Early Alteration of Coronary Hemodynamics in Late Restenosis after Coronary Angioplasty

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SUMMARY

It is not known whether changes in coronary hemodynamics may antedate the development of restenosis after percutaneous coronary transluminal angioplasty (PTCA). The purpose of this study was to evaluate the early change in coronary microvascular function in patients with late restenosis after PTCA.

Coronary hemodynamics were studied in series before, immediately after, 2 weeks and 3 months after successful PTCA in 12 male patients with a single lesion of the left anterior descending coronary artery. In each patient, great cardiac venous flow (GCVF) and oxygen content were measured both at baseline and during hyperemia induced by adenosine infusion. The sequential changes of coronary hemodynamics were compared between patients with and without restenosis at 3 months after PTCA.

Basic characteristics did not differ between the patients with \((n = 6)\) and those without restenosis \((n = 6)\). Luminal diameter stenosis (in percentage) was also similar between the two groups both before \((79.2 \pm 18.4\% \text{ vs } 83.0 \pm 9.6\%, p = \text{NS})\) and up to 2 weeks after PTCA \((25.8 \pm 10.9\% \text{ vs } 28.5 \pm 7.9\%, p = \text{NS})\). In patients without restenosis, basal and hyperemic GCVF was unchanged up to 2 weeks after PTCA. There was a significant increase in CFR 3 months after PTCA. In patients with restenosis, basal GCVF was significantly increased and hyperemic GCVF was unchanged immediately after PTCA. However, 2 weeks after PTCA, basal GCVF was decreased while luminal diameter was still preserved. In comparison with those without restenosis, patients with restenosis had significantly lower CFR before \((1.98 \pm 0.42 \text{ vs } 2.69 \pm 0.46, p = 0.019)\), immediately after \((1.47 \pm 0.27 \text{ vs } 2.24 \pm 0.47, p = 0.006)\) and 3 months after PTCA \((1.51 \pm 0.32 \text{ vs } 3.40 \pm 0.54, p = 0.001)\).

In patients without restenosis, the recovery of coronary microvascular function was delayed up to 3 months after PTCA. In patients with late restenosis, basal coronary microvascular tone was altered within 2 weeks after

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In patients with significant coronary arterial stenosis, angiographic and hemodynamic improvement of epicardial coronary arterial diameter after percutaneous transluminal coronary angioplasty (PTCA) may not always permit immediate increment of baseline coronary blood flow.¹,² In more than half of the patients, coronary flow reserve (CFR) remained impaired immediately and 24 hours after a successful PTCA.³ This abnormality could be normalized by several months in most of the patients without restenosis.³,⁴ Several possible factors have been attributed to the delayed restoration of coronary microcirculation after PTCA, which included preexisting coronary microvascular dysfunction, procedure-related endothelial damage, medial injury, platelet activation, release of vasoactive substance, microembolization from platelet aggregate, thrombus and ruptured atheroma fragments, reperfusion injury, and temporary impairment of coronary autoregulation after PTCA resulting from long-standing ischemia.⁵ Some of these factors may also result in permanent damage to coronary microvasculatures which could not completely recover from late restenosis after PTCA. It is not known whether this permanent damage, if it exists, may be related to the development of late restenosis. In previous studies CFR was evaluated mainly in patients without late restenosis after PTCA. Little is known about the serial changes of coronary hemodynamics early after PTCA, especially in patients with late restenosis.³,⁴,⁶ Thus, to evaluate whether and how coronary microvascular function is altered early in patients with late restenosis after PTCA, both coronary angiograms and hemodynamics were prospectively studied before, immediately after, 2 weeks after and 3 months after successful PTCA in a group of male patients with a single stenotic lesion of the left anterior descending coronary artery. The sequential changes of coronary hemodynamics were compared between patients with and those without late restenosis.

**Methods**

**Study patients:** Between January 1995 and December 1996, 30 consecutive patients with single vessel disease of the left anterior descending artery scheduled for elective PTCA were initially evaluated. They all had a history of stable angina for ≥ 1 year, a positive result in the treadmill exercise test, and single coronary stenosis (≥ 70% luminal diameter stenosis) in the proximal or middle segment of the left anterior descending coronary artery by coronary angiogram within 2
months before this study. Patients with previous myocardial infarction, previous PTCA, unstable angina, valvular heart disease, congestive heart failure, left ventricular hypertrophy or generalized hypokinesis of the left ventricle by echocardiogram, and angiographically evident collateral circulation were excluded. The pharmacological treatment in these patients consisted of nitrates, calcium antagonists and β-blocking agents. All medication except sublingual nitroglycerin was stopped > 24 hours before cardiac catheterization. The study protocol was approved by the Institutional Review Board and each patient gave their informed written consent.

