Involvement of Rho-Kinase Activation in the Pathogenesis of Coronary Hyperconstricting Responses Induced by Drug-Eluting Stents in Patients With Coronary Artery Disease

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Background: Activation of Rho-kinase plays a central role in the pathogenesis of drug-eluting stents (DES)-induced coronary hyperconstricting responses in pigs in vivo has been previously demonstrated. In the present study, Rho-kinase activation involved in those responses in patients with coronary artery disease (CAD) is examined.

Methods and Results: In 24 patients with CAD who underwent coronary intervention with either DES or bare-metal stents (BMS), coronary vasomotor responses to intracoronary acetylcholine (ACh) before and after intracoronary pre-treatment with a Rho-kinase inhibitor, fasudil was examined. Coronary vasomotor responses by quantitative coronary angiography (QCA) and coronary vascular structure by optical coherence tomography (OCT) was evaluated. QCA showed that the coronary vasoconstricting responses to ACh were significantly enhanced in the DES group compared with the BMS group both at the proximal and the distal segments adjacent to the stents (proximal: BMS −13.0±10.7% vs. DES −25.4±14.3%, P=0.036; distal: BMS −24.4±12.2% vs. DES −43.8±14.7%, P=0.003). Importantly, fasudil markedly attenuated the enhanced vasoconstricting responses to ACh in the DES group (proximal 10.2±11.7%, distal 14.4±10.5% vs. before fasudil, both P<0.01). In the OCT imaging analysis, there was no significant correlation between intimal thickness and coronary vasoconstriction to ACh.

Conclusions: These results indicate that Rho-kinase activation is substantially involved in the pathogenesis of the DES-induced coronary hyperconstricting responses in patients with CAD, suggesting the therapeutic importance of Rho-kinase pathway. (*Circ J* 2012; **76**: 2552–2560)

Key Words: Acetylcholine; Drug-eluting stent; Optical coherence tomography; Percutaneous coronary intervention; Vasospasm

Bare-metal stents (BMS) and, more recently, drug-eluting stents (DES), such as sirolimus-eluting (Cypher™) and paclitaxel-eluting stents (Taxus™), have further improved early results and reduced the risk of restenosis.[1,2] However, DES have also not been shown to improve long-term survival of patients with coronary artery disease (CAD) compared with BMS.[3] Moreover, there is a concern on the safety issues of DES, given the potential for late stent thrombosis, especially after discontinuation of dual antiplatelet therapy.[4] Another concern is the DES-induced impairment of coronary vasomotion.[5–10] Indeed, enhanced coronary vasoconstriction in response to acetylcholine (ACh)[5–8] or exercise[9] was demonstrated in the coronary segments adjacent to DES, but not in those adjacent to BMS, and sudden cardiac arrest was reported among patients with severe coronary vasospasm following DES implantation.[10] Patients implanted with DES have a higher rate of positive exercise stress test than patients implanted with BMS 1 month after percutaneous coronary intervention (PCI),[11] which might also indicate DES-induced vasomotor dysfunction.

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Rho-kinase is one of the downstream effectors of the small

Figure 1. Patient flow diagram. ACh, acetylcholine; BMS, bare metal stent; CAG, coronary angiography; DES, drug-eluting stent; LAD and LCX, the left anterior descending and circumflex coronary arteries.

GTP-binding protein Rho and consists of 2 isoforms, ROCK1/Rho-kinase β and ROCK2/Rho-kinase α.[12,13]

We have previously demonstrated that activation of Rho-kinase plays a central role in the pathogenesis of coronary vasospasm in pigs and humans, and DES-induced coronary hyperconstricting responses in pigs.[14–23] Fasudil is a potent and selective inhibitor of Rho-kinase and we have already reported that fasudil was effective in preventing ACh-induced coronary artery spasm.[20] In the current study, we thus examined whether Rho-kinase activation is also involved in the DES-induced coronary hyperconstricting responses in patients with CAD by using fasudil. Furthermore, we examined structural changes of the coronary segments with DES-induced hyperconstricting responses using optical coherence tomography (OCT).[24]

Methods

All procedures were performed according to the protocols approved by the Institutional Review Board of Tohoku University.

Study Patients

From September 2007 to March 2010, a total of 84 patients were treated with a single stent for a de novo lesion in either the left anterior descending coronary artery (LAD) or the left circumflex coronary artery (LCX) (**Figure 1**). They were diagnosed with stable or unstable angina, or silent myocardial ischemia and were treated with a single stent for a de novo lesion in a native coronary artery. All lesions had a percent

Table 1. Baseline Characteristics			
	BMS (n=9)	DES (n=15)	P value
Age (years)	69.9±8.4	69.2±11.0	0.874
Male, n (%)	7 (78)	10 (67)	0.562
Follow-up duration (days)	227±69	289±74	0.066
Hypertension, n (%)	9 (100)	10 (67)	0.052
Diabetes mellitus, n (%)	5 (56)	6 (40)	0.459
Hyperlipidemia, n (%)	6 (67)	8 (53)	0.521
Smoking, n (%)	6 (67)	7 (47)	0.341
ACS, n (%)	3 (33)	0	0.017
LVEF (%)	73±8	74±12	0.931
Fasting glucose (mg/dl)	137±47	117±54	0.361
HbA1c (%)	6.3±1.1	6.3±1.2	0.972
hsCRP (mg/dl)	0.14±0.21	0.15±0.24	0.896
Total cholesterol (mg/dl)	165±28	160±37	0.708
LDL-cholesterol (mg/dl)	95±33	87±32	0.559
HDL-cholesterol (mg/dl)	46±7	44±10	0.615
ACE-I/ARB, n (%)	7 (78)	11 (73)	0.808
β-blocker, n (%)	6 (67)	10 (67)	1
CCB, n (%)	6 (67)	9 (60)	0.744
Nitrates, n (%)	4 (44)	3 (20)	0.202
Statin, n (%)	6 (67)	12 (80)	0.465

