Doppler-Derived Intracoronary Physiology Indices Predict the Occurrence of Microvascular Injury and Microvascular Perfusion Deficits After Angiographically Successful Primary Percutaneous Coronary Intervention

Paul F.A. Teunissen, MD; Guus A. de Waard, MD; Maurits R. Hollander, MD; Lourens F.H.J. Robbers, MD; Ibrahim Danad, MD; P. Stefan Biesbroek, MD; Raquel P. Amier, MD; Mauro Echavarría-Pinto, MD; Alicia Quirós, PhD; Christopher Broyd, MD, PhD; Martijn W. Heymans, PhD; Robin Nijveldt, MD, PhD; Adriaan A. Lammertsma, PhD; Pieter G. Rajmakers, PhD; Cornelis P. Allaart, MD, PhD; Jorrit S. Lemkes, MD; Yolande E. Appelman, MD, PhD; Koen M. Marques, MD, PhD; Jean G.F. Bronzwaer, MD, PhD; Anton J.G. Horrevoets, PhD; Albert C. van Rossum, MD, PhD; Javier Escaned, MD, PhD; Aernout M. Beek, MD, PhD; Paul Knaapen, MD, PhD; Niels van Royen, MD, PhD

Background—A total of 40% to 50% of patients with ST-segment–elevation myocardial infarction develop microvascular injury (MVI) despite angiographically successful primary percutaneous coronary intervention (PCI). We investigated whether hyperemic microvascular resistance (HMR) immediately after angiographically successful PCI predicts MVI at cardiovascular magnetic resonance and reduced myocardial blood flow at positron emission tomography (PET).

Methods and Results—Sixty patients with ST-segment–elevation myocardial infarction were included in this prospective study. Immediately after successful PCI, intracoronary pressure–flow measurements were performed and analyzed off-line to calculate HMR and indices derived from the pressure–velocity loops, including pressure at zero flow. Cardiovascular magnetic resonance and H$_2^{15}$O PET imaging were performed 4 to 6 days after PCI. Using cardiovascular magnetic resonance, MVI was defined as a subendocardial recess of myocardium with low signal intensity within a gadolinium-enhanced area. Myocardial perfusion was quantified using H$_2^{15}$O PET. Reference HMR values were obtained in 16 stable patients undergoing coronary angiography. Complete data sets were available in 48 patients of which 24 developed MVI. Adequate pressure–velocity loops were obtained in 29 patients. HMR in the culprit artery in patients with MVI was significantly higher than in patients without MVI (MVI, 3.3±1.50 mm Hg/cm per second versus no MVI, 2.4±1.26 mm Hg/cm per second; P=0.03). MVI was associated with higher pressure at zero flow (45.68±13.16 versus 32.01±14.98 mm Hg; P=0.015). Multivariable analysis showed HMR to independently predict MVI (P=0.04). The optimal cutoff value for HMR was 2.5 mm Hg/cm per second. High HMR was associated with decreased myocardial blood flow on PET (myocardial perfusion reserve <2.0, 3.18±1.42 mm Hg/cm per second versus myocardial perfusion reserve ≥2.0, 2.24±1.19 mm Hg/cm per second; P=0.04).

Conclusions—Doppler–flow–derived physiological indices of coronary resistance (HMR) and extravascular compression (pressure at zero flow) obtained immediately after successful primary PCI predict MVI and decreased PET myocardial blood flow.

Clinical Trial Registration—URL: http://www.trialregister.nl. Unique identifier: NTR3164. (Circ Cardiovasc Interv. 2015;8:e001786. DOI: 10.1161/CIRCINTERVENTIONS.114.001786.)

Key Words: microcirculation ■ myocardial infarction ■ reperfusion
WHAT IS KNOWN

• Despite successful primary percutaneous coronary intervention, 40% to 50% of patients with ST-segment–elevation myocardial infarction develop microvascular injury, which is related to worse outcome.
• Elevated intracoronary microvascular resistance as measured by thermodilution (index of microcirculatory resistance) is linked to the development of microvascular injury after reperfused ST-segment–elevation myocardial infarction.

WHAT THE STUDY ADDS

• Elevated Doppler-flow velocity–derived hyperemic microvascular resistance relates to cardiac magnetic resonance–defined microvascular injury and to H215O positron emission tomography–quantified perfusion deficits at follow-up.
• An hyperemic microvascular resistance of 2.5 mm Hg/cm per second can serve as a cutoff for identifying patients at risk for developing extensive microvascular injury.
• Increased hyperemic microvascular resistance is associated with a worse outcome as assessed by cardiac magnetic resonance at 3-month follow-up.

Between 40% and 50% of patients with acute myocardial infarction develop cardiovascular magnetic resonance (CMR)–defined microvascular injury (MVI), despite successful treatment with primary percutaneous coronary intervention (PCI) and complete restoration of epicardial coronary flow as visualized by standard coronary angiography.1 CMR-defined MVI is assessed by T2-weighted imaging and late gadolinium enhancement. MVI refers to the areas within the infarcted myocardium where wash-in of contrast medium is severely impaired, as opposed to the wash-in (and delayed wash-out) of the contrast medium in the remaining areas of the infarct. It has been postulated that within these areas devoid of contrast, the microvasculature is obstructed, hence the term microvascular obstruction. Recently, however, it was shown that CMR-defined microvascular obstruction actually contains intramyocardial hemorrhage and complete microvascular destruction.2 Therefore, the term MVI seems to be more appropriate.

The occurrence of MVI is linked to negative remodeling and left ventricular dysfunction, leading to decreased long-term survival, increased morbidity, and reduced quality of life as compared with patients with ST-segment–elevation myocardial infarction (STEMI) without MVI.3 MVI is related to ischemia–reperfusion damage and can potentially be reversed by pharmacological treatment in addition to the standard PCI treatment. To develop additional therapies to prevent MVI, identification of patients at risk is necessary. Ideally, this identification takes place immediately after PCI to expand the therapeutic window and still have the opportunity of local delivery of the compound of choice.

