Impaired Digital Reactive Hyperemia and the Risk of Restenosis after Primary Coronary Intervention in Patients with Acute Coronary Syndrome

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Aim: Reactive hyperemia peripheral arterial tonometry (RH-PAT) can be used to noninvasively assess the vascular function with respect to the digital microcirculation. Abnormalities are associated with coronary endothelial dysfunction. We therefore investigated whether impaired digital reactive hyperemia is associated with restenosis after percutaneous coronary intervention (PCI) in patients with acute coronary syndrome (ACS).

Methods: This study included 86 patients with ACS who underwent successful primary PCI of native vessels for de novo lesions. The reactive hyperemia index (RHI) was calculated using RH-PAT at three weeks and eight months after ACS. The RHI was defined as the ratio of the digital pulse volume during reactive hyperemia to that observed at baseline. Restenosis was defined as diameter stenosis of ≥ 50% in the in-segment area based on the findings of quantitative coronary angiography performed at eight months.

Results: Restenosis was detected in 17 patients (20%). There were no differences in the RHI at three weeks between the patients with and without restenosis (1.70 vs. 1.87; \(p=0.13\)); however, the RHI values at eight months were significantly attenuated in the patients with restenosis versus those without (1.75 vs. 2.12; \(p=0.03\)). A univariate logistic regression analysis showed that the eight-month RHI (<2, obtained from a receiver operating characteristic analysis) was a significant risk factor for restenosis (odds ratio: 4.23, 95% confidence interval: 1.25 to 14.28, \(p=0.02\)).

Conclusions: Impairment of the digital hyperemic response at eight months is associated with restenosis after primary intervention in patients with ACS, suggesting the potential of RH-PAT as a non-invasive test for identifying patients with a high risk of restenosis.


Key words: Digital reactive hyperemia, Endothelial function, Percutaneous coronary intervention, Restenosis

Introduction

Percutaneous coronary intervention (PCI) with stenting is effective and widely used to treat patients with acute coronary syndrome (ACS). However, in-stent restenosis (ISR) due to intimal hyperplasia occurs in 10%-30% of such patients within six months after stenting, depending on various clinical, angiographic and procedural features. Therefore, the ability to identify patients with a high risk of restenosis after PCI is attracting attention, as it may help to predict clinical events and optimize management.

Endothelial vasomotor dysfunction is a systemic disorder that contributes to the development of atherosclerosis\(^1\). Many studies of the coronary vasomotor response to acetylcholine and brachial artery flow-mediated dilatation (FMD) have shown that endothelial vasomotor dysfunction is a significant risk factor.
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Methods

Study Patients

Patients experiencing their first episode of ACS who had undergone primary PCI were enrolled. ACS was defined as unstable angina pectoris and non-ST-segment elevation myocardial infarction (MI) or ST-segment elevation MI. The diagnosis was based on the identification of at least two of the following findings: 1) symptoms suggestive of ACS; 2) ischemic changes on an electrocardiogram; and 3) elevation (≥2 times normal) of the serum creatine kinase, creatine kinase myocardial band or troponin T level. The exclusion criteria were cardiogenic shock, clinically significant valvular disease, infarction related to a grafted vessel, stroke, chronic hepatic or inflammatory disease, chronic renal failure (serum creatinine > 1.5 mg/dl), severe infection and any disease that severely shortened life expectancy.

![Study Flow Chart](image)

ACS = acute coronary syndrome; RH-PAT = reactive hyperemia peripheral arterial tonometry; PCI = percutaneous coronary intervention.

Accordingly, the present study was conducted to investigate whether an impaired RHI is associated with restenosis in ACS patients with a history of primary PCI.

for future cardiovascular events. Furthermore, coronary endothelial dysfunction may be regarded as either healing or an abnormal vascular response to injury, characterized by enhanced neointimal hyperplasia following catheter-based coronary intervention, particularly stenting. An impaired FMD has been demonstrated to independently predict the occurrence of ISR after PCI.