**Quantitative coronary cineangiography:** In each patient, coronary angiography was performed after a 0.3 mg nitroglycerin intracoronary injection via the right femoral approach with the standard Judkins method. The 2 projections with the best lesion demonstration by a biplane angiographic system were kept in place throughout the entire procedure. The severity of the coronary lesion was expressed in diameter stenosis measured by a computer-based on-line quantitative coronary image system. In summary, the boundaries of a selected coronary artery segment were detected automatically from optically magnified and video-digitized regions of interest in a cineframe at the diastolic phase of the left ventricle. Calibration of the diameter data in absolute values (millimeters) was achieved by detecting the boundaries of a section of the contrast catheter and comparing the mean diameter in pixels with the known size in millimeters. Pin-cushion distortion was corrected. A computer estimation of the original arterial dimensions at the site of obstruction was used to define the reference regions. The interpolated percentage diameter stenosis was then calculated by averaging the values from 2, preferably orthogonal, projections.

**Coronary hemodynamic study:** In each patient, great cardiac venous flow (GCVF) was measured by thermodilution immediately before PTCA. The method we used has been partly described by others\(^5\text{-}^9\) and us\(^10,11\) previously. In brief, a 7F Baim thermodilution coronary sinus flow catheter (Electro-catheter Corp., Rahway, NJ, USA) was inserted via the right internal jugular vein, and positioned in the great cardiac vein with the tip wedged into the junction of the great cardiac vein and coronary sinus. Correct placement was documented by the injection of a small amount (3–5 cc) of contrast medium via the end hole of the catheter and recorded on cine films. After the patients' condition stabilized, GCVF was measured with 40–50 cc of room temperature saline infused through the thermodilution catheter at a constant speed of 50 ml/min by a Harvard pump (Harvard Apparatus, South Natick, MA). The value of GCVF was obtained simultaneously via the Baim coronary sinus flow analyzer and calculator (Electro-catheter Corp.). After the baseline measurement, saline and adenosine (2.5 mg) were injected sequentially, using a mechanical pump, at a rate of 6 cc/
min for 2 minutes, via a coronary catheter into the left main coronary artery. The changes in aortic pressure, heart rate and GCVF responding to the intracoronary administration were recorded during the last 30 seconds of injection. These changes were also recorded 30 seconds after an intracoronary bolus injection of 0.3 mg of nitroglycerin. The injection would be stopped immediately if severe chest pain, significant ST elevation in electrocardiographic monitoring, and marked bradycardia with a heart rate < 40 beats/min were noted. The minimum interval between each injection was 5 minutes. The next injection was started only after the value of GCVF was returned to baseline from the previous injection. Immediately after each measurement of GCVF, a 1–3 cc blood sample was drawn from the great cardiac vein and ascending aorta respectively to determine their oxygen content. Coronary angiogram was then performed to evaluate the diameter change of the left anterior descending coronary artery.

**Parameters of coronary and systemic hemodynamics:** In each patient, maximum GCVF was obtained during peak hyperemia achieved by the adenosine infusion. The ratio of maximum to baseline GCVF during saline infusion was defined as CFR. Coronary vascular resistance was calculated as the quotient of mean aortic pressure and GCVF. To evaluate myocardial metabolism, myocardial oxygen extraction was calculated as the difference in oxygen content between the ascending aorta and great cardiac vein. Myocardial oxygen consumption in the territories of the left anterior descending coronary artery was then obtained by the formula: myocardial oxygen extraction × GCVF. Rate-pressure product (RPP), an index of left ventricular work, was also calculated as: heart rate × systolic blood pressure. The ratio of myocardial oxygen consumption to RPP (MVO/RPP) was referred to as an index of regional myocardial efficiency.

