Vasodilatory Effect of Subsequent Administration of Fasudil, a Rho-Kinase Inhibitor, Surpasses That of Nitroglycerin at the Concentric Coronary Stenosis in Patients With Stable Angina Pectoris

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Background Recent studies have suggested that the Rho/Rho-kinase mediated pathway (Rho-kinase pathway) regulates the vasomotion of arteries in pathological conditions. However, it remains unclear regarding whether this pathway regulates the coronary vasomotion of atherosclerotic lesions.

Methods and Results The coronary diameter at the concentric stenotic site, which is considered to reflect the whole circumferential atherosclerosis, in patients with stable angina pectoris (SAP; n=11) and the control site in patients with SAP and chest pain syndrome (CPS; n=9), was measured at baseline and after the intracoronary administration of nitroglycerin (200 μg) and the subsequent intravenous infusion of fasudil (30 mg for 30 min), a Rho-kinase inhibitor, during coronary angiography. The change in the diameter with fasudil at the concentric stenotic site (22.0±10.0%) was significantly higher than that with nitroglycerin (4.7±6.0%, p<0.001) in patients with SAP. Meanwhile, the vasodilatory effect of nitroglycerin and fasudil at the control site was similar in both group of patients (25.5±17.3% and 21.9±14.9% in SAP and 34.4±20.8% and 33.2±23.6% in CPS, respectively).

Conclusions The vasodilatory effect of the subsequent administration of fasudil surpassed that of nitroglycerin at the concentric coronary stenosis in patients with SAP, thus suggesting that the Rho-kinase pathway regulates the coronary vasomotion of atherosclerotic lesions. (Circ J 2006; 70: 402–408)

Key Words: Atherosclerosis; Coronary vasomotion; Fasudil; Rho-kinase; Stable angina pectoris

Coronary arteries exert a vasomotor action that responds to numerous stimuli such as neurohumoral factors, endothelium-derived substances, and artificially administered vasoactive agents in a sensitive manner. Indeed, intact epicardial coronary arteries dilate promptly after the administration of nitrates or other kinds of vasodilators. In contrast, it remains controversial as to whether the coronary atherosclerotic site responds to vasodilatory agents; this continues to be an important topic in terms of the treatment of stable angina pectoris (SAP). In clinical situations, Kaski et al and Yamagishi et al reported that the vasodilatory potential at the coronary atherosclerotic site was impaired. In contrast, McPherson et al suggested in their report that the coronary atherosclerotic site had a vasodilating ability. It should be emphasized, however, that these clinical studies only adopted nitrates for the evaluation of coronary vasomotion at the site of atherosclerotic lesions. Therefore, other vasodilators than nitrates should be used to more accurately assess the vasodilatory potential at atherosclerotic lesions.

It has recently been reported that the Rho/Rho-kinase mediated pathway (Rho-kinase pathway) is involved in the pathogenesis of various cardiovascular disorders. Rho-kinase is one of the downstream effectors of small GTPase Rho, and it plays a pivotal role in diverse cellular functions, such as actin cytoskeleton organization, cell adhesion and motility, cytokinesis, gene expression, and smooth muscle contraction. In clinical situations, the Rho-kinase pathway contributes to the occurrence of both epicardial and microvascular coronary artery spasm and the augmentation of peripheral vascular resistance in both patients with hypertension and normotensive current smokers. These findings suggest that the Rho-kinase pathway regulates the vasomotion of arteries suffering from pathological conditions. It remains unclear, however, as to whether this pathway is also involved in the regulation of coronary vasomotion at the atherosclerotic site, which is one of the most prevalent diseased states in the arterial wall.