Results are expressed as mean±SD.
ACE-I, angiotensin converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; BMS, bare-metal stents; CCB, calcium channel blocker; DES, drug-eluting stents; Hb, hemoglobin; hsCRP, high-sensitivity C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; n, number.

| Table 2. Angiographic Characteristics			
	BMS (n=9)	DES (n=15)	P value
Lesion-LAD, n (%)	9 (100)	13 (87)	0.152
Lesion-LCX, n (%)	0	2 (13)	0.253
Lesion type B2 or C, n (%)	4 (44)	10 (67)	0.285
Stent diameter (mm)	3.3±0.4	3.0±0.4	0.069
Stent length (mm)	15.0±5.2	22.0±6.3	0.014
Balloon to artery ratio	1.1±0.1	1.1±0.1	0.169
Maximal pressure (atm)	14.0±5.6	18.7±5.1	0.052
Pre-PCI mean RVD (mm)	3.0±0.6	2.8±0.3	0.067
MLD (mm)	0.9±0.3	0.7±0.3	0.204
% DS	68.4±9.8	72.9±10.3	0.322
Post-PCI mean RVD (mm)	3.0±0.5	2.8±0.4	0.258
MLD (mm)	2.8±0.4	2.6±0.4	0.366
% DS	7.4±6.6	7.8±5.0	0.864
Acute gain (mm)	1.9±0.4	1.9±0.5	0.966
Proximal segment (mm)	2.9±0.6	2.7±0.4	0.211
Distal segment (mm)	2.4±0.3	2.2±0.4	0.298
Follow-up mean RVD (mm)	2.9±0.5	2.8±0.3	0.711
MLD (mm)	2.0±0.4	2.4±0.3	0.0081
% DS	32.3±11.6	14.5±5.7	0.0014
Late loss (mm)	0.9±0.5	0.2±0.2	0.0045
Proximal segment (mm)	2.8±0.6	2.6±0.5	0.298
Distal segment (mm)	2.4±0.4	2.2±0.5	0.191

Results are expressed as mean±SD. The diameter of the proximal and the distal segment adjacent to the stent was measured after intracoronary administration of isosorbide dinitrate.
MLD, minimum lumen diameter; LAD, left anterior descending artery; LCX, left circumflex artery; % DS, percent diameter stenosis; PCI, percutaneous coronary intervention; RVD, reference vessel diameter. Other abbreviations as in Table 1.

diameter stenosis greater than 50% and less than 100%, and were treated with intravascular ultrasound-guided stenting. The stent implantation was performed so that the minimum stent lumen cross-sectional area was enlarged more than 80% of the average of the proximal and distal reference lumen area and full stent-vessel wall apposition was confirmed by intravascular ultrasound. All procedural decisions, including device selection and adjunctive pharmacotherapy, were made at the discretion of the individual PCI operator. The patients were divided into the following 2 groups according to the type of stent: the BMS group (n=43) and the DES group (n=41). Follow-up coronary angiography was scheduled 6 to 10 months after PCI. In the BMS group, 10 patients did not undergo follow-up coronary angiography and 24 patients were excluded because of stent restenosis (n=11), remaining organic stenosis (n=5) including the left main trunk (LMT) lesion (n=3), renal dysfunction (n=1), or others (n=7), whereas in the DES group, 3 patients did not undergo follow-up coronary angiography and 21 patients were excluded because of stent restenosis (n=3), remaining organic stenosis (n=8) including the LMT lesion (n=6), left ventricular or renal dysfunction (n=5), or others (n=5). Finally, the present study included 9 patients for BMS group treated with Driver™ (Medtronic, Minneapolis, MN, USA; n=4), MULTI-LINK VISION™ (Guidant, Santa Clara, CA, USA; n=3), and Liberté™ (Boston Scientific, Natick, MA, USA; n=2). Because 1 patient developed severe coronary vasospasm following ACh provocation test and required intracoronary isosorbide dinitrate (ISDN) to relieve it, the DES group consisted of 15 patients treated with Cypher™ (Johnson & Johnson, New Brunswick, NJ, USA; n=15) (Figure 1). In the present study, the rate of restenosis noted in the follow-up

coronary angiography was 26% (11/43) in the BMS group and was 7% (3/41) in the DES group.