Using ultrasound to assess the FMD of the brachial artery is a popular technique for investigating the endothelial vasomotor function, although it is limited to the research setting due to various technical problems. Reactive hyperemia peripheral arterial tonometry (RH-PAT) is a noninvasive technique for assessing the peripheral microvascular endothelial function by measuring changes in the digital pulse volume during reactive hyperemia. The reactive hyperemia index (RHI) measured using RH-PAT is decreased in patients who exhibit coronary endothelial dysfunction following the intracoronary infusion of acetylcholine and is correlated with multiple cardiovascular risk factors. However, no studies have yet evaluated the relationship between the RHI and the risk of restenosis in ACS patients undergoing PCI.
due to stroke ($n = 1$), rectal cancer ($n = 1$), pancytopenia caused by ticlopidine ($n = 1$) and loss to follow-up ($n = 2$). The remaining 86 patients underwent RH-PAT and coronary angiography at eight months after primary PCI. This study was conducted according to the guidelines of our institutional ethics committee, and written informed consent was obtained from all participants.

**PCI and Adjunct Medical Therapy**

Baseline demographic data and a complete history, including cardiovascular risk factors, were obtained. All patients underwent emergency diagnostic coronary angiography and reperfusion using primary PCI via the femoral artery. Loading doses of aspirin (200 mg) and clopidogrel (300 mg) were administered immediately after each patient agreed to undergo PCI. Anticoagulation was achieved with unfractionated heparin (100 IU/kg), maintaining an activated clotting time of $\geq 250$ seconds. Aspiration thrombectomy, balloon angioplasty and stenting were performed according to standard techniques under intravascular ultrasound guidance. Predilatation, direct stenting and post-stenting balloon inflation were performed at the operator’s discretion. The procedure was considered successful if the amount of residual stenosis was $< 25\%$ with a Thrombolysis In Myocardial Infarction (TIMI) flow grade of 3.

The post-procedural medication regimen comprised aspirin (100 mg/day) for life and ticlopidine (200 mg/day) or clopidogrel (75 mg/day) for $\geq 6$ months. During hospitalization, the patients received angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta-blockers, calcium-channel blockers and statins. After discharge, each patient received individualized optimum therapy, including medications and lifestyle modification, for secondary prevention according to the Japanese Circulation Society guidelines. The therapeutic goals were a low-density lipoprotein (LDL) cholesterol level of $< 100$ mg/dl, a blood pressure of $< 140/90$ mmHg (130/80 mmHg for patients with diabetes mellitus or chronic kidney disease) and a glycated hemoglobin (HbA1c) level of $< 6.5\%$.

**Performance of RH-PAT**

RH-PAT was performed using an Endo-PAT2000 (Itamar Medical Inc., Caesarea, Israel) according to the reported method. Vasoactive drugs (nitrates, ACE inhibitors, ARB and calcium-channel blockers) were withheld for 12 hours before the test, which was performed at both three weeks and eight months after PCI. Because the peripheral vascular tone shows circadian variation, RH-PAT was always performed in the early morning in a quiet, dimly lit, temperature-controlled room with the subject fasting. A blood pressure cuff was placed on one upper arm, while the contralateral arm served as the control. Sensors were placed on each index finger, and the baseline pulse amplitude was measured for five minutes. The cuff was then inflated to 60 mmHg above the systolic pressure or 200 mmHg at maximum for five minutes, after which it was rapidly deflated to induce reactive hyperemia, and the pulse amplitude was recorded for another five minutes. The data were digitally analyzed online using Endo-PAT2000 software program (version 3.2.4). The average pulse amplitude between 60 and 90 seconds after cuff deflation (control arm $= A$; occluded arm $= C$) was divided by that observed at 150 seconds before inflation (control arm $= B$; occluded arm $= D$) for each arm, and the RHI was subsequently calculated as the average of these two values: $\text{RHI} = (C/D)/(A/B) \times$ baseline correction factor.