We therefore hypothesized that the degree of coronary vasodilatation at the atherosclerotic site with pharmacological inhibition of the Rho-kinase pathway was more potent than that with nitrates. In the present study, to confirm this hypothesis, we compared the vasodilatory effect of nitroglycerin (NTG) with the subsequent administration of fasudil, a Rho-kinase inhibitor, at a site of concentric coronary stenosis, which was considered to reflect the whole circumferential atherosclerosis in the arterial wall in patients with SAP.
Methods

Study Patients

In the present study, we consecutively enrolled 11 patients with SAP (age: 66±5 years, 8 males, SAP group) and 9 patients with chest pain syndrome (CPS) (age: 63±5 years, 4 males, CPS group). The patients with SAP were those who fulfilled all of the following criteria: (1) the typical ischemic chest symptoms on effort; (2) positive finding(s) for myocardial ischemia of effort detected by ambulatory or exercise stress electrocardiography (ECG), or myocardial perfusion imaging; and (3) concentric stenosis of more than 50% but not exceeding 90% according to the classification of the American Heart Association (AHA) committee report28 on the epicardial coronary arteries and no calcification on coronary angiography with visual estimations. The diagnosis of CPS was made when: (1) atypical chest symptoms developed during rest or effort without any ischemic ECG change; (2) no organic stenosis in the epicardial coronary arteries were documented with coronary angiography; and (3) a negative result for coronary spasm was obtained with the acetylcholine (ACh) provocation test. Any patients with a previous myocardial infarction, an age of 80 years or more, a left ventricular ejection fraction of less than 40%, abnormal systolic blood pressure (SBP, <100 mmHg or >180 mmHg), or acute coronary syndrome were excluded from this study. Anti-anginal drugs, except for sublingual NTG, were withdrawn at least 24 h before the start of the study.

Preparation of Each Drug

In the present study, NTG (Nipponkayaku, Tokyo), ACh (Daiichi Pharmaceutical, Tokyo), and fasudil (Asahikasei Pharma, Tokyo) were used. Each drug was dissolved in a concentration of 50 μg/ml, 20 μg/ml, and 0.3 mg/ml of physiological saline, respectively, immediately before use.

Study Protocol

The study protocol was approved by the ethics committee of Tama-Nagayama Hospital, Nippon Medical School. Written informed consent was obtained from all patients. Coronary angiography was performed by using the Judkins technique through a femoral puncture in the morning (09.00–10.00 h). Baseline angiograms of both the right and left coronary arteries were taken orthogonally in the right and left anterior oblique positions to clearly visualize both the stenotic sites and each coronary artery, including its branches. The grade of coronary stenosis according to the AHA classification28 and the morphology of the stenosis were visually assessed using the 2 orthogonal projections with an agreement among the 3 experienced cardiologists who were present in the laboratory. Concentric stenosis was defined as symmetrical luminal narrowing established by the 2 orthogonal projections. In the CPS group, the ACh test was performed to rule out coronary spasm when no organic stenosis in the epicardial coronary arteries had been confirmed by baseline angiography. Coronary spasm was defined as the total or subtotal occlusion or severe vasoconstriction in the epicardial coronary arteries with ischemic ST-T segment changes on ECG and typical anginal chest symptoms. In cases where spasm could not be provoked after the intracoronary injection of ACh with incremental doses of 50 and 100 μg into the left coronary artery (LCA) and 20 and 50 μg into the right coronary artery (RCA), the ACh test was judged to be negative. In the SAP group, the ACh test was not performed, and 200 μg of NTG was infused into the RCA and LCA separately for 10 s after the baseline angiography. In the CPS group, NTG was administered in the same manner after the completion of the ACh test. In all patients, 30 mg of fasudil was then infused into the antecubital vein for 30 min. Because the plasma half-lives of the α and β phases of NTG were approximately 0.4 and 5.3 min, respectively,29 we started the infusion of fasudil 5 min after the administration of NTG. The doses of NTG and fasudil used in the present study were thought to exert adequate vasodilatory effects.30–32 At 1 min after the administration of NTG and at the end of the infusion of fasudil, coronary angiography was repeated and the grade and morphology of the stenosis was visually re-assessed.

