Usefulness of the index of microcirculatory resistance for invasively assessing myocardial viability immediately after primary angioplasty for anterior myocardial infarction

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Aims

The aim of this study is to evaluate the usefulness of the index of microcirculatory resistance (IMR) for predicting myocardial viability and left ventricular (LV) function recovery in acute myocardial infarction (AMI).

Methods and results

After successful primary percutaneous coronary intervention in 40 patients with anterior AMI, IMR was measured using a pressure-temperature sensor-tipped coronary guidewire. Myocardial viability was quantified by 18F-fluorodeoxyglucose (FDG) positron emission tomography in 38 patients. Echocardiographic regional wall motion was analysed to calculate the anterior wall motion score (A-WMS) and percent change in A-WMS after revascularization and at 6-month follow-up. IMR correlated significantly with regional myocardial FDG uptake ($r = -0.738$, $P < 0.001$) and it demonstrated significant correlation with percent change in A-WMS ($r = -0.464$, $P = 0.003$). The area under the receiver operating curve of IMR for predicting LV function recovery was 0.89 [95% CI 0.888–0.894].

Conclusion

Index of microcirculatory resistance, a new index representing microvascular integrity, is a reliable early on-site determinant of myocardial viability and LV recovery after primary stenting for AMI.

Keywords

Myocardial viability • Acute myocardial infarction • Microvascular integrity • Index of microcirculatory resistance • FDG PET

Introduction

To predict recovery of left ventricular (LV) function and clinical outcomes in patients with acute myocardial infarction (AMI), it is important to assess myocardial viability, the most important determinants of which are microvascular function and integrity. Despite the importance of microvascular coronary damage for prognosis, accurate evaluation of microvascular function is challenging immediately after reperfusion in AMI. Recently, a novel index of microcirculatory resistance (IMR) was proposed and validated for assessing the status of microcirculation; the technological advance of measuring pressure and estimating coronary artery flow simultaneously using a single pressure-temperature sensor-tipped coronary wire made it possible. Fearon et al. reported that IMR was an independent predictor of acute microvascular damage after AMI and of 3-month LV functional recovery. However, there has not been an IMR study in homogenously selected patients with a similar culprit vessel location, and it is important that acute microvascular damage be assessed by more accurate and quantitative parameters to compare with IMR.

The aim of this study is to examine whether IMR measured immediately after reperfusion could predict the myocardial viability...
Methods

Patient selection
Forty-nine consecutive patients who had a first anterior AMI underwent primary percutaneous coronary intervention (PCI) with stenting ≤24 h of the onset of symptoms. The diagnosis of AMI was based on continuous chest pain of ≥30 min in conjunction with persistent ST-segment elevation in the precordial leads and an increase in serum creatine kinase (CK)-MB three or more times the normal value. Nine patients were excluded according to our exclusion criteria, which consisted of cardiogenic shock, old age ≥80 years, prior MI, previous coronary bypass grafting, culprit lesion located at distal coronary artery, and significant arrhythmia rendering an invasive coronary physiological study inappropriate. The remaining 40 patients were enrolled in this study. Informed consent was obtained from each patient before the procedure and the study protocol was approved by the Ethics Committee of our institution.

Primary angioplasty and angiographic analysis
At admission, all patients were pretreated with aspirin (300 mg) and clopidogrel (300–600 mg) orally and an intravenous infusion of heparin was administered to attain a minimum 300 s of activated clotting time during the procedure. PCI was performed by inserting a 7F sheath in the femoral artery according to standard clinical practices regarding stent implantation. Patients received conventional drug therapy according to individual needs, which was determined by the attending physician. Patients who underwent stent implantation received anti-platelet treatment with a clopidogrel (75 mg/day) and aspirin (100 mg/day) regimen. All cineangiograms were reviewed and analysed with a computer-assisted, automated edge-detection algorithm (Philips Medical System, Eindhoven, The Netherlands) using standard quantitative definitions and measurements. Thrombolysis in Myocardial Infarction (TIMI) flow grade and TIMI myocardial perfusion grade (TMPG) were evaluated using a scale of 0–3 from the final coronary angiogram after PCI.9 Collateral flow was graded according to the Rentrop classification of 0–3 from the initial coronary angiogram.10

Measurement of index of microcirculatory resistance
After successful primary stenting, a coronary pressure wire (Radi Medical Systems, Uppsala, Sweden) was calibrated outside the body, equalized to the guiding catheter pressure with the sensor positioned at the ostium of the guiding catheter, and then advanced to a point distal to the culprit lesion.