Study Protocol

At least 24 h before catheterization except for sublingual nitroglycerin when needed, long-acting nitrates, calcium-channel blockers (CCB), and β-blockers were discontinued, whereas angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and statins were not discontinued in the present study. Following the baseline coronary angiography, the ACh provocation test was performed as reported previously.[25] Briefly, ACh was administrated into the left coronary artery with stent implantation in an escalating manner (12.5, 25, 50, and 100 μg). A positive response to ACh was defined as the development of >90% stenosis accompanied by chest pain and/or ischemic electrocardiogram (ECG) changes.[26] After intracoronary administration of ACh, we carefully followed the patient by continuously monitoring arterial pressure and 12-lead ECG and by taking serial coronary arteriograms at 1-min intervals. Within a few minutes after ACh infusion, coronary spasm and ischemic ECG changes spontaneously subsided without nitrates or any other treatment. Thereafter, fasudil (300 μg/min) (Asahi Kasei Pharma, Tokyo, Japan), a specific Rho-kinase inhibitor, was infused over 15 min into the left coronary artery via a Judkins catheter. ACh was subsequently re-infused in an escalating manner from 12.5 μg to the same dose that had induced a positive response.[20,21] Fasudil administration (300 μg/min for 15 min IC) achieves plasma concentration of 3.7 μmol/L,[19] which is enough to inhibit Rho-kinase as its IC50 value is
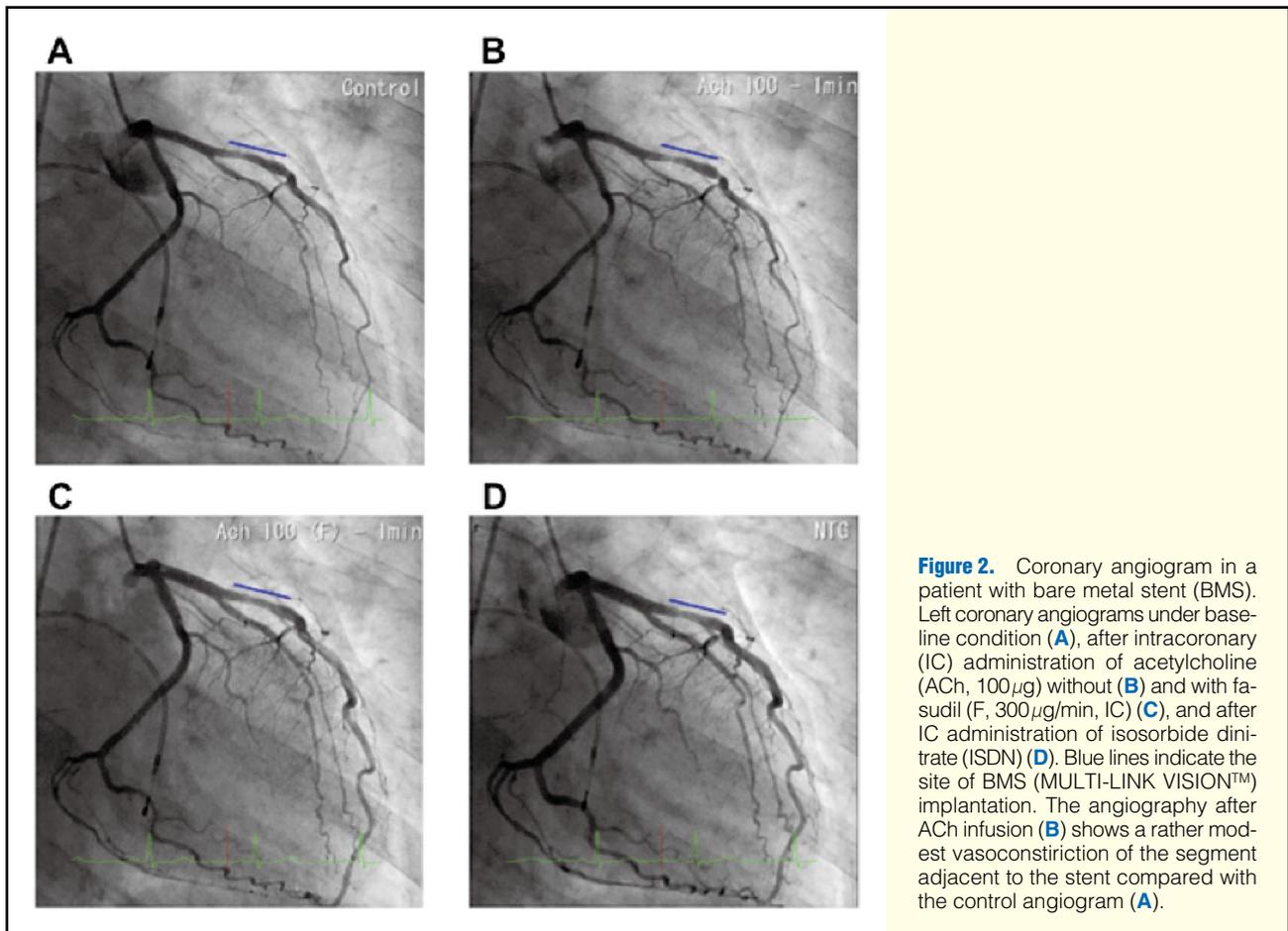
Figure 2. Coronary angiogram in a patient with bare metal stent (BMS). Left coronary angiograms under baseline condition (**A**), after intracoronary (IC) administration of acetylcholine (ACh, 100μg) without (**B**) and with fasudil (F, 300μg/min, IC) (**C**), and after IC administration of isosorbide dinitrate (ISDN) (**D**). Blue lines indicate the site of BMS (MULTI-LINK VISION™) implantation. The angiography after ACh infusion (**B**) shows a rather modest vasoconstiriction of the segment adjacent to the stent compared with the control angiogram (**A**).