Although established angiographic parameters such as myocardial blush grade (MBG) and corrected thrombolysis in myocardial infarction (TIMI) flow have been used to predict long-term clinical outcome after acute myocardial infarction in the past, recent studies have shown the inaccuracy of these parameters to reliably predict occurrence of MVI as visualized by CMR in the days after the acute event.4,5 A dysfunctional microvasculature in patients who develop MVI should be reflected by higher microvascular resistance. The main purpose of the current study was to assess whether increased hyperemic microvascular resistance (HMR) derived from Doppler-flow velocity measurements is related to the occurrence of MVI as determined by CMR at days 4 to 6 in patients with angiographic optimal restoration of flow after primary PCI. A secondary objective was to assess the relationship between HMR and absolute myocardial perfusion as quantified by H215O positron emission tomography (PET) 4 to 6 days after primary PCI.

Methods

Patient Population

In this prospective study, 60 consecutive patients with acute STEMI presenting at the catheterization laboratory within 6 hours after onset of symptoms and successfully treated by primary PCI were included between December 2011 and February 2013. Exclusion criteria are specified in the Methods in the Data Supplement. To define normal values of HMR, 16 patients referred for invasive coronary angiography because of anginal complaints, from a cohort described earlier6 served as a control group. In this group, fractional flow reserve (FFR), coronary flow reserve (CFR) and HMR were measured in 1 to 3 coronary arteries. For the present study, vessels without angiographic abnormalities were selected.

Study Protocol

Immediately after successful PCI after standard procedures, patients were asked for oral informed consent at the catheterization laboratory, which was witnessed by an independent person. After informed consent was obtained, intracoronary pressure–flow measurements were performed in the infarct-related artery and in a reference artery. Written informed consent was obtained at the cardiac care unit within 24 hours after PCI. H215O PET and CMR were performed 4 to 6 days after PCI, within 24 hours from each other. The protocol was approved by the Medical Ethics Review Committee of the VU University Medical Center in Amsterdam and was in line with the principles of the Declaration of Helsinki.7

Coronary Intervention and Intracoronary Pressure and Flow Measurements

Primary PCI procedure and medication administration were performed according to the standard procedures and are specified in the Methods in the Data Supplement. Angiographic estimates of myocardial flow, TIMI flow, corrected TIMI frame count (cTFI), MBG, and Quantitative Blush Evaluator were obtained and are specified in the Methods in the Data Supplement. Immediately after successful revascularization and stent-placement, intracoronary nitrates (300 μg) were administered and a 0.014-in pressure–flow sensor-tipped wire (ComboWire Guidewire REF 9500, Volcano Corporation, San Diego, CA) was inserted in the culprit artery via a guiding catheter. Three combined pressure and flow velocity recordings were performed at baseline. Pressure and flow velocity measurements were repeated under conditions of pharmacologically induced peak hyperemia by intracoronary injection of 150 μg of adenosine. In addition, baseline and hyperemic measurements were performed in a coronary artery without a significant stenosis (>50% angiographic stenosis) to serve
Male sex 21 (88%) 15 (63%) 0.09
Age, y 58±8 60±10 0.35
Weight, kg 85±12 84±17 0.83
BMI, kg/m² 27±2 28±4 0.58
CAD risk factors
Diabetes mellitus 1 (4%) 5 (21%) 0.19
Hypertension 4 (17%) 5 (21%) 1.00
Hypercholesterolemia 2 (8%) 6 (25%) 0.25
Smoking history 18 (75%) 20 (83%) 0.72
Family history 16 (67%) 10 (42%) 0.15
Functional parameters assessed by CMR at 4–6 d
LVEDV, mL 94.1±13.0 86.1±21.5 0.12
LVESV, mL 50.5±11.7 40.1±19.4 0.03
LVEF, % 46.8±6.3 55.0±8.0 <0.001
Infarct size (percentage of the LV) 24.6±10.4 10.2±6.9 <0.001
Volume of MVI, cm³ 4.2±3.5 n/a n/a
Duration of symptoms, h 1.8±1.3 1.6±1.0 0.59
Time to reperfusion, h 2.0±1.4 2.1±1.4 0.74
CK-MB peak, U/L 263±220 79±73 <0.01
LAD 16 (67%) 11 (46%) 0.24
LCX 2 (8%) 3 (13%) 1.00
RCA 6 (25%) 10 (42%) 0.36
Platelet glycoprotein IIb/IIIa inhibitors 12 (50%) 2 (8%) <0.01
TIMI 3 flow grade post-PCI 23 (96%) 23 (96%) 1.00
cTFC 24.4±9.9 27.7±13.1 0.33
Incomplete (<70%) ST-segment resolution post PCI 16 (67%) 11 (46%) 0.24

Data are n or mean±SD. BMI indicates body mass index; CAD, coronary artery disease; CK-MB, creatine kinase-myocardial band; CMR, cardiovascular magnetic resonance; cTFC, corrected TIMI frame count; LAD, left anterior descending artery; LCX, left circumflex artery; LV, left ventricle; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; MVI, microvascular injury; n/a, not applicable; PCI, percutaneous coronary intervention; RCA, right coronary artery; and TIMI, thrombolysis in myocardial infarction.

Cardiovascular Magnetic Resonance Imaging
CMR was performed both between 4 and 6 days, as well as 3 months after PCI using a 1.5 Tesla MR-scanner (Magnetom Avanto, Siemens, Erlangen, Germany). MVI was identified in late gadolinium enhancement images as hypointense recesses within the hyperenhanced myocardium. The size of the area of MVI was calculated by manual delineation of the hypointense areas on late gadolinium enhancement images and was expressed in square centimeter. The total volume of MVI in cubic centimeter was calculated by multiplying the area size with [slice thickness+slice gap]. Further details on acquisition and analysis and definitions of CMR parameters are specified in the Methods in the Data Supplement.
The posterior power calculations were done in SAS 9.3 with the Proc Power Logistic procedure with as input parameters the odds ratio, the response probability of MVI, the mean and SD of the predictor HMR, and the number of patients.

