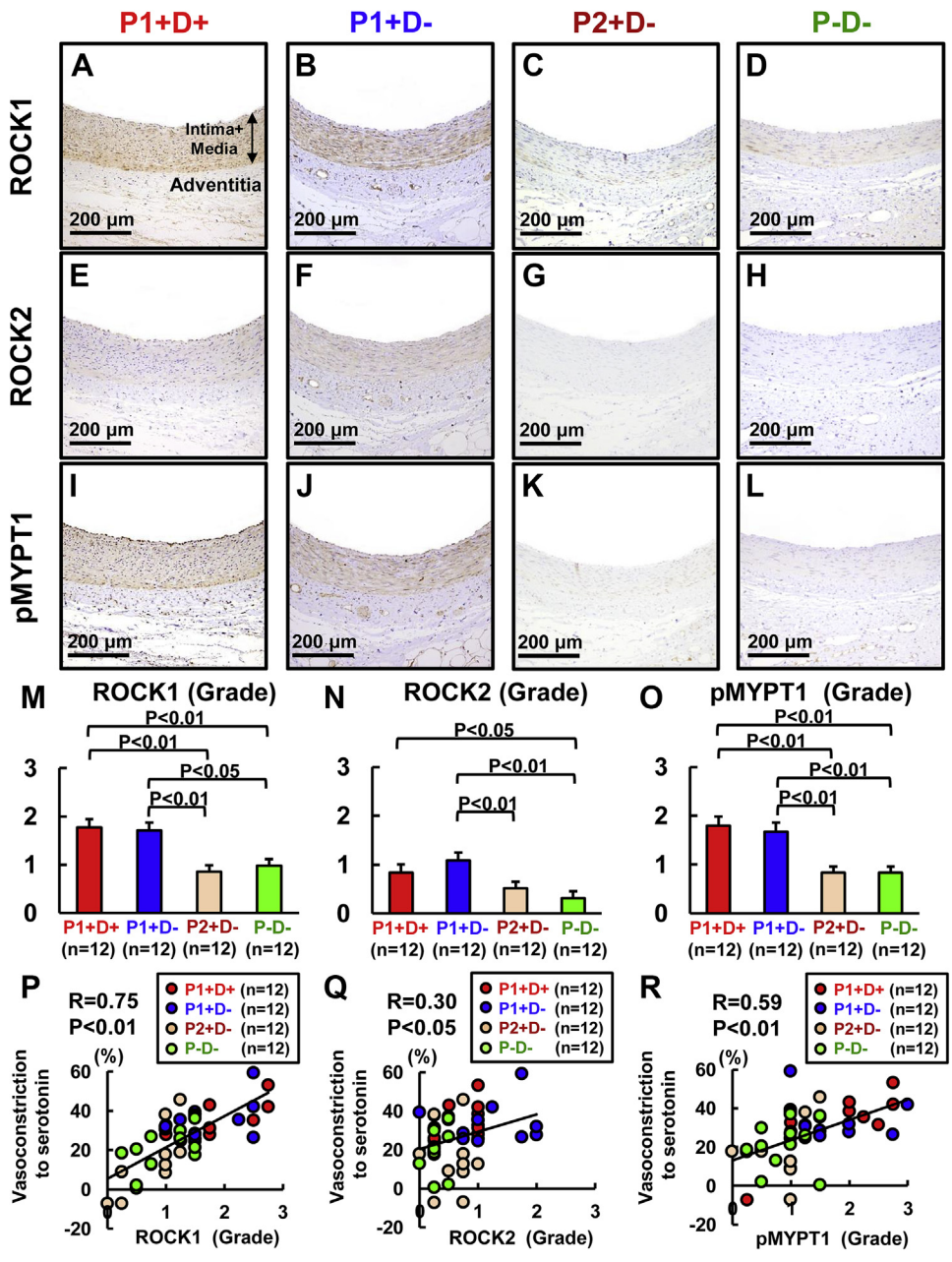
POTENTIAL BENEFITS OF PDLLA-PCL COPOLYMERS ON DES-INDUCED CORONARY HYPERREACTIVITY. Polymer blends of the PDLLA and the PCL matrix, termed PDLLA-PCL copolymers, have actively been used as biocompatible materials in clinical practice (27). The PDLLA-PCL polymers have achieved on higher biocompatibility and resorbed within 3 months (22,23) compared with the current PLA polymers that are resorbed for 6 to 9 months (24). Intriguingly, the stents with PDLLA-PCL copolymers alone (P2+D−) could dramatically ameliorate coronary hyperconstricting responses compared with the stents with PLA polymers alone (P1+D−). In the present study, an equivalent amount of polymers was applied to both P1+D− and P2+D− stents using the same abluminal-coating method (**Figure 1**) (10,28). It is thus conceivable that the total amount of polymer residues was much lower at the P2+D− sites compared with the P1+D− sites at 1 month after stent implantation. Although it was difficult to obtain detailed data on the degradation of each polymer after P1+D− and P2+D− stent implantation in pigs in vivo, the profound reduction of PDLLA-PCL polymer residues at the P2+D− sites may exert inhibitory effects on coronary hyperconstricting responses.