<1.9μmol/L in vitro.[27] Finally, a coronary vasodilating response to intracoronary ISDN (2mg) was examined. For ethical reasons, patients with a total or subtotal vasospastic occlusion were excluded from the study, as were patients who had severe chest pain, hypotension, or both; these patients were immediately treated with intracoronary ISDN. Quantitative coronary angiography (QCA) was performed with a validated densitometric analysis system (CardioAgent™, Toshiba Medical, Tokyo, Japan).[28] Our previous study demonstrated that the present QCA analysis has a high intraobserver (99%) and interobserver reproducibilities (98%)[23]

Coronary vasomotor responses to ACh were quantified as percent change in luminal diameter compared with that after intracoronary infusion of ISDN. Coronary segments assessed by QCA included the stented segment, the proximal and distal segment adjacent to the stent (at least 5 to 10mm apart from proximal and distal stent edges), and a non-stented reference segment.[10,23] When the stent was implanted in LAD, LCX was set as the reference vessel, and vice versa.

OCT Imaging Analysis

We also performed OCT examination in the subset of patients as follows.[29] After a coronary vasodilating response to intracoronary ISDN was examined, an over-the-wire type occlusion balloon catheter (Helios™, LightLab Imaging Inc, Westford, MA, USA) and an OCT imaging probe (ImageWire™, LightLab Imaging Inc) were inserted into the stented coronary artery. The entire length of the stent was imaged using an automatic pullback device moving at 1mm/s and the OCT image clearly

visualized the stent cross-section.[30] OCT data were recorded and were analyzed using proprietary off-line software provided by the manufacturer. In the OCT images, the intima was identified as the signal-rich layer nearest the lumen and its thickness was measured.[29,30] Neointimal thickness was measured as the distance between the endo-luminal surface of neointima and stent strut with a measurement line as perpendicular as possible to the surfaces of them.

Statistical Analysis

Statistical analysis was performed using SAS 9.1 software (SAS Institute, Cary, NC, USA). Continuous data are summarized as mean±SD. Unpaired or paired t-test was used to analyze differences in continuous variables. Fisher and chi-square tests were used to analyze differences between categorical variables. One-way ANOVA was used to test differences between the BMS group and the DES group and post-test Bonferroni multiple comparisons for paired data. Correlation among variables was determined using linear regression analysis. A linear regression line was calculated using the least-squares method to assess the correlation between 2 parameters. A P-value less than 0.05 was considered statistically significant.

Results

Baseline Characteristics

The mean interval from stent implantation to follow-up coronary angiography was similar between the BMS group (227±
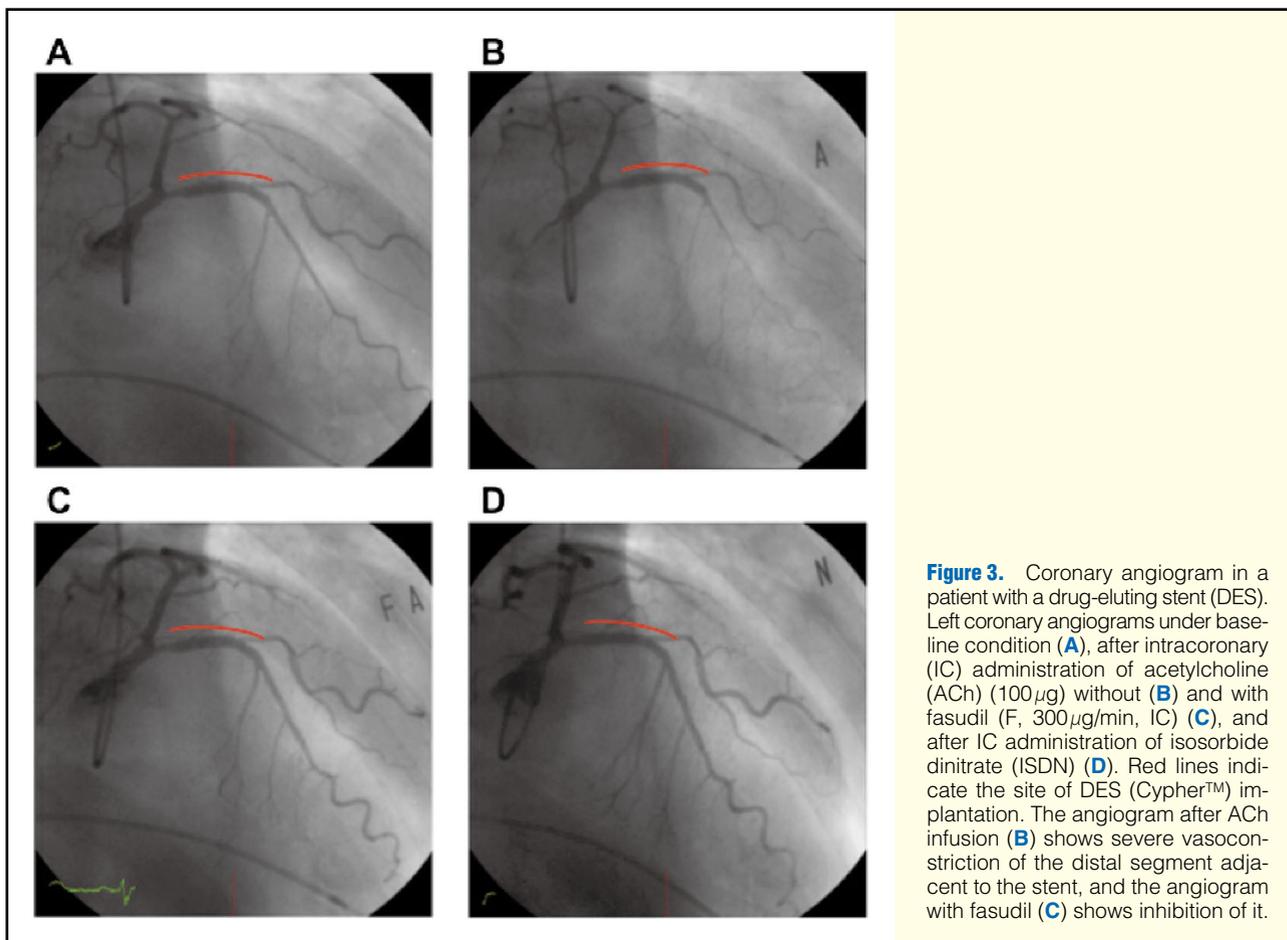
Figure 3. Coronary angiogram in a patient with a drug-eluting stent (DES). Left coronary angiograms under baseline condition (**A**), after intracoronary (IC) administration of acetylcholine (ACh) (100 μg) without (**B**) and with fasudil (F, 300 μg/min, IC) (**C**), and after IC administration of isosorbide dinitrate (ISDN) (**D**). Red lines indicate the site of DES (Cypher™) implantation. The angiogram after ACh infusion (**B**) shows severe vasoconstriction of the distal segment adjacent to the stent, and the angiogram with fasudil (**C**) shows inhibition of it.