**Percutaneous transluminal coronary angioplasty and direct coronary atherectomy:** In each patient, oral aspirin (324 mg) and intravenous heparin (10,000 units) were given before PTCA. By using a monorail balloon catheter system, coronary dilation was performed with variable balloon sizes, inflation pressure and inflation time by a team of 2 experienced operators. To achieve an acceptable result, additional direct coronary atherectomy was performed when residual luminal diameter stenosis was > 50% after PTCA. The method we used for PTCA and direct coronary atherectomy has been described elsewhere recently. Immediately after a successful PTCA and/or direct coronary atherectomy (< 50% residual stenosis) was obtained, the coronary angiographic and hemodynamic studies were repeated.

**Follow-up study:** All patients were followed up regularly at out patient clinics after successful PTCA. The clinical symptoms, if any, were recorded. Coronary angiogram and hemodynamic study were repeated 2 weeks and 3 months later,
respectively. Angiographic restenosis was defined as ≥ 50% stenosis of coronary luminal diameter.

**Statistical analysis:** All variables are expressed as mean ± SD. The differences between patients with and without late restenosis were analyzed using unpaired Student's t test. The differences in serial changes of parameters before, immediately after, 2 weeks and 3 months after PTCA were analyzed with repeated measurement of one-way analysis of the variance (ANOVA) and paired Student's t test when appropriate. A p value < 0.05 was considered to be significant in each analysis.

**RESULTS**

**Patient characteristics:** Of the 30 patients initially evaluated, 13 were enrolled and PTCA was successfully performed in 12. The reasons for exclusion included previous myocardial infarction in 2, recent onset of unstable angina in 2, significant valvular heart disease in 2, congestive heart failure in 1, left ventricular hypertrophy by echocardiogram in 4, generalized hypokinesia of the left ventricle by left ventriculogram in 3, and angiographically evident collateral circulation in 3 patients. Of the 13 patients enrolled, one developed acute closure of the target coronary artery during PTCA. He then underwent emergent coronary artery bypass grafting successfully. Thus, the study protocol was completed in a total of 12 patients, all male, aged 62 to 73 (mean 65 ± 3) years. Among them,

<table>
<thead>
<tr>
<th>Table I. Basic Characteristics of Study Patients</th>
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<tbody>
<tr>
<td>Restenosis (n = 6)</td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Sex</td>
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<td>DM</td>
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<td>Smoking</td>
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<td>Glucose (mg/dl)</td>
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<td>Triglyceride (mg/dl)</td>
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<tr>
<td>Total Cholesterol (mg/dl)</td>
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<tr>
<td>Radionuclide ejection fraction (%)</td>
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<tr>
<td>Coronary intervention</td>
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<tr>
<td>PTCA alone</td>
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<tr>
<td>PTCA + atherectomy</td>
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<td>Follow-up period (month)</td>
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DM = diabetes mellitus; PTCA = percutaneous transluminal coronary angioplasty.
Table II. Baseline Lesion Characteristics and Luminal Diameter Stenosis (%) in Patients with and without Restenosis after Percutaneous Transluminal Coronary Angioplasty (PTCA)

<table>
<thead>
<tr>
<th>Baseline lesion characteristics</th>
<th>Restenosis (n = 6)</th>
<th>Non-restenosis (n = 6)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion type A</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Reference vessel diameter (mm)</td>
<td>2.7 ± 0.6</td>
<td>3.9 ± 0.7</td>
<td>0.019</td>
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<tr>
<td>Minimal lumen diameter (mm)</td>
<td>0.5 ± 0.5</td>
<td>0.6 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Lesion length (mm)</td>
<td>11.7 ± 3.8</td>
<td>11.1 ± 3.9</td>
<td>NS</td>
</tr>
<tr>
<td>Luminal diameter stenosis (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>79.2 ± 18.4</td>
<td>83.0 ± 9.6</td>
<td>NS</td>
</tr>
<tr>
<td>Immediately after PTCA</td>
<td>27.8 ± 11.2</td>
<td>31.8 ± 8.9</td>
<td>NS</td>
</tr>
<tr>
<td>2 weeks after PTCA</td>
<td>25.8 ± 10.9</td>
<td>28.5 ± 7.9</td>
<td>NS</td>
</tr>
<tr>
<td>3 months after PTCA</td>
<td>79.0 ± 11.2</td>
<td>35.2 ± 6.3</td>
<td>0.001</td>
</tr>
</tbody>
</table>

the desired angiographic results (< 40% residual stenosis of coronary diameter) after coronary intervention were reached in 9 patients with PTCA alone and in the other 3 with PTCA followed by direct coronary atherectomy. There was no difference between patients receiving PTCA only and those with both PTCA and direct coronary atherectomy. Three months after coronary intervention, angiographic restenosis (≥ 50% luminal diameter stenosis) was noted in 6 patients. There was no difference in basic characteristics between patients with and those without restenosis (Table I). Recurrent angina was noted in 3 patients, 2 with restenosis and the other one without, during the follow-up period.