INFLAMMATORY CHANGES AND RHO-KINASE ACTIVATION AFTER DES IMPLANTATION. In the present study, histological examination demonstrated that inflammatory changes at stent implantation sites and stent edges were significantly enhanced at the P1+D+ and P1+D− sites compared with the P2+D− and P−D− sites. Furthermore, there was a significant positive correlation between the extent of inflammatory changes and that of serotonin-induced coronary vasoconstriction. At the stent edges, more intense inflammatory changes were noted in the coronary adventitia compared with the intima or media. We previously demonstrated that the stent deployment initiates adventitial inflammatory changes and that chronic adventitial inflammatory changes are able to induce coronary spasm in pigs in vivo (29,30). Taken together, the present results indicate that inflammatory changes after DES implantation are closely associated with the enhanced coronary vasoconstricting responses in which polymer residues may play a major role.

We have also previously demonstrated that Rho-kinase expression/activation in vascular smooth muscle cells plays a key role in the pathogenesis of coronary spasm (16–19) and DES-induced coronary hyperconstricting responses (11–13) in pigs. The present results showed that Rho-kinase expression and activation at the stent edges were enhanced, especially in the medial vascular smooth muscle cells of the P1+D+ and P1+D− sites compared with the P2+D− and P−D− sites. Intriguingly, significant positive correlations were noted between the extent of Rho-kinase expression/activation and that of serotonin-induced coronary vasoconstriction. Because inflammatory stimuli up-regulates Rho-kinase expression/activity (31), it is highly possible that the polymer coating itself enhances coronary vasoconstricting responses through widespread inflammation around the stents with resultant Rho-kinase up-regulation and activation in the medial vascular smooth muscle cells at the stent edges. Moreover, small amount of polymer residues might minimize inflammatory changes and resultant Rho-kinase activation.

POTENTIAL THERAPY FOR THE INHIBITION OF DES-ENHANCED VASOCONSTRICTION. PLA polymers have a biocompatible property resorbed for 6 to 9 months and have already been applied to the commercially available coronary stents (24). In the present study, PLA polymers appeared to show the mild but appreciable inflammatory changes and enhance coronary vasoconstricting responses, regardless of the PLA biocompatibility. A pig study

FIGURE 5 Immunohistological Analysis of Rho-kinase Expression and Activity



Representative immunostainings of P1+D+, P1+D−, P2+D−, and P−D− edges for Rho-kinase β (ROCK1) **(A to D)**, Rho-kinase α (ROCK 2) **(E to H)** and phosphorylated myosin phosphatase target subunit 1 (pMYPT1) (a marker of Rho-kinase activity) **(I to L)** 1 month after stent implantation. Results of the semiquantitative analysis for the extent of ROCK1 **(M)**, ROCK2 **(N)**, and pMYPT1 **(O)**. Immunoreactivities for ROCK1 and pMYPT1 were significantly enhanced in the medial layer of the P1+D+ and P1+D- edges compared with the P2+D- and P-D- edges **(M to O)**. There were significant positive correlations between the extent of Rho-kinase expression/activation and that of serotonin-induced coronary vasoconstriction **(P to R)**. Results are expressed as mean ± SEM **(M to O)**. Abbreviations as in Figure 1.