Results

Sixty patients (47 men) were included in this study (mean age, 59±9 years; range, 45–83). In 52 patients, CMR scanning was performed. In 1 patient, technical problems occurred during scanning, 4 patients refused CMR scanning because of anxiety or claustrophobia, and 2 patients did not fit in the CMR scanner because of obesity. In 1 patient, a proximal dissection of a coronary artery occurred during the procedure. For patient safety and to prevent invalid data, no invasive measurements were performed and this patient was excluded from further analysis. Clinical demographics and angiographic characteristics are shown in Tables 1 and 2. Typical examples of Combowire measurements, late gadolinium enhancement CMR imaging, and PET imaging are shown in Figure 1.

Clinical Characteristics

Cardiac catheterization was performed via the radial approach in 55 patients (93%) and via femoral approach in 4 patients (7%). Left anterior descending artery, right coronary artery, and left circumflex artery were considered to be the culprit artery in 30 (51%), 24 (41%), and 5 (9%) patients, respectively. Mean time between onset of symptoms and start of primary PCI was 1.9±1.3 hours. Mean time to reperfusion was 2.2±1.5 hours. Median creatine kinase-myocardial band peak was 127 U/L (interquartile range, 40–205).

Angiographic Estimates of Microvascular Function

After PCI, TIMI flow grade was 3 in 57 patients (97%) and 2 in 2 patients (3%). MBG was scored as 3 in 48 patients (81%) and as 2 in 11 patients (19%). Using Quantitative Blush Evaluator, a mean score of 17.7±8.1 was obtained. Mean cTFC was 25.7±11.7. Angiographic parameters were not significantly different between patients with and without MVI (TIMI 3 flow, 23 versus 23 patients, *P*=1.00; cTFC, 24.4±9.9 versus 25.7±11.7).

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Increased HMR Is Associated With Occurrence of MVI

CMR parameters of left ventricular end-diastolic volume, left ventricular end-systolic volume, left ventricular ejection fraction (LVEF), infarct size, and area of MVI are shown in Table 1. Twenty-four of the 48 patients had CMR-defined MVI (50%). Hemodynamic data in patients with and without MVI and impaired PET MBF, respectively, are shown in Tables 3 and 4 and Figure 3A through 3D. In the culprit artery, mean HMR was significantly higher in patients with MVI compared with those without MVI, whereas CFR and FFR were comparable between both groups. In the reference artery HMR, CFR and FFR were not significantly different between patients with and without MVI.

In a univariable analysis, sex, family history of CAD and HMR were predictors of MVI. In a multivariable analysis, HMR and sex remained independent predictors of MVI. Data are shown in Table 5. The area under the receiver operating characteristic curve for HMR for the detection of MVI was 0.68 (95% confidence interval [CI], 0.53–0.83; P = 0.03; Figure 4A). The best cutoff value for HMR was 2.5 mm Hg/cm per second, giving a sensitivity of 71% (95% CI, 58%–84%) and a specificity of 63% (95% CI, 49%–77%).

When stratifying between extensive and mild/absent total volume of MVI using the mean of 2.1 ± 3.2 cm³, extensive MVI significantly predicts impaired LVEF and increased final infarct size at 3-month follow-up CMR (43.9 ± 7.0 versus 55.4 ± 8.3; P < 0.01 for LVEF and 17.9 ± 6.1 versus 10.2 ± 6.4; P < 0.001 for final infarct size, respectively). The area under the receiver operating characteristic curve for HMR to predict extensive volumetric MVI was 0.80 (95% CI, 0.67–0.93; P < 0.01), yielding again an optimal cutoff of 2.5 mm Hg/cm per second, with a sensitivity of 93% (95% CI, 87%–99%) and a specificity of 65% (95% CI, 52%–78%; Figure 4B). We also found a significant correlation between HMR and total volume of MVI (r = 0.46; P < 0.01). Using the 2.5 cutoff, volume of MVI was clearly increased in patients with an elevated HMR (HMR ≥ 2.5 mm Hg/cm per second, 3.3 ± 3.7 cm³ versus HMR < 2.5 mm Hg/cm per second, 0.6 ± 1.7 cm³; P < 0.01; Figure 5).

HMR and Other CMR Parameters

A significant correlation was found between HMR and CMR-defined infarct size as a percentage of LV (r = 0.41; P < 0.01). When using the 2.5 cutoff, CMR-defined infarct size was strongly increased in patients with an elevated HMR (HMR ≥ 2.5 mm Hg/cm per second, 22.1 ± 12.5% versus

### Table 3. Pressure/Flow Measurements in Patients With and Without Cardiovascular Magnetic Resonance–Derived MVI 4 to 6 Days After Percutaneous Coronary Intervention