**Coronary Angiography Evaluation and Definitions**

Coronary angiography was performed before and immediately after PCI and at the planned eight-month follow-up visit. The American College of Cardiology/American Heart Association grading system (type A, B1, B2 and C) was used to characterize the lesion morphology. Bifurcation lesions were defined as lesions requiring guide wire protection of the side branch. Digital angiograms were analyzed offline with the use of an automated edge-detection system (CardioAgent, Toshiba Medical Systems Corp., Tochigi, Japan). The measurements were obtained on cineangiograms recorded following intracoronary nitroglycerin administration. The contrast-filled non-tapered catheter tip was used for calibration. The evaluated angiographic parameters included the reference vessel diameter, minimal stent diameter and diameter stenosis.

The study endpoint was the eight-month incidence of restenosis, which was defined as diameter stenosis of $\geq 50\%$ within the stent or within a 5-mm border proximal or distal to the stent based on the findings of quantitative coronary angiography, irrespective of the presence or absence of ischemic signs or symptoms.

**Statistical Analysis**

Continuous variables with a normal distribution are expressed as the mean (standard deviation [SD]), whereas variables with a skewed distribution are expressed as the median (interquartile range [IQR]).
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Total stent lengths (median 28 [IQR 23-36] vs. median 20 [IQR 15-28]; \( p = 0.001 \)) than those receiving BMS, although there were no significant differences in the level of final diameter stenosis between the two stent types. At three weeks after primary PCI, the RHI values were comparable between the patients with and without restenosis (median 1.70 [IQR 1.46-2.14] vs. median 1.87 [IQR 1.65-2.19]; \( p = 0.13 \)). However, the RHI values at eight months were significantly lower in the patients with restenosis than in those without (median 1.75 [IQR 1.46-2.06] vs. median 2.12 [IQR 1.61-2.45]; \( p = 0.03 \)) (Table 1). A ROC curve was constructed to assess whether the eight-month RHI could be used to identify patients with restenosis, with an AUC of 0.67 (95% confidence interval [CI]: 0.54-0.81; \( p = 0.03 \)). Furthermore, an eight-month RHI of 2.0 was identified as the best cut-off value for distinguishing between patients with and without restenosis. When the eight-month RHI was <2.0, the sensitivity and specificity for detecting restenosis were 77% and 57%, respectively.

### Clinical, Angiographic and PCI Procedural Characteristics in the Patients with Eight-month RHI of <2 and \( \geq 2 \)

The clinical, angiographic and PCI procedural characteristics of the patients with an eight-month RHI above or below 2 are shown in Table 2 and Table 3, respectively. The two groups were similar with regard to age, gender, family history of coronary artery disease, hypertension, diabetes mellitus, hypercholesterolemia, type of ACS, the left ventricular ejection function and medications on admission. The culprit vessel, lesion type, reference vessel diameter, stent type, stent diameter, total stent length, final diameter stenosis and post-procedural TIMI flow grade were also similar between the groups. The patients with an eight-month RHI <2 included a greater proportion of current smokers and had significantly higher body mass index (BMI) values, lower HDL cholesterol levels and a higher prevalence of multivessel disease. Overall, the atherosclerotic risk factors were improved at eight months compared to the baseline values fol-

### Results

#### RHI Measurement and Restenosis

Restenosis was found in 17 patients (20%) on eight-month coronary angiography. Of these 17 patients, five (29%) received bare-metal stents (BMS), nine (53%) received drug-eluting stents (DES) (one patient treated with a sirolimus-eluting stent, eight patients treated with paclitaxel-eluting stents) and three (18%) received plain old balloon angioplasty. The patients receiving DES exhibited smaller reference vessel diameters (median 2.67 [IQR 2.36-3.07] vs. median 3.08 [IQR 2.88-3.36]; \( p < 0.001 \)) and longer total stent lengths (median 28 [IQR 23-36] vs. median 20 [IQR 15-28]; \( p = 0.001 \)) than those receiving BMS, although there were no significant differences in the level of final diameter stenosis between the two stent types. At three weeks after primary PCI, the RHI values were comparable between the patients with and without restenosis (median 1.70 [IQR 1.46-2.14] vs. median 1.87 [IQR 1.65-2.19]; \( p = 0.13 \)). However, the RHI values at eight months were significantly lower in the patients with restenosis than in those without (median 1.75 [IQR 1.46-2.06] vs. median 2.12 [IQR 1.61-2.45]; \( p = 0.03 \)) (Table 1). A ROC curve was constructed to assess whether the eight-month RHI could be used to identify patients with restenosis, with an AUC of 0.67 (95% confidence interval [CI]: 0.54-0.81; \( p = 0.03 \)). Furthermore, an eight-month RHI of 2.0 was identified as the best cut-off value for distinguishing between patients with and without restenosis. When the eight-month RHI was <2.0, the sensitivity and specificity for detecting restenosis were 77% and 57%, respectively.