69 days) and the DES group (289±74 days). The baseline characteristics of the study patients were also similar between the 2 groups, except for the prevalence of patients with acute coronary syndrome (BMS 33% vs. DES 0%, P=0.017) (**Table 1**). Left ventricular ejection fraction was well preserved in both groups and high-sensitivity C-reactive protein (hsCRP) level was similar between the 2 groups (**Table 1**).

Angiographic Data
The stent length was significantly longer (P=0.014) in the DES group than in the BMS group (**Table 2**). However, no difference was noted for maximal inflation pressure, balloon to artery ratio or other QCA data immediately after PCI between the 2 groups. In the follow-up coronary angiography, the BMS group revealed a higher percent diameter stenosis and a greater late loss compared with the DES group (**Table 2**). Mean diameter stenosis at follow-up period was 32.3±11.6% in the BMS group and 14.5±5.7% in the DES group (P=0.0014). Similarly, the mean late loss was 0.9±0.5 mm in the BMS group and 0.2±0.2 mm in the DES group (P=0.0045) (**Table 2**).
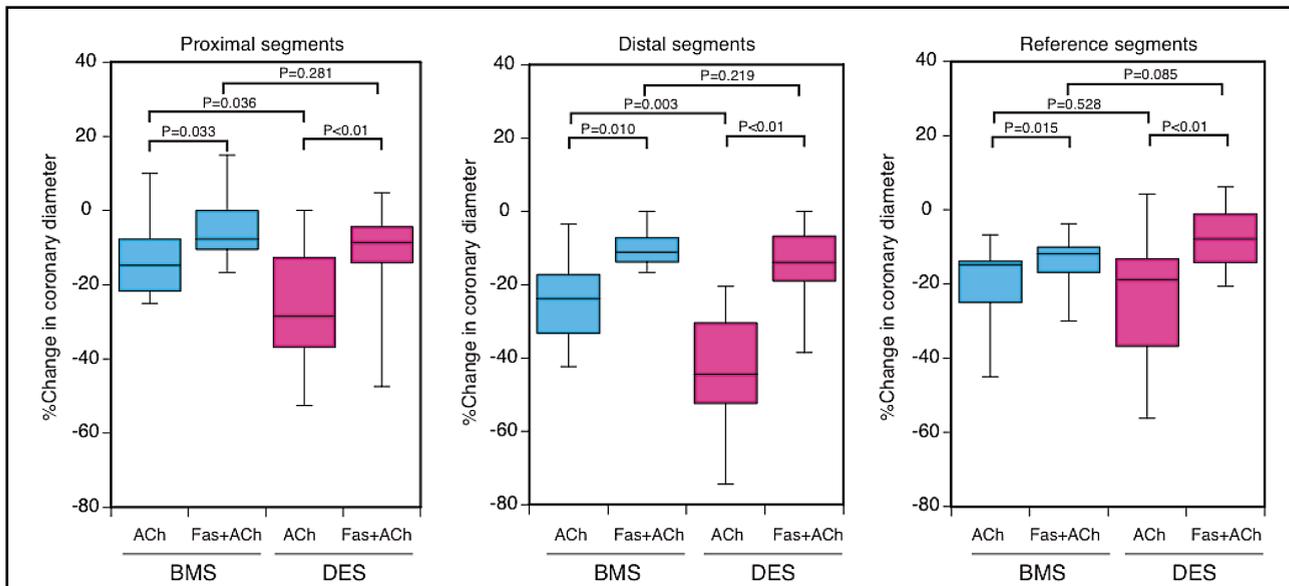
Coronary Vasomotor Responses to ACh Without and With Fasudil Pre-Treatment
Figure 2 (the BMS group) and **Figure 3** (the DES group) show the representative coronary angiograms of the left coronary arteries during the ACh provocation test. The maximal dose of ACh used was similar between the 2 groups (BMS 86±28 μg vs. DES 68±32 μg, P=0.183). The diameters of the proximal and the distal segments adjacent to the stents were also similar

between the 2 groups throughout the study period (**Table 2**). However, QCA showed that the coronary vasoconstricting responses to ACh were significantly enhanced in the DES group compared with the BMS group, both at the proximal and distal segments adjacent to the stents (proximal: BMS −13.0±10.7% vs. DES −25.4±14.3%, P=0.036; distal: BMS −24.4±12.2% vs. DES −43.8±14.7%, P=0.003) (**Figure 4**). Although 3 acute coronary syndrome (ACS) patients were included in the BMS group, there was no difference in the coronary vasomotor responses in the chronic phase between those with and without ACS in the BMS group (**Figure S1**). In contrast, in the reference (non-stented) segments, the vasoconstricting responses to ACh were similar between the 2 groups (**Figure 4**). Moreover, in the stented segment, there was no significant change in coronary diameter in both groups.