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MVI at 4–6 d (n=24)</th>
<th>No MVI at 4–6 d (n=24)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Culprit artery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperemic microvascular resistance</td>
<td>3.33±1.50</td>
<td>2.41±1.26</td>
<td>0.03</td>
</tr>
<tr>
<td>Coronary flow reserve</td>
<td>1.60±0.41</td>
<td>1.89±0.96</td>
<td>0.19</td>
</tr>
<tr>
<td>Fractional flow reserve</td>
<td>0.99 (0.94–1.00)</td>
<td>0.95 (0.91–0.99)</td>
<td>0.10</td>
</tr>
<tr>
<td>Resting flow velocity, cm/s</td>
<td>19.1±12.1</td>
<td>23.6±12.2</td>
<td>0.20</td>
</tr>
<tr>
<td>Resting Pa, mm Hg</td>
<td>86.7±10.3</td>
<td>83.7±10.6</td>
<td>0.32</td>
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<tr>
<td>Resting Pd, mm Hg</td>
<td>84.4±10.4</td>
<td>81.7±11.7</td>
<td>0.40</td>
</tr>
<tr>
<td>Hyperemic flow velocity, cm/s</td>
<td>31.1±18.7</td>
<td>41.9±23.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Hyperemic Pa, mm Hg</td>
<td>82.2±13.9</td>
<td>82.0±12.3</td>
<td>0.98</td>
</tr>
<tr>
<td>Hyperemic Pd, mm Hg</td>
<td>78.9±13.8</td>
<td>77.0±12.6</td>
<td>0.64</td>
</tr>
<tr>
<td><strong>Reference artery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperemic microvascular resistance</td>
<td>2.83±1.06</td>
<td>2.34±1.27</td>
<td>0.17</td>
</tr>
<tr>
<td>Coronary flow reserve</td>
<td>1.69±0.48</td>
<td>2.01±0.86</td>
<td>0.14</td>
</tr>
<tr>
<td>Fractional flow reserve</td>
<td>1.00 (0.98–1.00)</td>
<td>0.98 (0.93–1.00)</td>
<td>0.06</td>
</tr>
<tr>
<td>Resting flow velocity, cm/s</td>
<td>19.1±7.2</td>
<td>21.9±11.4</td>
<td>0.35</td>
</tr>
<tr>
<td>Resting Pa, mm Hg</td>
<td>87.1±11.1</td>
<td>86.8±11.3</td>
<td>0.91</td>
</tr>
<tr>
<td>Resting Pd, mm Hg</td>
<td>85.8±11.5</td>
<td>84.9±11.1</td>
<td>0.81</td>
</tr>
<tr>
<td>Hyperemic flow velocity, cm/s</td>
<td>31.5±13.3</td>
<td>40.6±19.9</td>
<td>0.09</td>
</tr>
<tr>
<td>Hyperemic Pa, mm Hg</td>
<td>80.4±10.9</td>
<td>82.3±15.3</td>
<td>0.64</td>
</tr>
<tr>
<td>Hyperemic Pd, mm Hg</td>
<td>78.6±11.6</td>
<td>78.2±12.9</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Data are n or mean±SD or median and interquartile range. Hyperemic microvascular resistance is expressed in mm Hg/cm per second. MVI indicates microvascular injury; Pa, aortic pressure; and Pd, distal pressure.
Table 4. Pressure/Flow Measurements in Patients With Normal and Abnormal Positron Emission Tomography–Derived MBF 4 to 6 Days After Percutaneous Coronary Intervention

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Abnormal MBF</th>
<th>Normal MBF</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culprit artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperemic microvascular resistance</td>
<td>3.18±1.42</td>
<td>2.24±1.19</td>
<td>0.04</td>
</tr>
<tr>
<td>Coronary flow reserve</td>
<td>1.59±0.46</td>
<td>2.02±1.09</td>
<td>0.07</td>
</tr>
<tr>
<td>Fractional flow reserve</td>
<td>0.98 (0.91–1.00)</td>
<td>0.95 (0.92–0.99)</td>
<td>0.10</td>
</tr>
<tr>
<td>Resting flow velocity, cm/s</td>
<td>20.0±13.9</td>
<td>24.1±11.9</td>
<td>0.33</td>
</tr>
<tr>
<td>Resting Pa, mm Hg</td>
<td>86.4±11.4</td>
<td>84.0±9.9</td>
<td>0.50</td>
</tr>
<tr>
<td>Resting Pd, mm Hg</td>
<td>84.5±11.5</td>
<td>81.3±11.5</td>
<td>0.40</td>
</tr>
<tr>
<td>Hyperemic flow velocity, cm/s</td>
<td>29.1±15.0</td>
<td>45.7±23.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Hyperemic Pa, mm Hg</td>
<td>82.6±13.9</td>
<td>84.7±10.6</td>
<td>0.62</td>
</tr>
<tr>
<td>Hyperemic Pd, mm Hg</td>
<td>79.0±15.1</td>
<td>79.6±11.6</td>
<td>0.89</td>
</tr>
<tr>
<td>Reference artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperemic microvascular resistance</td>
<td>2.68±0.81</td>
<td>2.17±1.12</td>
<td>0.11</td>
</tr>
<tr>
<td>Coronary flow reserve</td>
<td>1.77±0.53</td>
<td>2.10±1.00</td>
<td>0.30</td>
</tr>
<tr>
<td>Fractional flow reserve</td>
<td>0.98 (0.92–1.00)</td>
<td>1.00 (0.98–1.00)</td>
<td>0.06</td>
</tr>
<tr>
<td>Resting flow velocity, cm/s</td>
<td>18.1±6.3</td>
<td>23.6±12.8</td>
<td>0.19</td>
</tr>
<tr>
<td>Resting Pa, mm Hg</td>
<td>87.6±12.1</td>
<td>87.5±11.3</td>
<td>0.99</td>
</tr>
<tr>
<td>Resting Pd, mm Hg</td>
<td>86.3±12.4</td>
<td>85.1±11.0</td>
<td>0.77</td>
</tr>
<tr>
<td>Hyperemic flow velocity, cm/s</td>
<td>30.2±7.1</td>
<td>44.9±21.5</td>
<td>0.04</td>
</tr>
<tr>
<td>Hyperemic Pa, mm Hg</td>
<td>82.1±12.7</td>
<td>82.2±14.0</td>
<td>0.99</td>
</tr>
<tr>
<td>Hyperemic Pd, mm Hg</td>
<td>79.4±11.2</td>
<td>77.1±12.4</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Data are n or mean±SD or median and interquartile range. Abnormal MBF: MPR<2.0; Normal MBF: MPR≥2.0. Hyperemic microvascular resistance is expressed in mm Hg/cm per second. MBF indicates myocardial blood flow; MPR, myocardial perfusion reserve; Pa, aortic pressure; and Pd, distal pressure.

HMR<2.5 mm Hg/cm per second, 12.5±7.3%; P<0.01). For 768 analyzed segments, segmental wall thickening was significantly lower in patients with an elevated HMR (HMR≥2.5 mm Hg/cm per second, 3.13±2.14 mm versus HMR<2.5 mm Hg/cm per second, 3.49±1.87 mm; P=0.01). Increased HMR was also associated with a worse outcome as assessed by CMR at 3-month follow-up, showing increased final infarct size and an impaired LVEF (Table 6). Patients with an HMR in the culprit artery above the cutoff value of 2.5 mm Hg/cm per second had a significantly higher creatine kinase-myocardial band peak as compared with their counterparts with normal HMR (229±231 versus 92±108; P=0.02).