#### Table 1. RHI Values in the Patients with and without Restenosis

<table>
<thead>
<tr>
<th></th>
<th>Restenosis ((n=17))</th>
<th>No Restenosis ((n=69))</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-week RHI</td>
<td>1.70 [1.46-2.14]</td>
<td>1.87 [1.65-2.19]</td>
<td>0.13</td>
</tr>
<tr>
<td>8-month RHI</td>
<td>1.75 [1.46-2.06]</td>
<td>2.12 [1.61-2.45]</td>
<td>0.03</td>
</tr>
</tbody>
</table>

The data are expressed as the median [25th to 75th percentiles].

RHI = reactive hyperemia index.

Continuous variables were analyzed using the unpaired \( t \)-test or Mann-Whitney \( U \)-test, as appropriate. Categorical variables are presented as percentages, and proportions were compared using the \( \chi^2 \) test or Fisher’s exact test, as appropriate. Receiver operating characteristic (ROC) curves were constructed to predict the incidence of restenosis using the RHI data. The area under the curve (AUC) as well as sensitivity and specificity were calculated to assess the predictive value of the RHI, with an AUC of 0.50 indicating zero accuracy and an AUC of 1.00 indicating maximum accuracy. The AUC values were compared using the algorithm of DeLong et al.\(^{10}\) to determine the cut-off value that maximized the sum of the sensitivity and specificity\(^{11}\). The relationships between restenosis and significant variables were investigated using a logistic regression analysis. The following variables were evaluated in the univariate model: RHI, age, gender, hypertension, diabetes mellitus, hypercholesterolemia, cigarette smoking, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, HbA1c, highsensitivity C-reactive protein, multivessel disease, lesion type B2/C, bifurcation lesion, small-vessel disease (reference vessel diameter < 2.5 mm), total stent length (> 20 mm) and final diameter stenosis. For all analyses, a two-tailed \( p \) value of < 0.05 was considered to be significant. The statistical analysis was performed using the SPSS software package (version 19.0, SPSS Inc., Tokyo, Japan).
RHI as a Risk Factor for Restenosis

Restenosis was detected in 13 patients (30%) with an eight-month RHI of <2 and in four (9%) patients with an eight-month RHI of ≥2 (p=0.015) (Fig. 2). In the univariate logistic regression analysis,

Table 2. Clinical Characteristics of the Patients with an Eight-month RHI of <2 or ≥ 2