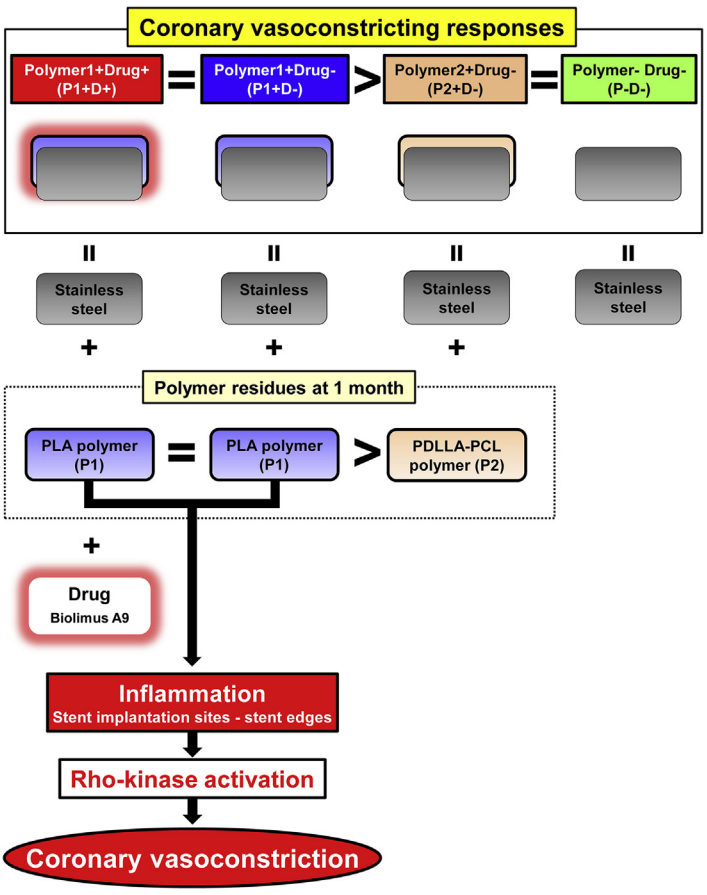
demonstrated that mild inflammatory changes are prominent around DES with PLA polymers in pigs (28), supporting the present result. Notably, it was recently reported that unremitting angina attack 5 months after successful implantation of a bioresorbable vascular scaffold made of PLA polymers

was caused by coronary vasospastic responses (32). Thus, novel polymer technology with higher biocompatibility is needed for an extreme reduction of hyperreactivity to polymer residues and resultant unfavorable effects. On the basis of the present results, the PDLLA-PCL copolymer coating could be a promising biomaterial to ensure the long-term safety of DES implantation. In fact, the newly developed sirolimus-eluting stents with PDLLA-PCL copolymers (Online Figure 1) showed the 9-month short-term safety and efficacy profiles similar to those of EES (23) and preserved normal coronary vasomotor responses to maximal atrial pacing in humans (22). The long-term efficacy of this novel DES system should be examined in future studies with a special reference to angina due to DES-induced coronary hyperconstricting responses.

We previously demonstrated that Rho-kinase inhibitors are effective for coronary spasm in patients with vasospastic angina (16–19). In the present study, hydroxyfasudil, a selective Rho-kinase inhibitor, prevented serotonin-induced coronary hyperconstriction in vivo, indicating that Rho-kinase inhibitors could be another therapeutic option for DES-induced coronary hyperconstricting responses.

STUDY LIMITATIONS. Several limitations should be mentioned for the present study. First, because the present study was performed in normal pigs without pre-existing coronary atherosclerotic lesions, caution should be used when extrapolating the present findings to the clinical settings. However, the present study with normal pigs allowed us to fully examine the foreign body reaction to the biomaterials. Second, because we did not have facilities to prepare the durable polymer-coated stents, the roles of nonbioabsorbable durable polymers applied to the most widely used EES remain to be elucidated (Online Figure 1). However, we were able to demonstrate the beneficial effects of novel biocompatible PDLLA-PCL copolymers compared with the PLA polymers. Third, we used serotonin to examine coronary vasoconstricting responses, as previously described (11–13,16–18). Although acetylcholine is most frequently used to provoke coronary artery spasm in the clinical setting, serotonin may better mimic spontaneous coronary spasm in humans than acetylcholine (33). Finally, the effects of endothelial shear stress on the altered vascular responses after stent implantation remain to be examined in future studies. However, for precise quantitative coronary angiography analysis, the stents were gently deployed across the major side branches in the present study, predisposed to the development of low endothelial shear stress and subsequent inflammatory changes (34). Furthermore, all parameters evaluated in the present study were not affected by the measurement position (e.g., proximal site vs. distal site). Because endothelial shear stress is also driven by the thick-strut stents (35), thinner strut stents (1,24) may be useful to address this issue in future studies.

FIGURE 6 Summary of the Present Study and Working Hypothesis



Coronary vasoconstricting responses were enhanced in the P1+D+ and P1+D− sites compared with P−D− sites 1 month after stent implantation in pigs in vivo, suggesting that the polymer coating plays a major role in DES-induced coronary hyperconstriction. PLA polymer coating initiates the mild but appreciable extent of inflammatory changes in the stent sites and in the coronary adventitia of the stent edges. At the stent edge, adventitial inflammation subsequently enhances Rho-kinase expression and activity in the medial vascular smooth muscle cells. Finally, DES-induced coronary hyperconstricting responses occur. In contrast, PDLLA-PCL P2+D- dramatically ameliorates DES-induced coronary hyperconstricting responses to its excellent biocompatible property. Abbreviations as in Figure 1.