**Increased HMR Is Associated With Decreased Regional MBF**

PET scanning was performed 4 to 6 days after PCI in 51 of the 52 patients who had CMR scans (1 patient refused PET). In the infarcted region, baseline and hyperemic MBF were 0.94±0.20 and 1.66±0.55 mL/min per gram, respectively, resulting in a MPR of 1.81±0.61. In the remote region, baseline MBF, hyperemic MBF, and MPR were 0.96±0.30, 2.20±0.56, and 2.42±0.76 mL/min per gram, respectively. Mean HMR was significantly higher in patients with abnormal perfusion than in patients with normal myocardial perfusion (MPR<2.0, 3.26±1.41 versus MPR≥2.0, 2.24±1.19; P=0.03). The CFR and FFR in the infarct area were comparable in patients with abnormal perfusion and normal myocardial perfusion. In the reference area, HMR, CFR, and FFR were similar between patients with an abnormal and a normal myocardial perfusion in the infarct area. Data are shown in Table 4. In a univariable analysis, HMR was a predictor of decreased MPR on PET imaging. In a multivariable analysis, HMR remained an independent predictor of decreased MPR on PET imaging. Data are shown in Table 5. Invasively measured hyperemic Doppler flow velocity was significantly correlated to PET-derived MPR (r=0.56; P<0.001). Also, a significant correlation was found between HMR and PET-derived hyperemic coronary resistance (r=0.40; P=0.01; Figure I in the Data Supplement).

The presence of CMR-derived MVI was related to decreased PET-derived hyperemic MBF (MVI, 1.43±0.45 versus no MVI, 1.85±0.55 mL/min per gram; P<0.01) and depicted in Figure 3E and 3F. Figure 6 shows HMR in patients divided into groups of patients with normal PET perfusion and no MVI, patients with discordant PET perfusion and MVI measurements, and patients with both abnormal PET perfusion and MVI. HMR was significantly higher in patients with abnormal PET perfusion and MVI compared with patients with normal PET perfusion and no MVI (P=0.01). Furthermore, a significant trend was found with increase in HMR from patients with abnormal PET perfusion and no MVI, patients with discordant PET perfusion and MVI measurements, and patients with abnormal PET perfusion and MVI (P<0.01).

**Pressure–Flow Relationship**

Of the 48 patients used for the primary analysis, IHDVPS and PZF could be determined in 29 patients according to the predefined selection criterion requiring the linear relationship to have a coefficient of determination (R²) ≥0.90. A significant, negative correlation was observed between HMR and IHDVPS (r=−0.52; P=0.004), while a significant, positive correlation was observed between HMR and PZF (r=0.55; P=0.002). No relationship was found between IHDVPS and PZF (r=0.29; P=0.13). IHDVPS did not discriminate between patients with or without the development of MVI (1.47 (interquartile range, 0.82–2.69) versus 1.39 (interquartile range, 0.99–2.55) mm Hg/cm per second, respectively; P=0.77). PZF was significantly higher in patients with MVI (45.68±13.16 versus 32.01±14.98 mm Hg; P=0.015 for presence or absence of MVI, 48.54±13.72 versus 34.01±13.67 mm Hg; P=0.009 for extensive MVI; Figure 7). The area under the receiver operating characteristic curve for PZF to predict MVI was 0.75 (95% CI, 0.55–0.89; P=0.01) and for extensive MVI 0.77 (95% CI, 0.58–0.91; P<0.01).

**Discussion**

The key finding of this study is that Doppler-derived indices of coronary resistance (HMR) and extravascular compression (PZF), measured immediately after successful primary PCI, can predict the occurrence of CMR-defined MVI and PET-derived flow impairment in the first days after myocardial infarction. The present study is the first to provide an HMR cutoff value for the prediction of MVI at 4 to 6 days. This is a step forward toward identification during the acute STEMI phase of patients who may benefit from adjunctive therapy.
after PCI to prevent or attenuate MVI. Besides the relationship that we demonstrate between HMR and CMR-defined MVI in a categorical approach, we also found a clear correlation when MVI was expressed as a continuous variable.

Angiographic overt no-reflow is associated with high mortality and morbidity. Occurrence of angiographically detected no-reflow is rare and most patients show complete angiographic restoration of epicardial flow after primary PCI. Nevertheless, as illustrated by the CMR findings in our study, in these patients myocardial damage and MVI frequently develop despite successful revascularization. MVI or hidden no-reflow is related to left ventricular dysfunction, heart failure, and mortality.

Of importance is the finding that MVI is only in part established at the time of reperfusion. In the first 2 days after reperfusion, a delayed decrease in flow to initially adequately reperfused areas causes additional myocardial damage. This knowledge of the progressive development of MVI over time has led to several experimental and clinical attempts to detect MVI at an early stage and to prevent further increase of MVI.

Unfortunately, normalization of ECG or more elaborate angiographic parameters such as cTFC or myocardial blush grade do not accurately predict the occurrence of MVI. Therefore, it is important to develop additional diagnostic tools to predict occurrence of MVI already in the catheterization laboratory before initiating trials aiming to prevent MVI.