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>RHI &lt;2 (n=43)</th>
<th>RHI ≥ 2 (n=43)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>61 [55-68]</td>
<td>66 [59-73]</td>
<td>0.82</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>79</td>
<td>74</td>
<td>0.61</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25 [24-28]</td>
<td>24 [22-26]</td>
<td>0.039</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>56</td>
<td>49</td>
<td>0.52</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>35</td>
<td>23</td>
<td>0.24</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>56</td>
<td>44</td>
<td>0.28</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>51</td>
<td>28</td>
<td>0.027</td>
</tr>
<tr>
<td>Family history of CAD, %</td>
<td>12</td>
<td>28</td>
<td>0.06</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>120 [100-126]</td>
<td>116 [107-127]</td>
<td>0.90</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>70 [64-85]</td>
<td>66 [60-74]</td>
<td>0.19</td>
</tr>
<tr>
<td>Type of ACS, %</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>STEMI</td>
<td>65</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>NSTEMI/UAP</td>
<td>35</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Laboratory findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol, mg/dl</td>
<td>121 (31)</td>
<td>114 (30)</td>
<td>0.98</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
<td>44 [40-49]</td>
<td>49 [43-57]</td>
<td>0.009</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>115 [70-165]</td>
<td>127 [86-167]</td>
<td>0.95</td>
</tr>
<tr>
<td>Fasting blood glucose, mg/dl</td>
<td>91 [83-115]</td>
<td>98 [86-115]</td>
<td>0.94</td>
</tr>
<tr>
<td>HbA1C, %</td>
<td>5.5 [5.3-5.9]</td>
<td>5.4 [5.2-6.4]</td>
<td>0.20</td>
</tr>
<tr>
<td>Max CK, IU/l</td>
<td>2558 [1321-3835]</td>
<td>1681 [1032-3321]</td>
<td>0.98</td>
</tr>
<tr>
<td>BNP pg/ml</td>
<td>116 [41-231]</td>
<td>161 [94-244]</td>
<td>0.98</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>62 (11)</td>
<td>57 (15)</td>
<td>0.37</td>
</tr>
<tr>
<td>Medications on admission, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>12</td>
<td>17</td>
<td>0.53</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>5</td>
<td>2</td>
<td>0.50</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>17</td>
<td>26</td>
<td>0.29</td>
</tr>
<tr>
<td>Nitrates</td>
<td>7</td>
<td>5</td>
<td>0.50</td>
</tr>
<tr>
<td>Diuretics</td>
<td>5</td>
<td>2</td>
<td>0.50</td>
</tr>
<tr>
<td>Statin</td>
<td>12</td>
<td>7</td>
<td>0.36</td>
</tr>
<tr>
<td>Sulfonlurea</td>
<td>7</td>
<td>10</td>
<td>0.50</td>
</tr>
<tr>
<td>Metformin</td>
<td>2</td>
<td>2</td>
<td>0.75</td>
</tr>
<tr>
<td>α-Gl</td>
<td>7</td>
<td>5</td>
<td>0.50</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>2</td>
<td>2</td>
<td>0.75</td>
</tr>
<tr>
<td>Insulin</td>
<td>2</td>
<td>2</td>
<td>0.75</td>
</tr>
</tbody>
</table>

The data are expressed as the percentage, mean (SD) or median [25th to 75th percentiles].

ACE=angiotensin-converting enzyme; ACS=acute coronary syndrome; ARB=angiotensin receptor blocker; α-Gl=alpha-glucosidase inhibitor; BMI=body mass index; BNP=brain natriuretic peptide; CAD=coronary artery disease; CK=creatine kinase; HbA1c=glycated hemoglobin; HDL=high-density lipoprotein; LDL=low-density lipoprotein; LVEF=left ventricular ejection fraction; NSTEMI=non-ST-elevation myocardial infarction; RHI=reactive hyperemia index; STEMI=ST-elevation myocardial infarction; UAP=unstable angina pectoris.

allowing the administration of optimum medical therapy and lifestyle modification (Table 4). There were no significant differences in the risk status at eight months between the two groups, except for higher BMI values and a greater proportion of current smokers among the patients with an eight-month RHI of <2. The patients with lower RHI values tended to use alpha-glucosidase inhibitors and pioglitazone more frequently; however, there were no other differences in medical treatment between the two groups.
endothelium in the process of restenosis after PCI remains unclear. Endothelial dysfunction produces an imbalance between vasodilator substances with antiproliferative properties, such as nitric oxide (NO), and vasoconstrictors with mitogenic properties, such as endothelin. Indeed, endothelial-derived NO suppresses smooth muscle proliferation and inhibits intimal hyperplasia after vascular injury.\(^{12, 13}\) Moreover, the local release of endothelin-1 occurs at sites of vascular injury.\(^{14}\) and endothelin receptor antagonists have been reported to attenuate stent restenosis.\(^{15}\) Endothelial dysfunction may also involve the vascular microcirculation, which includes the vasa vasorum, leading to vascular wall ischemia and neovascularization. Stent implantation contributes to vasa vasorum neovascularization and enhanced influx of macro-