The IMR is defined as simultaneously measured distal coronary pressure divided by the inverse of the thermodilution-derived hyperemic mean transit time (hTmn), or more simply, distal coronary pressure divided by the inverse of the thermodilution-derived hyperaemic states. Intra-observer and inter-observer variabilities of IMR were 3.0 ± 2.5% and 5.1 ± 4.3%, respectively.

18F-fluorodeoxyglucose positron emission tomography imaging
Because of the refusal of two patients, FDG PET was performed for 38 patients at 8 ± 1 days after primary PCI as a standard reference for detecting viable myocardium, using a whole-body PET scanner (Discovery ST Scanner; General Electric Medical Systems, Milwaukee, WI, USA). Patients had fasted for at least 6 h and were administered 50 g glucose orally and 4 IU insulin subcutaneously 90 min before FDG injection to promote FDG uptake. Plasma glucose, free fatty acid, and insulin levels were checked 30 min before FDG injection. When the plasma glucose level was not appropriate, patients were administered a rescue dose of glucose or insulin to stabilize the substrate environment. Computed tomography-based attenuation correction was performed followed by intravenous administration of ~370 MBq FDG. Emission scans were started after cardiac uptake of FDG (40–50 min later). Positron emission tomography acquisition data were reconstructed as transaxial tomograms by filtered back-projection employing a Hanning filter.

To analyse the FDG PET images, a 20-segment scoring system was used. In short, according to this system, three short-axis slices (apical, mid, and basal) are divided into six segments each, and two segments represent the apex. The average regional percentage uptake of FDG in the region of interest, which is representative of the myocardium of the left anterior descending artery (LAD) territory on the PET images, was calculated. Viable myocardial segment was defined as the segmental FDG uptake more than 50%.13,14

Echocardiographic analysis
An experienced reader blinded to the IMR results analysed echocardiographic measurements which were obtained within 24 h of presentation (baseline) and at ~6 ± 1 months after primary PCI (follow-up). According to the recommendation of the American Society of Echocardiography, the left ventricle was divided into 16 segments and each segment was scored with a semi-quantitative scoring system as follows: normal or hypokinesis = 1, hypokinesis = 2, akinesia (negligible thickening) = 3, dyskinesis (paradoxic systolic motion) = 4, and aneurysmal (diastolic deformation) = 5. Nine of 16 segments representative of the LAD were determined to assess the anterior wall motion score (A-WMS).15 The final A-WMS was derived as a sum of all scores for each segment. The percent change in A-WMS was calculated by subtracting the follow-up A-WMS from the baseline A-WMS, dividing by the baseline A-WMS and multiplying by 100%. A higher percent change implies better LV wall motion recovery. For each patient, wall motion recovery was defined as an improvement in wall thickening in two or more contiguous segments.16 Improved wall thickening was defined as a change from akinesia or severe...
hypokinesia to hypokinesia or normal wall thickening and from hypokinesia to normal wall thickening.

Statistical analyses

Data are presented as mean ± standard deviation for continuous variables and as frequency for categorical variables. Continuous variables were compared using Student’s t-test. Analyses of categorical variables were performed using the χ² test. Pearson’s correlation analysis was employed to examine the relationship of IMR to regional FDG uptake of infarct-related segments and to percent changes in A-WMS. The receiver operating characteristic curve (ROC) was employed to assess the accuracy and the optimal cut-off value of IMR for predicting LV wall motion recovery. The bootstrapping estimation was performed by R (ver. 2.7.2) for the calculation of 95% confidence interval of the area under ROC (AUROC). The optimal cut-off value was determined at the point where the sum of sensitivity and specificity was most high. All statistical analyses were performed using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA) except the bootstrapping estimation and a two-sided P-value of less than 0.05 was considered statistically significant.