Measurements of Coronary Flow and Microvascular Resistance in Patients With STEMI

In previous studies, Doppler-flow–derived CFR was identified as a prognostic marker for LV function recovery after STEMI. Bax et al studied 73 patients with an acute anterior myocardial infarction, who were successfully treated by primary PCI. Using echocardiography, recovery of left ventricular function was measured and immediately after PCI, intracoronary CFR, cTFC, TIMI flow, and MBG were assessed. In a multivariate analysis, CFR was shown to be the only independent predictor of LV function recovery at 6 months. In a 10-year follow-up of this cohort, CFR defined as abnormal (<2.1) measured in a reference artery directly after PCI was...
associated with an increased cardiac mortality.22 However, no CMR was performed and it is thus unknown whether there was an association with MVI. In a study by Hirsch et al,23 intracoronary measurements of CFR, performed 4 to 8 days after primary PCI, corresponded well to the assessment of MVI by CMR. At this time however, the window of opportunity for early treatment has passed. The results of our study showed a trend toward decreased CFR in patients who developed MVI. HMR seems to be a more sensitive predictor of MVI than CFR and this can possibly be explained by the incorporation of actual distal pressure into the calculation of HMR, and the fact that it is not influenced by natural variations in baseline flow or residual epicardial stenoses. For example, increased baseline blood flow in the reference artery during the acute phase after reperfused STEMI results in a low CFR. A low CFR in the reference artery is also related to a global decrease in hyperemic flow during the acute phase as shown by Uren et al.9 and Bax et al.24

Indices derived from intracoronary pressure–velocity loops can be also used to assess microcirculatory function. The diagnostic value of IHDVPS, which measures microcirculatory conductance in mid and late diastole, has been validated against findings in endomyocardial biopsies.25 Other authors have found a significant relationship between impaired microcirculatory conductance and estimates of myocardial salvage in STEMI.26,27 Although in our study the expected inverse relationship between resistance (HMR) and conductance (IHDVPS) was confirmed, we did not identify IHDVPS as a predictor of MVI. PZF, derived from pressure-velocity loop analysis, informs on the effect of intraventricular and interstitial myocardial pressure over collapsible elements of the microcirculation.28,29 The latter aspect is key in our study population because, as illustrated by CMR imaging, both edema and intramyocardial hemorrhage develop in a variable extent during STEMI and might cause microcirculatory compression.25,26 The relationship between PZF and the development of MVI in our study receives support from previous research, reporting a relationship between PZF after primary PCI and amount of viable myocardium assessed with PET or CMR.26,30 Further research is warranted to clarify whether IHDVPS and PZF can provide complementary information to HMR. At present, the clinical applicability of IHDVPS and PZF in the setting of acute STEMI is hampered by the difficulties associated with acquiring high-quality, artifact-free Doppler tracings that are required to generate pressure-velocity loops suitable for analysis.

Table 5. Univariable and Multivariable Analysis for Predicting MVI and for Predicting Decreased Myocardial Perfusion on PET Imaging

<table>
<thead>
<tr>
<th>Variable</th>
<th>Microvascular Injury on CMR</th>
<th>Decreased Myocardial Perfusion on PET</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariable Analysis</td>
<td>Multivariable Analysis</td>
</tr>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Sex</td>
<td>0.24 (0.06–1.03)</td>
<td>0.06</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>0.36 (0.11–1.16)</td>
<td>0.09</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6.05 (0.65–61.37)</td>
<td>0.11</td>
</tr>
<tr>
<td>cTFC*</td>
<td>0.98 (0.93–1.03)</td>
<td>0.33</td>
</tr>
<tr>
<td>Incomplete (≤70%) ST-segment resolution post PCI</td>
<td>0.79 (0.36–1.73)</td>
<td>0.55</td>
</tr>
<tr>
<td>TIMI 3 flow grade after PCI</td>
<td>1.00 (0.06–16.97)</td>
<td>1.00</td>
</tr>
<tr>
<td>HMR*</td>
<td>1.66 (1.04–2.64)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; CI, confidence interval; CMR, cardiovascular magnetic resonance; cTFC, corrected TIMI frame count; HMR, hyperemic microvascular resistance; OR, odds ratio; PCI, percutaneous coronary intervention; PET, positron emission tomography; and TIMI, thrombolysis in myocardial infarction.

*Odds ratio per unit increase.

Figure 4. Receiver operating characteristic (ROC) curves for (A) hyperemic microvascular resistance (HMR) to determine the presence of microvascular injury (MVI) and (B) HMR to determine extensive volumetric MVI of ≥2.09 cm³. AUC indicates area under the receiver operating characteristic curve; and CMR, cardiovascular magnetic resonance.
Index of microcirculatory resistance (IMR) is a thermodilution-based technique to measure microvascular resistance. In several clinical studies in patients with acute myocardial infarction, IMR measured immediately after primary PCI was linked to myocardial damage. A recently published report on 253 patients elegantly showed that IMR predicts clinical outcome at a mean follow-up of 2.8 years. Furthermore, McGeoch et al showed that IMR after PCI was elevated in patients who developed MVI compared with those who did not. Of note, in that study not only patients with primary PCI but also patients with successful thrombolysis or rescue PCI after failed thrombolysis were included. Payne et al showed that IMR was linked to MVI as assessed by CMR in a more homogeneous group of patients with STEMI treated by primary PCI. Doppler-flow velocity is an alternative technique to measure microvascular resistance. The Combowire has both a pressure and a Doppler-flow sensor. HMR is the ratio of distal coronary pressure and hyperemic flow velocity. In a relatively small study with 27 patients by Kitabata et al, HMR, CFR, and PZF were shown to all be related to creatine kinase-myocardial band peak, infarct size, and transmural extent of infarction, but HMR was the best predictor. In a later study, this same group found that HMR measured directly after primary PCI, but not CFR, to be a predictor of CMR-defined left ventricular remodeling at 8 months.

Measurement of HMR in patients without epicardial coronary artery disease, as performed in our study in the control group, has not been performed before. It provides the opportunity to compare HMR in a normal situation to HMR in patients after a myocardial infarction.

**HMR and PET-Derived MBF**

Another important finding of the present study is that an elevated HMR predicts abnormal MBF as measured by PET. To the best of our knowledge, this is the first time CMR and PET imaging were performed shortly after primary PCI and within 24 hours of each other. Hyperemic MBF was clearly reduced in patients with MVI. The highest HMR values were found in patients with both MVI and reduced MBF. This corroborates results from earlier studies suggesting decreased or absent flow in CMR-defined myocardial regions with MVI.