**Table 3.** Angiographic and PCI Procedural Characteristics of the Patients with an Eight-month RHI of < 2 or ≥ 2

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>RHI &lt; 2 (n = 43)</th>
<th>RHI ≥ 2 (n = 43)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culprit vessel, %</td>
<td></td>
<td></td>
<td>0.58</td>
</tr>
<tr>
<td>RCA</td>
<td>30</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>58</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>LCx</td>
<td>10</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>LMT</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Multivessel disease, %</td>
<td>49</td>
<td>28</td>
<td>0.046</td>
</tr>
<tr>
<td>Lesion type B2/C, %</td>
<td>78</td>
<td>71</td>
<td>0.45</td>
</tr>
<tr>
<td>Bifurcation lesion, %</td>
<td>40</td>
<td>36</td>
<td>0.65</td>
</tr>
<tr>
<td>Reference vessel diameter, mm</td>
<td>2.94 (0.40)</td>
<td>2.86 (0.69)</td>
<td>0.82</td>
</tr>
<tr>
<td>BMS, %</td>
<td>44</td>
<td>37</td>
<td>0.51</td>
</tr>
<tr>
<td>DES, %</td>
<td>49</td>
<td>61</td>
<td>0.28</td>
</tr>
<tr>
<td>Sirolimus-eluting</td>
<td>19</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel-eluting</td>
<td>30</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Biolimus-eluting</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Other than stent (POBA), %</td>
<td>7</td>
<td>2</td>
<td>0.31</td>
</tr>
<tr>
<td>Stent diameter, mm</td>
<td>3.50 [3.00-3.50]</td>
<td>3.25 [3.00-3.50]</td>
<td>0.33</td>
</tr>
<tr>
<td>Total stent length, mm</td>
<td>23 [16-31]</td>
<td>27 [17-41]</td>
<td>0.45</td>
</tr>
<tr>
<td>No. of stents per patient</td>
<td>1.0 [1.0-1.5]</td>
<td>1.0 [1.0-2.0]</td>
<td>0.14</td>
</tr>
<tr>
<td>Maximal balloon diameter, mm</td>
<td>3.50 [3.25-3.75]</td>
<td>3.50 [3.00-4.00]</td>
<td>0.96</td>
</tr>
<tr>
<td>Maximal balloon pressure, atm</td>
<td>20 [16-22]</td>
<td>20 [18-21]</td>
<td>0.14</td>
</tr>
<tr>
<td>Minimum stent diameter, mm</td>
<td>2.95 (0.48)</td>
<td>2.95 (0.57)</td>
<td>0.68</td>
</tr>
<tr>
<td>Final diameter stenosis, %</td>
<td>16 (6)</td>
<td>15 (6)</td>
<td>0.95</td>
</tr>
<tr>
<td>Postprocedural TIMI flow grade, %</td>
<td>0</td>
<td>0</td>
<td>0.56</td>
</tr>
</tbody>
</table>

The data are expressed as the percentage, mean (SD) or median [25th to 75th percentiles].
BMS = bare-metal stent; DES = drug-eluting stent; LAD = left anterior descending; LCx = left circumflex; LMT = left main trunk; PCI = percutaneous coronary intervention; POBA = plain old balloon angioplasty; RCA = right coronary artery; RHI = reactive hyperemia index; TIMI = Thrombolysis in Myocardial Infarction.

diabetes mellitus and multivessel disease exhibited a trend toward being associated with a higher risk of restenosis. Only an eight-month RHI of < 2 was found to be significantly associated with a higher risk of restenosis (odds ratio: 4.23, 95% CI: 1.25 to 14.28, \(p=0.02\)), whereas the three-week RHI demonstrated no significant associations (Table 5).