Results

Baseline characteristics

The study population consisted of 36 men and 4 women with a mean age of 54 ± 12 years. Mean time from the onset of symptoms to coronary reperfusion was 346 ± 274 min. Mean peak CK value was 3504 ± 2283 U/L. Patients were classified into two groups according to wall motion recovery. The mean LV ejection fraction (EF) was 46 ± 6% at the time of the acute event. A total of 26 patients showed recovery of wall motion and 12 patients did not. Two patients who had normal LV systolic function without definite wall motion abnormalities at the time of primary PCI and 6-month follow-up were excluded in assessing LV wall motion recovery.

Table 1 Clinical characteristics of patients

<table>
<thead>
<tr>
<th></th>
<th>Entire patients (n = 40)</th>
<th>Recovery group (n = 26)*</th>
<th>Non-recovery group (n = 12)*</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD) (years)</td>
<td>54 (12)</td>
<td>53 (11)</td>
<td>56 (14)</td>
<td>0.444</td>
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<tr>
<td>Male, n (%)</td>
<td>36 (90.0)</td>
<td>24 (92.3)</td>
<td>10 (83.3)</td>
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<td>Hypertension, n (%)</td>
<td>15 (37.5)</td>
<td>10 (38.5)</td>
<td>5 (41.7)</td>
<td>0.851</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>7 (17.5)</td>
<td>5 (19.2)</td>
<td>2 (16.7)</td>
<td>0.850</td>
</tr>
<tr>
<td>Hypercholesterolaemia, n (%)</td>
<td>9 (22.5)</td>
<td>7 (26.9)</td>
<td>2 (16.7)</td>
<td>0.489</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>30 (75.0)</td>
<td>19 (73.1)</td>
<td>10 (83.3)</td>
<td>0.489</td>
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</table>

Results of reperfusion

<table>
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<th></th>
<th>Entire patients (n = 40)</th>
<th>Recovery group (n = 26)*</th>
<th>Non-recovery group (n = 12)*</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak CK, mean (SD) (IU)</td>
<td>3504 (2283)</td>
<td>2964 (2084)</td>
<td>5202 (1722)</td>
<td>0.003</td>
</tr>
<tr>
<td>Time to reperfusion, mean (SD) (min)</td>
<td>346 (274)</td>
<td>341 (249)</td>
<td>389 (335)</td>
<td>0.625</td>
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Coronary angiographic findings

<table>
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<th></th>
<th>Entire patients (n = 40)</th>
<th>Recovery group (n = 26)*</th>
<th>Non-recovery group (n = 12)*</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Location of occlusion</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Before septal, n (%)</td>
<td>33 (82.5)</td>
<td>21 (80.8)</td>
<td>11 (91.7)</td>
<td>0.330</td>
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<td>Between septal and diagonal, n (%)</td>
<td>7 (17.5)</td>
<td>5 (19.2)</td>
<td>1 (8.3)</td>
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<tr>
<td>Collateral flow before PCI</td>
<td></td>
<td></td>
<td></td>
<td>0.797</td>
</tr>
<tr>
<td>Grade 0, n (%)</td>
<td>23 (57.5)</td>
<td>15 (57.7)</td>
<td>6 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Grade 1, n (%)</td>
<td>10 (25.0)</td>
<td>5 (19.2)</td>
<td>5 (41.7)</td>
<td></td>
</tr>
<tr>
<td>Grade 2, n (%)</td>
<td>7 (17.5)</td>
<td>6 (23.1)</td>
<td>1 (8.3)</td>
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<tr>
<td>Grade 3, n (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
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<tr>
<td>TMPG after primary PCI</td>
<td></td>
<td></td>
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<td>0.039</td>
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<tr>
<td>Grade 0, n (%)</td>
<td>7 (17.5)</td>
<td>4 (15.4)</td>
<td>3 (25.0)</td>
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<tr>
<td>Grade 1, n (%)</td>
<td>9 (22.5)</td>
<td>4 (15.4)</td>
<td>5 (41.7)</td>
<td></td>
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<tr>
<td>Grade 2, n (%)</td>
<td>15 (37.5)</td>
<td>11 (42.3)</td>
<td>4 (33.3)</td>
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<tr>
<td>Grade 3, n (%)</td>
<td>9 (22.5)</td>
<td>7 (26.9)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>% DS after PCI, mean (SD) (%)</td>
<td>9 (5)</td>
<td>9 (6)</td>
<td>7 (3)</td>
<td>0.171</td>
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Medications at discharge