Quantitative Coronary Angiography (QCA)

The minimal luminal diameter (MLD) and the reference diameter (RD) of concentric stenotic sites in the SAP group and the diameter of the control site (control diameter; CD) in both groups were measured at the end-diastolic phase with offline QCA using the MDQM-QCA software package (version 2.00, Medcon, Tel Aviv) for Windows at baseline and after the administration of each drug. The coronary diameter was measured with the order of 10−2 mm, in accordance with the previous report.33 The percentage of diameter stenosis (%DS) was calculated as follows:

\[
\%DS = \left( \frac{RD - MLD}{RD} \right) \times 100 \%
\]

The control site was defined as follows: (1) the nonstenotic epicardial coronary segment (in the SAP group, it was sought in coronary arteries that did not contain the stenotic lesion measured with QCA); and (2) the coronary segment with a vessel size comparable to the RD of the SAP group after the administration of NTG. The percentage change in the diameter with NTG and fasudil was calculated from the diameter after the administration of each drug and that at baseline. Measurements were performed by 2 independent investigators who did not have any information on these patients.

Statistical Analysis

All data are expressed as mean±SD. Statistical analyses were performed by using the Stat View software (version 5.0, SAS institute, North Carolina, USA) for Macintosh. Differences in the clinical characteristics between the SAP and CPS groups were compared by using either Fisher’s exact test or the unpaired Student’s t-test as appropriate. A paired t-test was used to examine the hemodynamic changes with the administration of NTG or fasudil. Differences in the percentage change in the MLD or CD between the administrations of NTG and fasudil were analyzed by using the unpaired Student’s t-test. A repeated-measure analysis of variance (ANOVA) was used to compare the difference in the %DS at baseline and after the administration of NTG and fasudil. Post-hoc Bonferroni-Dunn tests were performed if the ANOVA showed significance. The correlation between the MLD and its percentage change with each drug was evaluated by using a linear regression analysis. A p-value of less than 0.05 was considered to be statistically significant.
Results

Patient Characteristics

None of the patients used sublingual NTG within the 12 h preceding the start of the present study. The patient characteristics are shown in Table 1. There were no statistical differences in the characteristics between the groups. Nine of 11 patients in the SAP group had taken anti-platelet agents because they had already been diagnosed for angina pectoris before the study. Although both groups showed a high prevalence of hyperlipidemia, only a few patients (approximately 20% in both groups) had taken statins.

Angiographical Findings and QCA Measurements

The angiographical findings in patients with SAP are shown in Table 2. Eight patients showed single vessel disease. The measurement of MLD was performed at 5 stenotic sites in the RCA, 4 sites in the left anterior descending coronary artery (LAD), and 2 sites in the left circumflex coronary artery (LCx). The measurement of CD could not be performed in 1 patient with SAP because of technical difficulties with QCA. In the 10 remaining patients, the measurements of CD were performed in the LAD (6 patients) and the LCx (3 patients). The morphology of the lesions did not change after the administration of either NTG or fasudil.

Table 1 Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SAP (n=11)</th>
<th>CPS (n=9)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>66±5</td>
<td>63±5</td>
<td>0.12</td>
</tr>
<tr>
<td>Male gender</td>
<td>8 (72.7%)</td>
<td>4 (44.4%)</td>
<td>0.36</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.4±2.6</td>
<td>24.2±2.2</td>
<td>0.91</td>
</tr>
<tr>
<td>Lipid profiles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>235±40</td>
<td>212±31</td>
<td>0.17</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>151±62</td>
<td>178±85</td>
<td>0.44</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>56±16</td>
<td>57±16</td>
<td>0.81</td>
</tr>
<tr>
<td>Coronary risk factors</td>
<td></td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>7 (63.6%)</td>
<td>4 (44.4%)</td>
<td>0.65</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>10 (90.9%)</td>
<td>8 (88.9%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2 (18.2%)</td>
<td>0 (0%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Currently smoking</td>
<td>3 (27.3%)</td>
<td>0 (0%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>9 (81.8%)</td>
<td>5 (55.6%)</td>
<td>0.34</td>
</tr>
<tr>
<td>ACE-I or ARB</td>
<td>2 (18.2%)</td>
<td>1 (11.1%)</td>
<td>&gt;0.99</td>
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<tr>
<td>Other antihypertensive agents</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Statins</td>
<td>2 (18.9%)</td>
<td>2 (22.2%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Antidiabetic agents</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>

Values are presented as mean±SD or the number of patients (% of total). SAP, stable angina pectoris; CPS, chest pain syndrome; BMI, body mass index; HDL, high density lipoprotein; ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers.