**Serial changes of coronary stenosis before and after PTCA:** Table II shows the baseline lesion characteristics and serial changes of coronary diameter stenosis (in percentage) in patients with and without restenosis at 3 months after PTCA. All stenotic lesions were type A lesions. Patients without restenosis had a larger reference vessel diameter at baseline as compared with those with restenosis (3.9 ± 0.7 vs. 2.7 ± 0.6 mm, \( p = 0.019 \)) (Table II). There were no differences in minimal lumen diameter, lesion length or coronary diameter stenosis between the two groups before, immediately and 2 weeks after PTCA. Three months after PTCA, patients with restenosis had markedly increased coronary diameter stenosis (79.0 ± 11.2%) compared with those without restenosis (35.2 ± 6.3%, \( p = 0.001 \)).

**Basal coronary hemodynamics before and after PTCA:** There was no difference in basal GCVF and CVR between patients with and without restenosis. Intracoronary saline infusion did not alter GCVF and CVR in any study patient. In the non-restenosis group, basal GCVF and CVR were unchanged throughout the whole course of the study (Figures 1 and 2). However, in patients with late restenosis, basal GCVF was increased (52 ± 25 vs. 58 ± 24 ml/min, \( p = 0.028 \)) immediately after PTCA and then reduced (44 ± 16 ml/min, \( p = 0.032 \)) 2 weeks later (Figure 1). Similar changes were noted in GCVF/RPP which was signifi-
cantly increased immediately after PTCA (0.0057 ± 0.0028 vs 0.0069 ± 0.0030 ml/mmHg/beat, $p = 0.021$) and decreased (0.0044 ± 0.0017 ml/mmHg/beat, $p = 0.011$) 2 weeks later. Basal CVR also tended to reduce (2.31 ± 1.50 vs 1.91 ± 1.08 mmHg/ml/min, $p = 0.081$) immediately after PTCA followed by a significant increase (2.53 ± 1.20 mmHg/ml/min, $p = 0.032$) 2 weeks later (Figure 2).

**Coronary hemodynamics during maximum hyperemia before and after PTCA:** As shown in Figures 1 and 2, hyperemic GCVF and CVR were unchanged immediately after and 2 weeks after PTCA in both groups. In patients with restenosis, hyperemic GCVF was reduced from 83 ± 25 ml/min at 2 weeks after to 61 ± 19 ml/min at 3 months after PTCA ($p = 0.003$). This was not seen in patients without restenosis. As compared with those without restenosis, patients with restenosis had significantly lower hyperemic GCVF at 2 weeks ($p = 0.036$) and at 3 months after PTCA ($p = 0.001$). Hyperemic CVR values were also higher in patients with than in those without late restenosis 3 months after PTCA ($p = 0.047$).

**Coronary flow reserve before and after PTCA:** In patients without
restenosis, CFR was unchanged both immediately after and 2 weeks after PTCA. However, in patients with restenosis, CFR was significantly reduced immediately after \( (p = 0.038) \) and increased 2 weeks after PTCA \( (p = 0.015) \) (Figure 3). Three months after PTCA, CFR had returned to normal \( (2.38 \pm 0.69 \text{ to } 3.40 \pm 0.54, p < 0.001) \) in patients without restenosis but had further reduced in those with restenosis \( (1.84 \pm 1.05 \text{ to } 1.51 \pm 0.32, p = 0.011) \). In addition, CFR was significantly lower in the restenosis group than in the non-restenosis group both before \( (1.97 \pm 0.42 \text{ vs } 2.68 \pm 0.45, p = 0.019) \), immediately after \( (1.47 \pm 0.27 \text{ vs } 2.24 \pm 0.47, p = 0.006) \) and 3 months after PTCA \( (1.51 \pm 0.32 \text{ vs } 3.40 \pm 0.54, p < 0.001) \).