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<th>Entire patients (n = 40)</th>
<th>Recovery group (n = 26)*</th>
<th>Non-recovery group (n = 12)*</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blocker, n (%)</td>
<td>35 (87.5)</td>
<td>22 (84.6)</td>
<td>11 (91.7)</td>
<td>0.550</td>
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<td>ACE-inhibitor or ARB, n (%)</td>
<td>38 (95.0)</td>
<td>25 (96.2)</td>
<td>12 (100.0)</td>
<td>0.491</td>
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<tr>
<td>Statin, n (%)</td>
<td>38 (95.0)</td>
<td>25 (96.2)</td>
<td>11 (91.7)</td>
<td>0.565</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; CK, creatine kinase; DS, diameter stenosis; IMR, index of microcirculatory resistance; PCI, percutaneous coronary intervention; SD, standard deviation; TMPG, Thrombolysis in Myocardial Infarction myocardial perfusion grade.

*Among total 40 patients, two patients who had normal LV systolic function without definite wall motion abnormalities at the time of primary PCI and 6-month follow-up were excluded in assessing LV wall motion recovery.
Usefulness of IMR for predicting myocardial viability and LV recovery in AMI

Relationship between index of microcirculatory resistance and left ventricular wall motion recovery

Although IMR demonstrated a negative correlation with percent change in A-WMS (Figure 1), change in LVEF did not correlate with IMR ($r = -0.464$, $P = 0.003$; $r = -0.269$, $P = 0.094$, respectively). On the basis of the ROC analysis, an optimal cut-off value of 33 U for IMR was chosen for predicting LV wall motion recovery (sensitivity 0.73, 95% CI 0.552–0.884; specificity 1.0, 95% CI 0.734–1.000 and AUROC 0.89, 95% CI 0.888–0.894). Among the 40 included patients, 21 patients showed IMR ≤33 and 19 patients revealed IMR > 33. The mean age and reperfusion time showed no significant differences between the two groups (52 ± 10 vs. 56 ± 13 years, $P = 0.146$; 303 ± 249 vs. 394 ± 300 min, $P = 0.314$, respectively). The prevalence of hypertension, diabetes mellitus, and hypercholesterolaemia were similar between the two groups (53% vs. 47%, $P = 0.935$; 14% vs. 21%, $P = 0.574$; 14% vs. 32%, $P = 0.191$). In-hospital medications showed no significant difference between the two groups as follows: beta-adrenergic blocker (91% vs. 84%, $P = 0.550$, respectively), angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker (91% vs. 100%, $P = 0.168$, respectively), and statins (95% vs. 95%, $P = 0.942$, respectively). Culprit vessels and lesions had similar location frequencies in both groups ($P = 0.270$). Infarction locations based on the ECG were anterior (53%) and anterolateral (47%) without significant difference between the two groups ($P = 0.358$). Final TIMI grade was 2 or 3 in all patients, and TMPG 3 achievement in the final angiogram after primary PCI was more frequent in the recovery group (27% vs. 0%, $P = 0.039$).

Figure 2 Comparison of percent change in anterior wall motion score (A-WMS) in patients presenting with an index of microcirculatory resistance (IMR) less than or equal to the optimal cut-off value for left ventricular wall motion recovery (=33 U) with those presenting with an IMR > 33 U.