Table 2 Angiographical Findings and the Site for QCA Measurements in Patients With SAP

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Stenotic site and grade</th>
<th>Stenotic site for QCA</th>
<th>Control site for QCA</th>
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<tbody>
<tr>
<td>1</td>
<td>#7.75%</td>
<td>#7.</td>
<td>#13.</td>
</tr>
<tr>
<td>2</td>
<td>#6.50%</td>
<td>#6.</td>
<td>#13.</td>
</tr>
<tr>
<td>3</td>
<td>#1.75%</td>
<td>#1.</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
<td>#14.50%</td>
<td>#14.</td>
<td>#7.</td>
</tr>
<tr>
<td>5</td>
<td>#4.90%, #7.75%, #14.99%</td>
<td>#4.</td>
<td>#13.</td>
</tr>
<tr>
<td>6</td>
<td>#1.90%, #7.75%</td>
<td>#1.</td>
<td>#12.</td>
</tr>
<tr>
<td>7</td>
<td>#3.75%</td>
<td>#3.</td>
<td>#7.</td>
</tr>
<tr>
<td>8</td>
<td>#2.75%, #14.100%</td>
<td>#2.</td>
<td>#7.</td>
</tr>
<tr>
<td>9</td>
<td>#12.75%</td>
<td>#12.</td>
<td>#4.</td>
</tr>
<tr>
<td>10</td>
<td>#6.75%</td>
<td>#6.</td>
<td>#13.</td>
</tr>
<tr>
<td>11</td>
<td>#6.90%</td>
<td>#6.</td>
<td>#12.</td>
</tr>
</tbody>
</table>

The coronary site and the grade of stenosis were allocated according to the classification of the American Heart Association. QCA, quantitative coronary angiography; SAP, stable angina pectoris; NA, not assessed.

Table 3 Hemodynamic Changes After the Administration of Fasudil

<table>
<thead>
<tr>
<th></th>
<th>SAP (n=11)</th>
<th>CPS (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Fasudil</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>154±15</td>
<td>146±16*</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>77±7</td>
<td>79±8</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>103±6</td>
<td>101±8</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>80±16</td>
<td>81±14</td>
</tr>
</tbody>
</table>

*p<0.01 vs the corresponding baseline value. Values are presented as mean±SD.

SAP, stable angina pectoris; CPS, chest pain syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; HR, heart rate.

coronary artery (LCx). The measurement of CD could not be performed in 1 patient with SAP because of technical difficulties with QCA. In the 10 remaining patients, the measurements of the CD were performed in 1 patient in the RCA, 3 patients in the LAD, and 6 patients in the LCx. In patients with CPS, the CD were measured in the LAD (6 patients) and the LCx (3 patients). The morphology of the lesions did not change after the administration of either NTG or fasudil.

Fig 1. Representative angiograms that illustrate the vasodilation with NTG and fasudil at the concentric coronary stenosis in a patient with stable angina pectoris. The administration of NTG only caused a slight change in the MLD; however, the subsequent administration of fasudil substantially increased the MLD at the stenotic site. MLD, minimal luminal diameter; NTG, nitroglycerin.
**Hemodynamic Stability During Drug Administration**

The intracoronary administration of NTG had no effect on the mean aortic pressure or heart rate. Both during and after the continuous infusion of fasudil, no adverse reaction, such as any obvious hypotension, was observed. Hemodynamic changes after the administration of fasudil are shown in Table 3. Although the SBP declined significantly at the end of the infusion of fasudil in the SAP group, other hemodynamic parameters were stable during the study.

**Changes in Coronary Diameter With NTG and Fasudil**

The representative angiograms that illustrate the vasodilation with NTG and fasudil at the concentric stenotic site are described in Fig 1. The intraobserver and interobserver correlation for the measurements of the coronary diameter were r=0.99 and 0.98, respectively (both p<0.001). At the baseline condition, the MLD in the SAP group was 1.34±0.39 mm and the CD in the SAP and CPS group was 1.98±0.48 mm and 1.97±0.38 mm, respectively. The vasodilatory effect of NTG and fasudil at the site of concentric stenosis is shown in Fig 2. The percentage change in the MLD with fasudil (22.0±10.0%) was significantly higher than that with NTG (4.7±6.0%). In contrast, the percentage changes

**Fig 2.** Coronary vasodilatory effect of NTG and fasudil at the site of concentric stenosis in the stable angina pectoris group. The percentage change in the MLD with fasudil was significantly higher than that with NTG. MLD, minimal luminal diameter; NTG, nitroglycerin.