**Limitations**

Because of the comprehensive study protocol, the number of patients that could be included was limited. A posterior power analysis revealed a power of 61% of HMR as a predictor of MVI using the odds ratio of 1.66 that was found in the univariable analysis as performed in our study. This implies that validation studies are warranted to corroborate
our findings. The use of Doppler–flow velocity comes with specific methodological considerations. First, Doppler–flow velocity tracings of sufficient quality must be obtained to accurately reflect true coronary flow velocity and to calculate HMR and CFR. To account for this, a stringent quality selection was applied in the present study. This possibly hampers the routine application of the Combowire in the clinical situation. To avoid biased and inaccurate estimations of PZF and HDVPS, we set as inclusion criteria a strong linearity between flow velocity and pressure within mid-to-late diastole, with a regression coefficient $R^2 \geq 0.90$ in $>3$ beats. Consequently, the parameters could be calculated in only 29 patients. It cannot be excluded that this stringent selection criterion produced misclassification bias. However, this seems unlikely as most of the exclusions were more likely related to the technical demands of stabilizing the sampling region of the Doppler sensor within the coronary artery. Also, in 1 patient, a dissection occurred during positioning of the Doppler wire. Furthermore, the control patients in the present study, who presented with chest pain and were referred for cardiac catheterization, might have had impaired endothelial and microvascular dysfunction, also because of a relatively high incidence of smoking and hypertension. As such, these values are not true control values.

Conclusions

Doppler-derived intracoronary indices provide important predictive information on the development of myocardial injury and the restoration of MBF. Elevated HMR ($>2.5 \text{ mmHg/cm per second}$) predicts MVI and is clearly related to other CMR parameters such as LVEF, segmental wall thickening, and infarct size, both at early as well as late follow-up. Finally, elevated HMR relates to PET-quantified perfusion deficits. The early availability of this tool, already in the catheterization laboratory, opens a window of opportunity for early adjunctive therapy aiming to prevent MVI and further improve outcome in primary PCI.

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Disclosures

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Doppler-Derived Intracoronary Physiology Indices Predict the Occurrence of Microvascular Injury and Microvascular Perfusion Deficits After Angiographically Successful Primary Percutaneous Coronary Intervention


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Supplemental Methods

Patient population
Patients with three-vessel disease and hemodynamically unstable patients were excluded from the study. Other exclusion criteria were previous myocardial infarction in the culprit coronary artery, previous coronary artery bypass graft (CABG) surgery, unsuccessful PCI (TIMI 0 or 1 flow after procedure) and refusal or inability to give informed consent.

Medication
In the ambulance, all patients received 5000 units of intravenous heparin, 500 mg of intravenous acetylsalicylic acid and 60 mg of prasugrel according to the local ambulance protocol for acute coronary syndromes. During the procedure 1.75 mg·kg⁻¹·h⁻¹ bivalirudin was administered intravenously and continued at a dosage of 0.25 mg·kg⁻¹·h⁻¹ for 4 hours. Use of a glycoprotein-IIb/IIIa inhibitor was left to the discretion of the operator. After successful PCI, aspirin, prasugrel, beta-blocker, ACE-inhibitor and statin therapy were prescribed to all patients according to current ACC/AHA/ESC guidelines.¹

Coronary intervention and intracoronary pressure and flow measurements
Cardiac catheterization was performed by either a transradial or a transfemoral approach, depending on the preference of the operators. Standard PCI procedures, including thrombus aspiration, were used to obtain coronary patency. Immediately after successful revascularization and stent-placement, intracoronary nitrates (300 µg) were administered to ensure maximal epicardial coronary dilation and a 0.014-inch pressure-flow sensor-tipped wire (ComboWire Guide Wire REF 9500, Volcano Corporation, San Diego, CA, USA) was inserted in the culprit artery via a guiding catheter.
Pressure equalization of this wire was performed with the sensor at the tip of the catheter before advancing the wire distal to the coronary stent. Three combined pressure and flow velocity recordings were performed at baseline. Pressure and flow velocity measurements were repeated under conditions of pharmacologically induced peak hyperemia by intracoronary injection of 150 μg of adenosine. In addition, baseline and hyperemic measurements were performed in a coronary artery without a significant stenosis (>50% angiographic stenosis) to serve as reference values.

**Off-line analyses of intracoronary pressure and flow measurements**

Computation of hyperemic microvascular resistance (HMR), coronary flow reserve (CFR) and fractional flow reserve (FFR) were performed off-line by two experienced analysts (GW and PT) blinded to CMR and PET results using custom software (written in Delphi v. 2010; Embarcadero, San Francisco, CA, USA). In case of disagreement, consensus was reached between the readers. Cycle averages of aortic pressure (Pa), distal pressure (Pd) and flow velocity were determined during at least three consecutive cycles of both resting and hyperemic conditions. HMR was defined as the ratio between Pd and flow velocity, CFR as the ratio between flow velocity during peak hyperemia and the flow velocity under resting conditions and FFR as the ratio between Pd and Pa during peak hyperemia. Physiological indices derived from the pressure-flow velocity relationship were calculated off-line at Hospital Clinico San Carlos (Madrid, Spain) by two investigators (ME and AQ) blinded to the results of other tests (CMR, PET) performed to the study population. Firstly, raw data was filtered according to Savitzky-Golay, to increase the signal-to-noise ratio without distorting the signals. The instantaneous hyperemic diastolic velocity-pressure slope (IHDVPS), equivalent to hyperemic diastolic conductance, was calculated from at least three beats as the slope of the distal pressure-flow velocity relationship during mid-to-end diastole under hyperemia. The diastolic period was identified using as reference the highest flow velocity (beginning of mid-diastole) and the sharp decrease in diastolic velocity at the end of diastole. Afterwards, the linearity of the pressure and flow velocity relationship within this fiducial part of the cardiac cycle was assessed with the coefficient of
determination ($R^2$), and a threshold of $R^2 \geq 0.90$ was set for including the beat in further analyses. Linear regression analyses were performed to the selected data, and the slope of the regression line (hyperemic diastolic coronary conductance, cm·s$^{-1}$·mmHg$^{-1}$) computed. The pressure at zero flow (PZF) is defined as the distal pressure at which the extrapolated linear distal pressure-flow velocity relationship intercepts a flow velocity of zero.