Pre-treatment with fasudil attenuated modest coronary vasoconstriction to ACh in the BMS group (proximal −5.1±9.3%, distal −9.6±5.4%, P=0.033 and P=0.010 vs. before fasudil, respectively) and severer coronary vasoconstriction to ACh in the DES group (proximal −10.2±11.7%, distal −14.4±10.5%, both P<0.01 vs. before fasudil), both at the proximal and distal segments adjacent to the stents (**Figure 4**). Furthermore, in the reference segments, similar changes were also observed (BMS: from −20.6±11.9% to −13.8±7.9%, P=0.015) (DES: from −25.0±18.2% to −8.0±7.5%, P<0.01). Importantly, coronary responses to ACh were similar in the pre-treatment with fasudil between the 2 groups.

In the overall analysis including segments proximal and distal to BMS and DES, there was a significant correlation be-

Figure 4. Coronary vasomotor responses to intracoronary acetylcholine (ACh). Changes in coronary diameters at the proximal and the distal segments adjacent to the stents and the reference segments in response to ACh before and after fasudil pre-treatment are shown. Coronary vasomotor responses to intracoronary acetylcholine are expressed as percent change in coronary diameter from that following isosorbide dinitrate (ISDN) administration. Fas, fasudil.
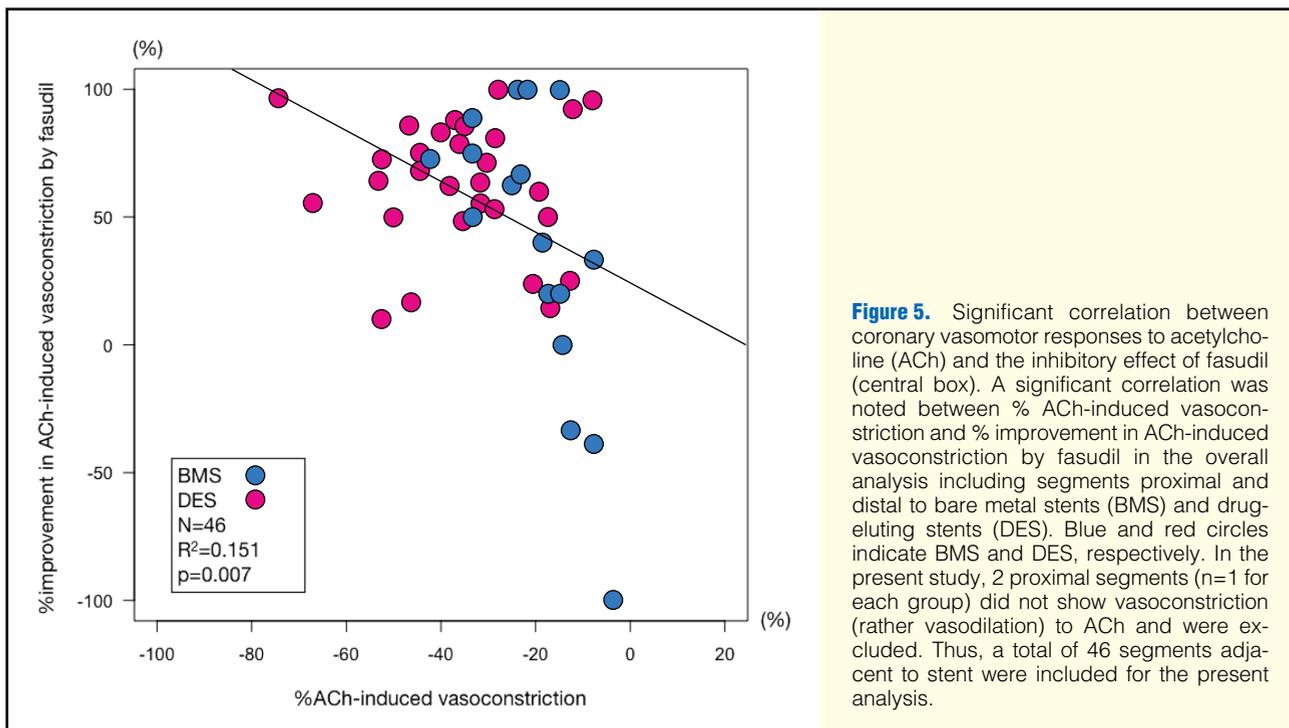

Figure 5. Significant correlation between coronary vasomotor responses to acetylcholine (ACh) and the inhibitory effect of fasudil (central box). A significant correlation was noted between % ACh-induced vasoconstriction and % improvement in ACh-induced vasoconstriction by fasudil in the overall analysis including segments proximal and distal to bare metal stents (BMS) and drug-eluting stents (DES). Blue and red circles indicate BMS and DES, respectively. In the present study, 2 proximal segments (n=1 for each group) did not show vasoconstriction (rather vasodilation) to ACh and were excluded. Thus, a total of 46 segments adjacent to stent were included for the present analysis.

tween % ACh-induced vasoconstriction and % improvement in ACh-induced vasoconstriction by fasudil ($R^2=0.151$, $P=0.007$) (**Figure 5**).