**Fig 3.** Coronary vasodilatory effect of NTG and fasudil at the control site in the stable angina pectoris (A) and chest pain syndrome (B) group. The administration of NTG and fasudil showed a similar percentage change in the CD in either group. CD, control diameter; NTG, nitroglycerin.

**Fig 4.** Correlations between the MLD and its percentage change with each drug. The percentage change in the MLD with nitroglycerin did not correlate with the baseline diameter (A). In contrast, the percentage change in the MLD with fasudil negatively correlated with the baseline diameter (B). MLD, minimal luminal diameter.
in the CD with NTG and fasudil were similar in both groups (25.5±17.3% and 21.9±14.9% in the SAP group, and 34.4±20.8% and 33.2±23.6% in the CPS group, respectively) (Figs 3A, B).

**Changes in %DS After the Administration of Each Drug**

The %DS at baseline and after the administration of NTG and fasudil was 41.2±12.6%, 47.2±10.6% and 38.4±11.1%, respectively; the administration of NTG significantly increased the %DS (p<0.05), and subsequent infusion of fasudil alleviated it (p<0.01 vs after NTG and p=NS vs baseline).

**Relationship Between the MLD and the Vasodilatory Effect of Each Drug**

The percentage change in the MLD with NTG did not correlate with the baseline diameter (Fig 4A). Meanwhile, the percentage change with fasudil negatively correlated with the baseline MLD (r=−0.73, p<0.01) (Fig 4B).

**Discussion**

Although the Rho-kinase pathway have been reported to be involved in the regulation of the vasomotion of arteries in several pathological conditions,13–16,23,24 its contribution to the coronary vasomotion at atherosclerotic sites has not yet been fully examined. In this regard, the present study has shown the possibilities that the Rho-kinase pathway, at least partially, mediates the coronary vasomotion at the site of concentric stenosis in patients with SAP.

Fasudil is known to be the only agent currently available in humans that inhibits the Rho-kinase activity.16 In smooth muscle cells, Rho-kinase phosphorylates the myosin light chain (MLC) via inactivation of MLC phosphatase (MLC-Ph)22 thus leading to muscle contraction independent of the cytosolic Ca2+ level. Therefore, the chief pharmacological mechanism of fasudil is the conversion of inactivated MLC-Ph to its activated form by the inhibition of Rho-kinase, which thus induces muscle relaxation. Although we did not measure the plasma concentration of fasudil in the present study, the mean plasma concentration at the end of the infusion of 0.4 mg/kg of fasudil for 30 min has been reported to be 215.7 ng/ml (approximately 0.7 μmol/L) in healthy subjects whose weights were 55 to 70 kg.30 In contrast, an in vitro study16 indicated that the inhibitory constant value of fasudil for Rho-kinase was 0.33 μmol/L. Therefore, the dose of fasudil used in the present study could be sufficient to inhibit the Rho-kinase activity. Regarding the dose of nitrates, it has been demonstrated in angiographical studies that the maximum coronary dilation with intracoronary NTG could be obtained with a dose of at least 150 μg and 50 μg at intact and stenotic segments, respectively.31,32 We therefore consider that the intracoronary administration of 200 μg of NTG is an adequate dose to exert the substantial vasodilatory effect at both the normal and stenotic segments.