CONCLUSIONS

The present study demonstrates the important roles of a 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.

ACKNOWLEDGMENTS The authors thank Dr. S. Yasuda and Dr. H. Ishibashi-Ueda for providing resin-embedded histological sections, Y. Watanabe and A. Nishihara for excellent technical assistance, Terumo Corporation for providing the originally developed coronary stents (P1+D+, P1+D−, P2+D−, and P−D− stents), and Asahi Kasei Pharma for providing hydroxyfasudil.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Yasuharu Matsumoto, Department of Cardiovascular Medicine, Tohoku University, Graduate School of Medicine, Seiryo-machi, Aoba-ku 1-1, Sendai 980-8574, Japan. E-mail: matsumoto@cardio.med.tohoku.ac.jp.

PERSPECTIVES

WHAT IS KNOWN? DES-induced coronary hyperconstricting responses remain an important concern, resulting in unremitting angina even after successful revascularization.

WHAT IS NEW? The present study demonstrates for the first time that of the 3 components of a DES (metal stent, polymer coating, and antiproliferative drug), the polymer coating plays a major role in the pathogenesis of DES-induced coronary hyperconstricting responses through inflammatory changes and subsequent Rho-kinase activation in pigs in vivo, which could be ameliorated by novel PDLLA-PCL copolymer technology.

WHAT IS NEXT? Thus, a novel DES system using a PDLLA-PCL copolymer could be a promising device to reduce vasomotion abnormalities after DES implantation.

REFERENCES

1. Stefanini GG, Holmes DR Jr. Drug-eluting coronary-artery stents. N Engl J Med 2013;368:254–65.

2. Morice MC, Serruys PW, Sousa, 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.

3. Spaulding C, Daemen J, Boersma E, Cutlip DE, Serruys PW. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med 2007;356:989–97.

4. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356:1503–16.

5. Pocock SJ, Henderson RA, Clayton T, et al. Quality of life after coronary angiography or continued medical treatment for angina: three-year follow-up in the RITA-2 trial. Randomized intervention treatment of angina. J Am Coll Cardiol 2000;35:907–14.

6. Serruys PW, Chevalier B, Dudek D, et al. A bioresorbable everolimus-eluting scaffold versus a metallic everolimus-eluting stent for ischaemic heart disease caused by de-novo native coronary artery lesions (ABSORB II): an interim 1-year analysis of clinical and procedural secondary outcomes from a randomised controlled trial. Lancet 2015;385:43–54.

7. Hamilos MI, Ostojic M, Beleslin B, et al. Differential effects of drug-eluting stents on local endothelium-dependent coronary vasomotion. J Am Coll Cardiol 2008;51:2123–9.

8. Pendyala LK, Yin X, Li J, Chen JP, Chronos N, Hou D. The first-generation drug-eluting stents and coronary endothelial dysfunction. J Am Coll Cardiol Intv 2009;2:1169–77.

9. Mitsutake Y, Ueno T, Yokoyama S, et al. Coronary endothelial dysfunction distal to stent of first-generation drug-eluting stents. J Am Coll Cardiol Intv 2012;5:966–73.

10. Pendyala LK, Matsumoto D, Shinke T, et al. Nobori stent shows less vascular inflammation and early recovery of endothelial function compared with Cypher stent. J Am Coll Cardiol Intv 2012;5:436–44.

11. Shiroto T, Yasuda S, Tsuburaya R, et al. Role of Rho-kinase in the pathogenesis of coronary hyperconstricting responses induced by drug-eluting stents in pigs in vivo. J Am Coll Cardiol 2009;54:2321–9.

12. Tsuburaya R, Yasuda S, Shiroto T, et al. Long-term treatment with nifedipine suppresses coronary hyperconstricting responses and inflammatory changes induced by paclitaxel-eluting stent in pigs in vivo: possible involvement of Rho-kinase pathway. Eur Heart J 2012;33:791–9.

13. Nishimiya K, Matsumoto Y, Takahashi J, et al. Association of adventitial vasa vasorum and inflammation with coronary hyperconstriction after drug-eluting stent implantation in pigs in vivo. Circ J 2015;79:1787–98.

14. Aizawa K, Yasuda S, Takahashi J, et al. Involvement of rho-kinase activation in the pathogenesis of coronary hyperconstricting responses induced by drug-eluting stents in patients with coronary artery disease. Circ J 2012;76:2552–60.