**Basal myocardial metabolism before and after PTCA:** Before PTCA, there was no difference in basal myocardial metabolism between patients with and without restenosis. Immediately after PTCA, basal oxygen saturation in the great cardiac vein was significantly increased \( (37 \pm 5 \text{ vs } 46 \pm 6\%, p = 0.008) \) and regional myocardial oxygen extraction \( (1133 \pm 127 \text{ vs } 953 \pm 136 \text{ ml/min}, p = 0.003) \) was reduced in patients without restenosis. These changes were not seen in patients with restenosis \( (36 \pm 9 \text{ vs } 37 \pm 5\%, p = \text{NS}; 1050 \pm 227 \text{ vs } \)
**Figure 3.** Serial changes of coronary flow reserve (CFR) before, and immediately, two weeks, and three months after PTCA in non-restenosis ($n = 6, \triangle$) and restenosis patients ($n = 6, \circ$). The * indicates $p < 0.05$ between the two groups.

**Figure 4.** Serial changes of calculated myocardial oxygen consumption ($\text{MVO}_2$) before, and immediately, two weeks, and three months after PTCA in non-restenosis ($n = 6, \triangle$) and restenosis patients ($n = 6, \circ$). The * indicates $p < 0.05$ between the two groups.
1049 ± 160 ml/min, $p =$ NS). Although oxygen saturation in the great cardiac vein immediately after PTCA was significantly higher ($p = 0.042$) in the patients without restenosis than those with, basal myocardial oxygen extraction was similar between these 2 groups. In both groups, these 2 parameters were kept constant 2 weeks and 3 months after PTCA.

**Myocardial oxygen consumption before and after PTCA:** Figure 4 shows the serial changes in MVO₂ at baseline and during maximum hyperemia by adenosine injection both before and after PTCA. There were no significant changes in either MVO₂ or MVO₂/RPP throughout the whole study course in patients without restenosis. In patients with late restenosis, basal MVO₂ tended to increase (499 ± 146 vs 591 ± 213 ml/min, $p = 0.086$) immediately after PTCA and decrease (445 ± 161 ml/min, $p = 0.061$) 2 weeks later. This resulted in a significant increase in MVO₂/RPP immediately after PTCA (0.0539 ± 0.0192 vs 0.0695 ± 0.0280 ml/mmHg x beat, $p = 0.043$) followed by a marked reduction (0.0449 ± 0.0191 ml/mmHg x beat, $p = 0.020$) 2 weeks later.

In patients without restenosis, MVO₂ was significantly increased by an adenosine injection either before or after PTCA ($p < 0.001$ in each occasion). On the contrary, MVO₂ was unchanged by adenosine injection in patients with late restenosis both before and after PTCA. As compared with those without restenosis, MVO₂ at maximum hyperemia was significantly less at 2 weeks (535 ± 147 vs 878 ± 192 ml/min, $p = 0.010$) and 3 months (348 ± 126 vs 1177 ± 527 ml/min, $p = 0.006$) after PTCA in patients with restenosis.

**DISCUSSION**

The results of the present study show that in a limited series, coronary hemodynamics are different early after PTCA between patients with and without late restenosis. In patients without restenosis, both basal and maximum GCVF and CFR were unchanged up to 2 weeks after PTCA while luminal diameter stenosis was significantly improved. Compatible with the previous finding of the lack of immediate improvement of basal coronary flow and/or CFR in some patients after PTCA,1–3 coronary microcirculation was persistently impaired up to 2 weeks after a successful PTCA in the present study. However, CFR was significantly improved at 3 months after PTCA, suggesting the late recovery of coronary microvascular function in our patients without restenosis.3,4) On the other hand, in patients with late restenosis, basal GCVF was significantly improved while CFR was reduced immediately after PTCA. Though the coronary artery was still angiographically patent, basal GCVF that was temporarily improved immediately after PTCA was reduced to the level before PTCA 2 weeks later. Accordingly, deterioration of the coronary microcirculation might precede
the development of angiographic restenosis after PTCA.