Coronary vasodilating responses to fasudil from the baseline diameter at the proximal and the distal segments adjacent to the stents were similar between the 2 groups (proximal: BMS 15.7±11.3% vs. DES 8.8±7.0%, P=0.076; distal: BMS

20.6±13.3% vs. DES 11.0±13.2%, P=0.101) with no significant difference in diameter changes in the reference segments (BMS 14.6±14.3% vs. 10.2±9.6%, P=0.370). Coronary vasodilating responses to ISDN from the baseline diameter at the proximal and the distal segments adjacent to the stents were also similar between the 2 groups (proximal: BMS 16.2±12.5% vs. DES 13.6±10.8%, P=0.593; distal: BMS 22.4±9.8% vs.
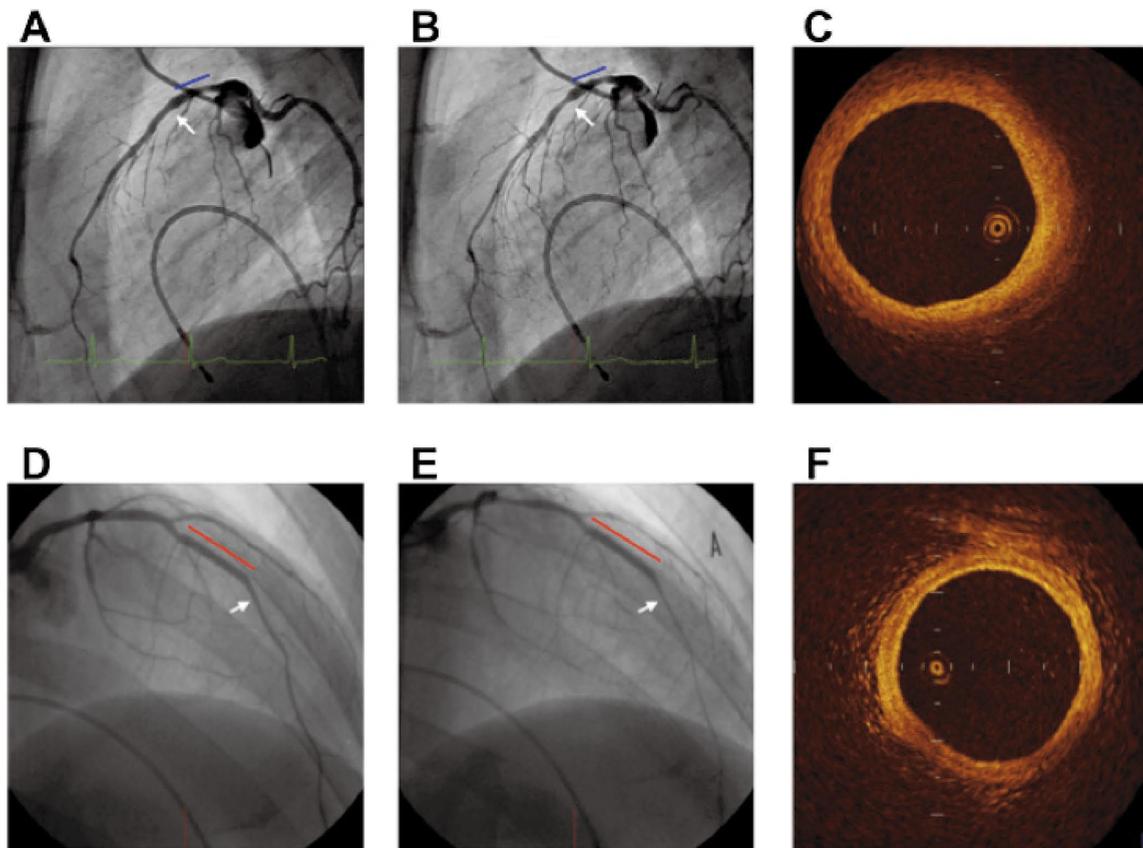
Figure 6. Optical coherence tomography (OCT) evaluation of stent-implanted coronary arteries. Left coronary angiogram under control baseline condition (**A**, bare metal stent (BMS); **D**, drug-eluting stent (DES)), after intracoronary administration of acetylcholine (ACh) (**B**, BMS; **E**, DES) and the images of the OCT at the distal segments adjacent to the stents (white arrows) (**C**, BMS; **F**, DES). Blue lines indicate the site of BMS implantation and red lines the site of DES implantation. The OCT images showed that at the distal segments, there was a comparable intimal thickness in the 2 groups without plaque formation.

DES 17.6±11.2%, P=0.302) with no significant difference in diameter changes in the reference segments (BMS 18.0±11.5% vs. DES 12.8±10.5%, P=0.262).

OCT Imaging Analysis

The measurable OCT images were obtained in the BMS (n=6) and the DES (n=14) groups. **Figure 6** shows coronary angiograms and OCT images of distal segments adjacent to stents where coronary vasoconstriction was induced by ACh infusion in the BMS and the DES groups. The OCT images showed that at the distal segments adjacent to the stents, there was a comparable intimal thickness in the 2 groups (BMS 168±84 μm vs. DES 169±50 μm, P=0.98), and that there was no significant correlation between the intimal thickness of the distal segments and coronary vasoconstriction to ACh (R²=0.010, P=0.732 for DES; R²=0.021, P=0.539 for DES and BMS). The neointimal thickness at the stent site in the DES group was significantly less than that measured in the BMS group (BMS 343±137 μm vs. DES 88±40 μm, P=0.006). No intracoronary thrombus formation was noted in the DES or the BMS group.