**Discussion**

The present study showed that impairment of the eight-month RHI is associated with restenosis at eight months after primary PCI for initial ACS. Therefore, the peripheral microvascular endothelial function may play an important role in the pathogenesis of restenosis. However, the role of the coronary endothelium in the process of restenosis after PCI remains unclear. Endothelial dysfunction produces an imbalance between vasodilator substances with antiproliferative properties, such as nitric oxide (NO), and vasoconstrictors with mitogenic properties, such as endothelin. Indeed, endothelial-derived NO suppresses smooth muscle proliferation and inhibits residual hyperplasia after vascular injury.\(^{12, 13}\) Moreover, the local release of endothelin-1 occurs at sites of vascular injury.\(^{14}\) and endothelin receptor antagonists have been reported to attenuate stent restenosis.\(^{15}\) Endothelial dysfunction may also involve the vascular microcirculation, which includes the vasa vasorum, leading to vascular wall ischemia and neovascularization. Stent implantation contributes to vasa vasorum neovascularization and enhanced influx of macro-

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Fingertip RH-PAT and Restenosis

phages at the sites of stent struts\textsuperscript{16} and promotes the inflammatory response, smooth muscle cell proliferation and restenosis. A previous study demonstrated that impairment of the FMD at six months after stenting is associated with late luminal loss and ISR of the native coronary arteries\textsuperscript{17}. These reports support our findings that assessing the coronary endothelial function by measuring the RHI at eight months can be used to identify patients who are likely to develop restenosis. In the current study, the three-week RHI was not found to be a significant predictor of the risk of restenosis. A possible explanation for this finding may be that regenerated endothelial cells do not line the luminal surface of the neointima at three weeks after stenting\textsuperscript{16, 18}.

In the presence of cardiovascular risk factors, endothelial cells suffer continuous damage, with repair being undertaken by proliferating local cells and circulating endothelial progenitor cells. Endothelial vasomotor dysfunction is reversible and alters in parallel with changes in the coronary risk status\textsuperscript{19, 20}. Our patients received well-established secondary preven-

<table>
<thead>
<tr>
<th>Table 4. Risk Status and Medications at Eight Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
</tr>
<tr>
<td>Current smoking, %</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dl</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
</tr>
<tr>
<td>HbA\textsubscript{1c}, %</td>
</tr>
<tr>
<td>hs-CRP, mg/dl</td>
</tr>
<tr>
<td>BNP, pg/ml</td>
</tr>
</tbody>
</table>

Medications, %

- Aspirin                                        100
- Clopidogrel                                    95
- ACE inhibitor or ARB                          95
- Beta-blocker                                   14
- Calcium-channel blocker                       26
- Statin                                         93
- Sulfonylurea                                   14
- Metformin                                      5
- \(\alpha\)-GI                                    26
- Pioglitazone                                   19
- Insulin                                       7

The data are expressed as the percentage, mean (SD) or median [25\(^{th}\) to 75\(^{th}\) percentiles].

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; \(\alpha\)-GI = alpha-glucosidase inhibitor; BMI = body mass index; BNP = brain natriuretic peptide; HbA\textsubscript{1c} = glycated hemoglobin; HDL = high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; RHI = reactive hyperemia index.

\[\text{Fig. 2. Incidence of Restenosis in the Patients with an Eight-month RHI of < 2 or ≥ 2}\]

RHI = reactive hyperemia index.
RH-PAT has the advantages of being completely non-invasive, simple to perform, less affected by operator error and more reproducible. Therefore, RH-PAT can be easily employed in clinical practice to identify patients with a high risk of restenosis. The results of the present study offer the potential clinical implication that patients with lower eight-month RHI values require an aggressive evaluation of myocardial ischemia due to the potential of restenosis.