**Reduced coronary flow reserve before PTCA in patients with restenosis:** It has been suggested that CFR is reduced in patients with polycythemia, diseases of the large or small coronary arteries, tachycardia, a large increase in left ventricular diastolic pressure or a marked increase in contractility.\(^{13,14}\) Recently, Dayanikli et al. reported that CFR, measured by positron emission tomography, is impaired in asymptomatic men at high risk for coronary artery disease.\(^{15}\) In the present study, CFR was much more reduced even before PTCA in patients with late restenosis than in those without. Since patients with visible collaterals to target vessels have been excluded from the study, the difference in baseline CFR can not be explained by the presence of collaterals. While the risk factors of coronary artery disease and angiographic luminal stenosis were similar between the groups, the finding of reduced CFR might reflect either more severe or fixed narrowing of the epicardial coronary vessels or the pre-existing impairment of coronary microvasculatures or both before PTCA in patients with late restenosis.\(^{16}\)

To eliminate the possible dynamic mechanisms in coronary stenosis, coronary angiograms were done routinely after intracoronary injection of nitroglycerin in the present study. In fact, patients with restenosis had a smaller reference vessel diameter at baseline as compared with those without. This finding is compatible with the present concept that PTCA on small coronary vessels may have more late restenosis than that on large ones.\(^{17}\) Besides, it is also possible that patients with smaller coronary vessels at baseline may have more diffuse atherosclerosis resulting in more reduced CFR even before PTCA. However, to clarify this issue, intravascular ultrasound may be helpful to determine the structure and true luminal diameter of conduit coronary vessels in future studies.\(^{17,18}\)

**Possible mechanisms of abnormal coronary hemodynamics after PTCA:** Recent studies have suggested that vascular smooth muscle damage, endothelial vasomotor mediator release or inhibition, and platelet activation with some platelet-mediated vasomotor products result in persistent coronary vasoconstriction after successful PTCA.\(^{19}\) It is also possible that a preexisting coronary microvascular dysfunction may limit the coronary flow responding to adenosine-induced hyperemia after successful PTCA. In the present study, basal GCVF was significantly increased but the hyperemic GCVF was unchanged resulting in the reduction of CFR immediately after PTCA in patients with late restenosis. It might be related to the effective increase in luminal diameter of coronary conduit vessels by PTCA without simultaneous improvement of pre-existing microvascular dysfunction. This assumption could be supported by the fact that 2 weeks after PTCA, basal GCVF was reduced and coronary vascular resistance was increased suggesting the early deterioration of basal coronary microvascular tone.
As compared with those without restenosis, patients with late restenosis in the present study had more impaired CFR both before and immediately after PTCA. It is likely that coronary microvascular function that was more impaired before or during PTCA was deteriorated sooner after PTCA. It has been shown that undesired vascular remodeling, involving both conduit and downstream microvascular vessels, rather than intima hyperplasia, contributes to late restenosis after PTCA.\textsuperscript{17} We thus speculate that the process of undesired vascular remodeling, especially in coronary microvascular vessels, might start very early within 2 weeks after PTCA.

**Differential myocardial metabolism in patients with and without restenosis:** In the present study, myocardial metabolism was diverse in patients with and without restenosis after PTCA. In patients without restenosis, MVO\textsubscript{2} increased significantly by adenosine injection both before and after PTCA suggesting relatively preserved myocardial metabolism and coronary microvascular function. However, in patients with restenosis, MVO\textsubscript{2} did not respond to adenosine injection in serial observations including that before and immediately after PTCA. Thus, in these patients, the abnormality of myocardial metabolism might exist before and persist after PTCA.

**Study limitations:** Due to the limited sample size, it is difficult to draw any definite conclusion in the present study. However, our results are compatible with other studies using different methods.\textsuperscript{19,20} Recently, a large-scale study showed that a distal CFR \( \leq 2.5 \) measured by Doppler flow-wire and a residual diameter stenosis > 35\% were associated with a significantly higher incidence of restenosis late after PTCA.\textsuperscript{19} Another recent study also showed that CFR evaluated using trans-esophageal echocardiography was reduced very early after PTCA in patients with late restenosis.\textsuperscript{20} Together with the results of our study, it seems that coronary microvascular insufficiency, either pre-existing or procedure-related, is related to the development of late restenosis after PTCA.

**Conclusions:** The recovery of coronary microvascular function was delayed up to 3 months after successful PTCA in patients without restenosis. On the other hand, in patients with late restenosis, basal coronary microvascular tone was increased within 2 weeks after PTCA when the coronary lumen was still patent. It seems that coronary microvascular function was deteriorated early before the development of angiographic restenosis. In these patients, basal coronary microvascular function, both before and early after PTCA, might be related to late angiographic outcomes. It would then be interesting to determine whether pre-treatment with medications that can improve coronary microvascular function\textsuperscript{17} could improve the long-term outcome in patients with reduced CFR before PTCA. Further large-scale studies are needed to clarify this issue.
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