Discussion

To the best of our knowledge, this is the first study that dem-

onstrates that Rho-kinase activation is substantially involved in the pathogenesis of DES-induced hyperconstricting responses in patients with CAD.

Rho-Kinase Activation and DES-Induced Coronary Hyperconstricting Responses

Enhanced Rho-kinase activity plays a central role in the pathogenesis of coronary vasospasm in humans.[12] Fasudil is a potent and selective inhibitor of Rho-kinase, and has an inhibitory effect on Rho-kinase 10 and 100 times more than on protein kinase C and myosin light chain kinase, respectively.[16] Intracoronary administration of fasudil or hydroxyfasudil[12] markedly inhibits coronary vasospasm in porcine models in vivo[14–19] and in humans.[20,21] In the porcine stent model, (a) DES (Cypher™ and Taxus™) enhanced coronary vasoconstricting responses as compared with BMS; (b) the hyperconstricting responses were abolished by hydroxyfasudil; and (c) Rho-kinase expression and activity were increased in the segments adjacent to DES.[23,31] In the present study, the previous experimental findings were confirmed in patients with CAD. Indeed, enhanced coronary vasoconstricting responses to ACh at the segments adjacent to the stents were markedly attenuated by fasudil. Thus, the present results indicate that Rho-kinase-mediated mechanism plays a pivotal role in the DES-induced coronary

hyperconstriction in response to ACh in patients with CAD.

Mechanisms of the DES-Induced Coronary Hyperconstricting Responses

In the present study, functional tests specific for the endothelium were not performed. However, in order to obtain some clues to the mechanisms of DES-induced coronary hyperconstricting responses in patients with CAD, OCT imaging analysis was performed as it provides detailed information on the intimal area of the coronary artery.[24,32] The results demonstrated that intimal hyperplasia might not play an important role. This is consistent to the previous finding that coronary vasospasm is associated with a variable degree of intimal hyperplasia in a swine model of coronary vasospasm.[33,34] Furthermore, diffusion of the sirolimus from the stent deployment site to the adjacent vascular tissue might not be involved in the mechanisms because OCT images showed relatively minor intimal tissue responses. Intracoronary thrombus formation, which could be detected by OCT,[29] was not found in the present patients treated with DES or BMS. Inflammatory cell accumulation, which also could be detectable by OCT,[35] might not be involved at least in the intimal side of the coronary arteries. However, it was reported that inflammatory responses of the coronary artery especially at the adventitia are accelerated at the DES site.[23,36] The expression and activity of Rho-kinase are accelerated by inflammatory stimuli, such as angiotensin II and interleukin-1β, through protein kinase C/Nf-κB pathway.[37] Because hsCRP value was similar between the 2 groups, systemic inflammatory responses might not be involved. Thus, it is conceivable that DES-induced local inflammatory responses of the coronary artery enhance Rho-kinase expression and activity with resultant coronary hyperconstricting responses in patients with CAD.[23]

Clinical Implications of the Study

Inflammatory responses to DES could be a result of a local hypersensitivity reaction to the non-bioresorbable durable polymer.[36] To avoid such an undesirable effect of polymers, biocompatible and bioresorbable polymers have been developed.[38] The recent studies demonstrated that coronary vasomotion was preserved with a new-generation biolimus-eluting stent with bioresorbable polymers as compared with the Cypher stent.[39,40] Since we are examining the Rho-kinase activation with a new generation of DES, we would like to report our findings separately in the future. However, it also should be emphasized that Cypher™ has already been deployed in millions of patients worldwide, and thus, aggressive efforts should be made to improve coronary vasomotion in those patients implanted with Cypher™. Rho-kinase inhibitors[12,20,21] and other vasculoprotective agents (eg, CCB and statins) might help to optimize the efficacy and the safety of DES, in addition to developing innovative devices.

Study Limitations

Several limitations should be mentioned for the present study. First, this study enrolled a relatively small number of patients and the BMS group included 3 different types of stent. Although the present findings remain to be confirmed in a future study with a large number of patients, it is practically difficult to perform ACh provocation tests in all patients with DES as delineated in the present study. Second, the exclusion rate of our study patients was relatively high; 79% (34/43) in the BMS group and 59% (24/41) in the DES group. However, this was based on our inclusion criteria as mentioned in the Methods section. Third, although the BMS and the DES groups showed

well-balanced baseline characteristics, the stent type was not randomized. Fourth, the information on the presence or absence of coronary spasm before PCI was not available as we did not perform spasm provocation test before PCI for obvious ethical reasons. Finally, in the clinical setting of vascular dysfunction, it should be noted that the discrimination between endothelial component and smooth muscle component is not easy and therefore further studies are needed.

Conclusion

The present study indicates that Rho-kinase activation is associated with the pathogenesis of the DES-induced coronary hyperconstricting responses in patients with CAD, suggesting the therapeutic importance of the Rho-kinase pathway in the DES-related coronary events.

Disclosures

Conflict of Interest: None.

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Supplementary Files

Supplementary File 1

Figure S1. Coronary vasomotor responses to intracoronary acetylcholine (ACh) in bare metal stent (BMS) patients.

Please find supplementary file(s);
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