The present study is associated with several limitations. First, only 86 patients were enrolled, and the study was conducted at a single center. In order to confirm the usefulness of measuring the RHI, further studies employing the same criteria in larger patient populations are needed. Second, this study included patients receiving BMS and DES. Previous studies have shown that DES delays the reendothelialization process resulting from the use of antiproliferative eluting drugs and polymer material\(^{18}\). Because our study population was small, we did not perform an evaluation of each stent type. Third, restenosis was defined based on the magnitude of lumen renarrowing on eight-month angiography; however, we acknowledge that coronary angiography cannot be used to reliably differentiate between thrombosis and restenosis as causes of lumen renarrowing. Fourth, we had no data regarding the use of interventions to improve the RHI, which may have resulted in a reduced rate of restenosis.

In conclusion, impairment of the digital hyperemic response at eight months is associated with restenosis in ACS patients with a history of primary PCI. Indeed, the patients exhibited improvements in the levels of LDL cholesterol, HbA\(_1c\) and brain natriuretic peptide, as well as the rate of smoking, after eight months. It is unclear why the eight-month RHI values were significantly attenuated in the patients with restenosis compared to that observed in the patients without restenosis, despite receiving similar treatment. The development of atherosclerosis, insufficient risk factor reduction in some patients, a genetic predisposition and/or the effects of undetermined risk factors may have prevented improvements in the RHI.

Table 5. Univariate Logistic Regression Analysis According to the Risk of Restenosis

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.05</td>
<td>0.99-1.11</td>
<td>0.10</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.02</td>
<td>0.29-3.57</td>
<td>0.98</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.39</td>
<td>0.47-4.07</td>
<td>0.55</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.72</td>
<td>0.91-8.16</td>
<td>0.07</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>0.86</td>
<td>0.30-2.50</td>
<td>0.79</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1.36</td>
<td>0.25-7.40</td>
<td>0.73</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>2.86</td>
<td>0.96-8.48</td>
<td>0.06</td>
</tr>
<tr>
<td>Lesion type B2/C</td>
<td>1</td>
<td>0.28-3.52</td>
<td>1</td>
</tr>
<tr>
<td>Bifurcation lesion</td>
<td>1.34</td>
<td>0.44-4.03</td>
<td>0.61</td>
</tr>
<tr>
<td>Small-vessel disease (&lt;2.5 mm)</td>
<td>1.29</td>
<td>0.36-4.60</td>
<td>0.70</td>
</tr>
<tr>
<td>Total stent length (&gt;20 mm)</td>
<td>2.88</td>
<td>0.59-14.08</td>
<td>0.19</td>
</tr>
<tr>
<td>Final diameter stenosis</td>
<td>0.95</td>
<td>0.87-1.04</td>
<td>0.26</td>
</tr>
<tr>
<td>3-week RHI</td>
<td>0.47</td>
<td>0.11-1.97</td>
<td>0.30</td>
</tr>
<tr>
<td>8-month RHI (&lt;2)</td>
<td>4.23</td>
<td>1.25-14.28</td>
<td>0.02</td>
</tr>
</tbody>
</table>

CI = confidence interval; OR = odds ratio; RHI = reactive hyperemia index.

Endothelial dysfunction is characterized by the impairment of endothelium-dependent vasodilation due to a reduced vasodilator bioactivity, particularly that of NO, and/or an increase in contractile factors\(^{21}\). The increase in digital pulse amplitude associated with reactive hyperemia is a complex response that reflects changes in the digital blood flow and microvessel dilation. The NO-mediated component accounts for approximately 60% of digital artery dilation, while other vasodilator components account for the remaining 40%\(^{22}\). In contrast, brachial artery FMD is primarily caused by NO, as the vessel is largely blocked by NO synthase inhibitors\(^{23}\). Therefore, RH-PAT may be used to measure components of vasodilation not reflected in FMD, providing at least a theoretical basis for a more comprehensive assessment of the vascular function. In fact, a large community-based cohort study found that FMD and RH-PAT show small differences in their relationships with various cardiovascular risk factors\(^{24}\). Compared with FMD,
invasive test for identifying patients at high risk of restenosis.

**Disclosure**

The authors declare no conflicts of interest.

**References**