**Angiographic measurements**

TIMI flow\(^4\) was assessed by two experienced readers (PB and MH) and in case of disagreement, consensus was reached between the readers. Corrected TIMI framecount (cTFC) and myocardial blush grade (MBG) were performed offline by the same readers, blinded to CMR and PET results, according to methods described previously\(^5,6\). Automatic myocardial blush quantification was also performed offline using the ‘Quantitative Blush Evaluator’ (QuBE) software package\(^7\) (PB and MH). All angiographic metrics were obtained after maximal epicardial vasodilation induced by intracoronary nitroglycerine.

**ST-resolution**

ST-resolution analyses were performed by two experienced readers (LV and PT) and in case of disagreement, consensus was reached between the readers. The ST-segment resolution was evaluated on a 12-lead electrocardiogram acquired pre-PCI and 1 hour after PCI. The sum of ST-segment elevation was measured 60 ms after the J point in leads I, aVL, and V1 to V6 for anterior and leads II, III, aVF, V5, and V6 for non-anterior acute myocardial infarctions, respectively. The percentage resolution of ST-segment elevation from before to after PCI was calculated and categorized as complete (≥70%), partial (30% to <70%), or no (<30%) ST-segment resolution. Incomplete reperfusion was defined as <70% ST-segment resolution on electrocardiography\(^8\).
CMR acquisition

CMR was performed both between 4 and 6 days, as well as 3 months after PCI using a 1.5 Tesla MR-scanner (Magnetom Avanto, Siemens, Erlangen, Germany) and a dedicated phased array cardiac receiver coil. Functional imaging was performed using retrospectively ECG-gated steady-state free precession cine imaging with breath-holding. Standard 3 long axis orientations (4-, 3- and 2-chamber view) and short axis orientation with full LV coverage were obtained (typical parameters: voxel size ~1.6x1.9x5.0 mm, slice thickness 5.0 mm, slice gap 5.0 mm, TR/TE 3.2/1.6 ms, flip angle 75°, field of view 360x400 mm, temporal resolution <50 ms).

After administration of 0.2 mmol/kg Gd-DOTA (Dotarem, Guerbet, Villepinte, France), LGE images were acquired after 10-15 minutes, using a 2-dimensional segmented inversion-recovery gradient-echo pulse sequence, with individual correction of the inversion time to null the signal of normal myocardium (slice thickness 5.0 mm, slice gap 5.0 mm, field of view 360x400 mm, pixel size ~1.4x1.4 mm, TR 2x RR interval, typical inversion time 250-400 ms). Cine and LGE images of each patient were matched by slice position.

Analysis and definitions of CMR parameters

All analyses were performed by two experienced readers (LR and AB), blinded to the intracoronary measurements and PET results, using dedicated off-line software (QMassMR v7.5, Medis, Leiden, the Netherlands). In case of disagreement, consensus was reached between the readers. Cine images were analyzed by manually tracing the endocardial and epicardial myocardial borders in both end-diastolic and end-systolic phases, providing myocardial volumes, end-diastolic myocardial mass and ejection fraction. Segmental wall thickening was calculated by subtracting end-diastolic from end-systolic wall thickness. Quantification of infarct size and size of the area containing microvascular injury (MVI) was performed on short axis LGE images. The total infarct size was standardized by dividing the infarct mass by the total left ventricular mass. In the Gadolinium-enhanced area, a region of interest (ROI) was drawn, containing myocardium with visually the highest signal intensity, whilst avoiding any MVI. A second ROI was drawn in a distant, unenhanced area of myocardium.
without artefacts. Quantification was performed using the full-width at half-maximum (FWHM) technique \(^9,10\). Microvascular injury was identified in LGE images as hypointense recesses within the hyperenhanced myocardium. The size of the area of MVI was calculated by manual delineation of the hypointense areas on LGE images, and was expressed in square centimeter. The total volume of MVO in cubic centimeter was calculated by multiplying the area size with [slice thickness + slice gap]. Myocardial oedema and myocardial salvage were derived from the T2w-images and myocardial salvage index was then calculated as previously described \(^11\).

**\( \text{H}_2\text{^15O} \)** positron emission tomography image acquisition

A scout computed tomography (CT) scan was performed for positioning, after which a dynamic \( \text{H}_2\text{^15O} \) PET perfusion scan was performed during resting conditions. This dynamic scan sequence was followed immediately by a respiration-averaged low dose CT scan to correct for attenuation during normal breathing. After an interval of 10 min to allow for decay of radioactivity an identical \( \text{H}_2\text{^15O} \) PET sequence was performed during hyperemia induced by intravenous adenosine infusion (140 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \)).

**Measurement of Regional Myocardial Blood Flow using \( \text{H}_2\text{^15O} \)** PET

Images were reconstructed using the 3D row action maximum likelihood algorithm into 22 frames (1 \( \times \) 10, 8 \( \times \) 5, 4 \( \times \) 10, 2 \( \times \) 15, 3 \( \times \) 20, 2 \( \times \) 30, and 2 \( \times \) 60), applying all appropriate corrections. Parametric myocardial blood flow (MBF) images were generated and quantitatively analyzed using in-house developed software, Cardiac VUer \(^12\). MBF per perfusable muscle within the voxel was converted to flow per perfusable mass of myocardial tissue (ml-min-1-g-1) using a conversion factor of 1.04 and analyzed on a per-segment basis according to the 17-segment model of the American Heart Association \(^13\). Myocardial perfusion reserve (MPR) was defined as the ratio of hyperemic and baseline MBF. A MPR cut-off of 2.0 was used to differentiate between normal and abnormal
myocardial perfusion\textsuperscript{14,15}. PET-derived coronary resistance was approximated by dividing hyperemic mean arterial blood pressure during PET by absolute PET-derived hyperemic MBF.
Supplemental Figures and Figure Legends

Supplemental Figure Legends

**Supplemental Figure 1:** PET-derived coronary resistance was approximated by dividing mean arterial blood pressure during PET by absolute hyperemic PET flow. A significant association exists between HMR and PET-derived coronary resistance.
Supplemental Figure 1:
Supplemental References