Relationship between index of microcirculatory resistance and myocardial viability

Mean IMR for the 40 included patients was 34 ± 24 U. IMR showed significant correlation with peak CK value, which is known as a biomarker measure of infarct size ($r = 0.49$, $P = 0.002$). Also, IMR correlated significantly with regional FDG uptake in PET imaging ($r = -0.738$, $P < 0.001$) (Figure 3). In patients in whom IMR was greater than 33 U, regional FDG uptake was significantly lower than in those patients in whom the IMR was less than or equal to 33 U (12 ± 18 vs. 32 ± 12, $P < 0.001$) (Figure 2). A significant difference was found in peak CK value between the group with IMR ≤33 and the group with IMR > 33 (2246 ± 1638 vs. 5096 ± 1778 U/L, $P < 0.001$, respectively).
Discussion

In a homogenously selected group of patients with first anterior AMI, we measured IMR immediately after primary coronary stenting using a coronary pressure wire as an on-site, quantitative measure of microvascular function to assess the usefulness of IMR for predicting myocardial viability and LV wall motion recovery. Our salient finding is that IMR was a useful on-site measure for predicting myocardial viability in earlier recovery phase and LV wall motion recovery at 6-month follow-up in patients with AMI after primary stenting.

Microvascular coronary damage is associated with poor clinical outcome even among patients achieving normal epicardial coronary artery flow after primary stenting for AMI. Furthermore, microvascular function and integrity is one of the most important determinants of myocardial viability and LV function recovery after AMI. However, accurate evaluation of microvascular function is challenging immediately after reperfusion in AMI, and current angiographic or Doppler-derived methods for evaluating microcirculatory status are limited because they are qualitative, affected by haemodynamic perturbations, might be subjective, or do not independently interrogate microcirculation.

Other invasive tools for assessing microvascular function, such as via intracoronary pressure wire, have been developed. Categoral flow index, defined as \( \frac{P_{cw} - P_v}{P_a - P_v} \), was reported to reflect a dysfunctional microcirculation in AMI, although controversies exist. Higher \( P_{cw} \) is likely to reflect simply larger infarctions associated with no-reflow, higher LV end-diastolic pressure, and poor contractile function rather than being specific for microvascular dysfunction.

New technological advances have made it feasible to measure IMR, which has made direct and independent interrogation of microvasculature possible. IMR is well correlated with true microvascular resistance and it is not significantly affected by the presence of an epicardial stenosis in an animal model. Furthermore, compared with coronary flow reserve (CFR), IMR provides a more reproducible assessment of microcirculation, independent of haemodynamic perturbations in humans.

When compared with current coronary physiological parameters, which were limited in early evaluations of microvascular integrity or myocardial viability, IMR proved to be a reliable and quantitative parameter for assessing myocardial viability in the acute stage of MI. The reliability of IMR to assess microvascular resistance in both acute and chronic states is supported by two
Usefulness of IMR for predicting myocardial viability and LV recovery in AMI

Our study included only a small number of patients with AMI who were successfully treated with primary PCI. Patients with cardiogenic shock, haemodynamic instability, or recurrent myocardial infarction were excluded from the study because physiological assessment of such patients was not feasible. Hence, our results may not be generalized to all patients receiving reperfusion therapy. In addition, the infarct-related arteries of the enrolled patients were homogenously LAD. Because physiological assessment and clinical impact may be affected by the locations of culprit arteries where measurements are performed, our results might not apply to other coronary arteries even though patients with distal culprit lesions or anatomical coronary variations were excluded. Finally, some limitations might exist in predicting functional recovery using FDG uptake during the sub-acute phase in AMI. However, several studies have reported that the method, following successful reperfusion of AMI, accurately predicted long-term LV functional recovery.27–30 Moreover, keeping the interval between invasive measurements and viability imaging short could minimize any long-term effects of different clinical factors among patients (e.g. medications, comorbidities, and restenosis) that might otherwise confound a direct comparison of the two assessments of myocardial viability.

Conclusion

Index of microcirculatory resistance, a new index for specific and quantitative assessment of coronary microcirculatory resistance, is a reliable on-site predictor of short-term myocardial viability and 6-month LV function recovery in patients undergoing primary PCI for AMI.

Conflict of interest: none declared.

References