In the present study, the percentage change in the diameter with NTG at the site of concentric stenosis revealed a mean of 4.7% in patients with SAP. Previous studies have reported the mean changes in the coronary diameter with nitrates at the concentric lesion ranging from approximately 3.9% to 10.0%. Therefore, our results seem to be in line with those in such previous reports. In contrast, the percentage change in the diameter with fasudil at the lesion (mean of 22.0%) was significantly higher than that with NTG. As concentric coronary stenosis consists of whole circumferential atherosclerosis,27 the present results suggest that even NTG with an adequate dose could not dilate the coronary atherosclerotic site. Regarding the impairment of vasodilation with nitrates at the atherosclerotic site, several possible mechanisms, such as the rigidity of ‘organic’ atherosclerosis and the atrophy of the medial smooth muscles at the lesion,24 were suggested in previous reports.8 However, the discrepant vasoactive manner between NTG and fasudil at the lesion could not be explained by such suggestions. Therefore, we propose that the coronary vasomotion at the atherosclerotic site is regulated by the Rho-kinase pathway. In contrast, McPherson et al reported that the coronary atherosclerotic site could respond to NTG7. However, the study by McPherson et al was conducted with patients undergoing open heart surgery, thus indicating that its particular conditions, such as patients being under general anesthesia, may have affected their results. Regarding the interaction between NTG and the Rho-kinase pathway in vascular smooth muscle cells, nitric oxide (NO) has been demonstrated to exert muscle relaxation not only via the lowering of the cytosolic Ca2+ level but also via the inhibition of the Rho-kinase pathway.35,36 These findings suggest that NTG, an exogenous NO donor, has a vasodilatory potential through the inhibition of the Rho-kinase pathway, at least in part. However, we consider that this could not be the case in the present study because the vasodilation with NTG was much less potent than that with fasudil at the stenotic site. Meanwhile, whether the coronary vasomotion at the non-stenotic segment was also regulated by the Rho-kinase pathway could not be determined in the present study, because the diameter after fasudil did not surpass that after NTG at the segment.

Recently, an anti-anginal effect of oral administration of fasudil in patients with stable effort angina was reported.7,8 In the present study, the administration of NTG resulted in a worsening of the severity in the stenotic grade at the lesion, while the infusion of fasudil ameliorated it because of the substantial vasodilatory effect at the lesion. Moreover, the vasodilatory effect of fasudil negatively correlated with the baseline diameter at the lesion. We, therefore, consider that these findings might be related to one of the mechanisms of the anti-anginal effect of fasudil.

The present study had some limitations. First, the %DS measured with QCA did not show a severe grade. Therefore, it was not definite that the coronary spasm was partially involved in the exertional myocardial ischemia in patients with SAP because we did not test the provocation of coronary spasm. The Rho-kinase pathway has been reported to play a key role in the pathogenesis of coronary spasm.24,25 Therefore, we should have evaluated the vasodilatory effect of fasudil at the atherosclerotic lesion with and without coronary spasm separately. Second, regarding the reduction in SBP during the administration of fasudil in patients with SAP, it was possible that the coronary vasodilation with fasudil was mediated via other mechanisms rather than its direct effect on the vascular smooth muscles; for example, the attenuation of the sympathetic nervous activity by the inhibition of the Rho-kinase pathway in the brain stem.29 Third, coronary angiography has been reported to misinterpret lesion eccentricity in the presence of vessel remodeling, which can be accurately detected by intravascular ultrasound (IVUS).40 It was, therefore, possible that all the concentric stenoses in the present study were not necessarily ‘truly concentric’, because we did not assess the.
lesion morphology using IVUS. Fourth, we infused fasudil after NTG in all cases in the present study. Therefore, the vasodilatory effect of fasudil might have been influenced by the pre-administration of NTG, even though an adequate time interval to ensure a decrease in the plasma concentration of NTG was sufficiently conducted. However, it was not realistic to evaluate the vasodilatory effect of NTG after the administration of fasudil in a same patient during a cardiac catheterization, because hydroxyfasudil, a main active metabolite of fasudil, has a long plasma half-life of from 4 to 5 h. Finally, the number of patients who participated in the present study was small; further studies with a larger number of patients are needed to verify the present study results.

In conclusion, we demonstrated that the vasodilatory effect of the subsequent administration of fasudil surpassed that of NTG at the concentric coronary stenosis in patients with SAP. These results suggest that the Rho-kinase pathway regulates the coronary vasomotion of atherosclerotic lesions. One of the mechanisms of the anti-anginal effect of fasudil might be attributed to coronary vasodilatation of atherosclerotic lesions via the inhibition of the Rho-kinase pathway.

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