15. Takeda M, Shiba N, Takahashi J, Shimokawa H. A case report of very late stent thrombosis with peri-stent coronary artery aneurysm and stent-related coronary vasospasm. Cardiovasc Interv Ther 2013;28:272–8.

16. Shimokawa H. 2014 Williams Harvey Lecture: Importance of coronary vasomotion abnormalities-from bench to bedside. Eur Heart J 2014;35:3180–93.

17. Kandabashi T, Shimokawa H, Miyata K, et al. Inhibition of myosin phosphatase by upregulated rho-kinase plays a key role for coronary artery spasm in a porcine model with interleukin-1b. Circulation 2000;101:1319–23.

18. Shimokawa H, Takeshita A. Rho-kinase is an important therapeutic target in cardiovascular medicine. Arterioscler Thromb Vasc Biol 2005;25:1767–75.

19. Masumoto A, Mohri M, Shimokawa H, Urakami L, Usui M, Takeshita A. Suppression of coronary artery spasm by the Rho-kinase inhibitor fasudil in patients with vasospastic angina. Circulation 2002;105:1545–7.

20. 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.

21. van der Giessen WJ, Lincoff AM, Schwartz RS, et al. Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. Circulation 1996;94:1690–7.

22. Stojkovic S, Neskovic AN, Mehmedbegovic Z, et al. Reduced sirolimus systemic exposure and improved bioresorbable polymer properties: new

allies for the treatment of patients with coronary artery disease. Fundam Clin Pharmacol 2015;29:95–105.

23. Saito S, Valdes-Chavarri M, Richardt G, et al. A randomized, prospective, intercontinental evaluation of a bioresorbable polymer sirolimus-eluting coronary stent system: the CENTURY II (Clinical Evaluation of New Terumo Drug-Eluting Coronary Stent System in the Treatment of Patients with Coronary Artery Disease). Eur Heart J 2014;35:2021–31.

24. Garg S, Bourantas C, Serruys PW. New concepts in the design of drug-eluting coronary stents. Nat Rev Cardiol 2013;10:248–60.

25. Ong P, Athanasiadis A, Perne A, et al. Coronary vasomotor abnormalities in patients with stable angina after successful stent implantation but without in-stent restenosis. Clin Res Cardiol 2014;103:11–9.

26. Maseri A, Beltrame JF, Shimokawa H. Role of coronary vasoconstriction in ischemic heart disease and search for novel therapeutic targets. Circ J 2009;73:394–403.

27. Todo M, Park SD, Takayama T, et al. Fracture micromechanisms of bioabsorbable PLLA/PCL polymer blends. Eng Fract Mech 2007;74:1872–83.

28. Tada N, Virmani R, Grant G, et al. Polymer-free biolimus A9-coated stent demonstrates more sustained intimal inhibition, improved healing, and reduced inflammation compared with a polymer-coated sirolimus-eluting cypher stent in a porcine model. Circ Cardiovasc Interv 2010;3:174–83.

29. Matsumoto Y, Uwatoku T, Shimokawa H, et al. Long-term inhibition of Rho-kinase suppresses neointimal formation after stent implantation in porcine coronary arteries: involvement of multiple mechanisms. Arterioscler Thromb Vasc Biol 2004;24:181–6.

30. Shimokawa H, Ito A, Fukumoto Y, et al. Chronic treatment with interleukin-1b induces coronary intimal lesions and vasospastic responses in pigs in vivo. The role of platelet-derived growth factor. J Clin Invest 1996;97:769–76.

31. Hiroki J, Shimokawa H, Higashi M, et al. Inflammatory stimuli upregulate Rho-kinase in human coronary vascular smooth muscle cells. J Mol Cell Cardiol 2004;37:537–46.

32. Lindemann H, Sechtem U, Ong P, et al. Recurrent angina due to epicardial coronary spasm after successful bioresorbable vascular scaffold implantation. Circ J 2015;79:1853–4.

33. Kanazawa K, Suematsu M, Ishida T, et al. Disparity between serotonin- and acetylcholine-provoked coronary artery spasm. Clin Cardiol 1997;20:146–52.

34. Farb A, Burke AP, Kolodgie FD, Virmani R. Effect of endothelial shear stress on the progression of coronary artery disease, vascular remodeling, and in-stent restenosis in humans. Circulation 2003;108:1701–6.

35. Katrati A, Mehilli J, Dirschinger J, et al. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO) trial. Circulation 2001;103:2816–21.

KEY WORDS inflammation, polymers, stents, Rho-kinase

APPENDIX For an expanded Methods section and supplemental references, tables, and figures, please see the online version of this article.