

Predictive Value of the Index of Microcirculatory Resistance in Patients With ST-Segment Elevation Myocardial Infarction

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| Objectives | The objective of this study is to evaluate the predictive value of the index of microcirculatory resistance (IMR) in patients undergoing primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI). |
| Background | Despite adequate epicardial artery reperfusion, a number of patients with STEMI have a poor prognosis because of microvascular damage. Assessing the status of the microvasculature in this setting remains challenging. |
| Methods | In 29 patients after primary PCI for STEMI, IMR was measured with a pressure sensor/thermistor-tipped guidewire. The Thrombolysis In Myocardial Infarction (TIMI) myocardial perfusion grade, TIMI frame count, coronary flow reserve, and ST-segment resolution were also recorded. |
| Results | The IMR correlated significantly with the peak creatinine kinase (CK) ($R = 0.61$, $p = 0.0005$) while the other measures of microvascular dysfunction did not. In patients with an IMR greater than the median value of 32 U, the peak CK was significantly higher compared with those having values ≤ 32 U ($3,128 \pm 1,634$ ng/ml vs. $1,201 \pm 911$ ng/ml, $p = 0.002$). The IMR correlated significantly with 3-month echocardiographic wall motion score (WMS) ($R = 0.59$, $p = 0.002$) while the other measures of microvascular function did not. The WMS at 3-month follow-up was significantly worse in the group with an IMR > 32 U compared with ≤ 32 U (28 ± 7 vs. 20 ± 4 , $p = 0.001$). On multivariate analysis, IMR was the strongest predictor of peak CK and 3-month WMS. The IMR was the only significant predictor of recovery of left ventricular function on the basis of the percent change in WMS ($R = 0.50$, $p < 0.01$). |
| Conclusions | Compared to standard measures, IMR appears to be a better predictor of microvascular damage after STEMI, both acutely and in short term follow-up. (J Am Coll Cardiol 2008;51:560-5) © 2008 by the American College of Cardiology Foundation |

Despite achieving normal epicardial coronary artery flow after primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI), a significant proportion of patients have a poor outcome because of microvascular coronary damage (1,2). However, a

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relatively simple quantitative method for evaluating the status of the microcirculation in individual patients with STEMI at the time of cardiac catheterization is lacking.

The index of microcirculatory resistance (IMR) is a new measure of microvasculature function using a pressure sensor/thermistor-tipped guidewire. The IMR has been validated in an animal model and tested in stable patients (3-7). The potential advantages of IMR over current methods for evaluating the microcirculation are its relative ease of performance and interpretation, its quantitative nature, its independence of the epicardial vessel, and its reproducibility. The goal of this study is to evaluate the ability of IMR measured after primary PCI for STEMI for predicting myocardial damage compared to other traditional methods for assessing the microvasculature.

Methods

Hemodynamically stable patients presenting with STEMI within 12 h of onset of symptoms or after failed fibrinolytic therapy who had persistent ST-segment elevation ≥ 1 mm

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Manuscript received June 12, 2007; revised manuscript received August 7, 2007, accepted August 27, 2007.

in contiguous leads on the electrocardiogram and who provided informed written consent were enrolled in this study. The study was approved by Stanford's Administrative Panel on Human Subjects in Medical Research.

Physiologic measurements. Primary PCI was performed in the standard fashion. Timing of and use of adjunctive pharmacology such as platelet glycoprotein IIb/IIIa receptor inhibitors was left to the discretion of the primary operator. After successful stenting of the culprit lesion, a coronary pressure wire (Radi Medical Systems, Uppsala, Sweden) was calibrated outside the body, equalized to the pressure reading from the guide catheter with the pressure sensor positioned at the ostium of the guide catheter, and then advanced to the distal two-thirds of the culprit vessel, which in the vast majority was beyond the stented region.

The IMR and thermodilution-derived coronary flow reserve (CFR) were calculated as previously described (3,8–10). In brief, 3 ml of room-temperature saline were injected down the culprit vessel 3 times at rest, and the resting transit times, which are inversely proportional to flow, were recorded and averaged. Maximal hyperemia was then induced using either a single bolus of 10 to 15 μg of intracoronary papaverine or 140 $\mu\text{g}/\text{kg}/\text{min}$ of intravenous adenosine via a central venous catheter. Three milliliters of room-temperature saline were again injected down the culprit vessel, and the hyperemic transit times were recorded and averaged. The mean aortic and distal coronary pressures were recorded during peak hyperemia.

The IMR was defined as distal coronary pressure divided by flow during peak hyperemia and calculated by dividing the mean distal coronary pressure by the inverse of the hyperemic transit time, or, more simply, multiplying the mean distal coronary pressure by the hyperemic transit time ($\text{mm Hg} \times \text{s}$, or U). Coronary flow reserve was defined as the mean resting transit time divided by the mean hyperemic transit time. Fractional flow reserve (FFR) was calculated by dividing the mean distal coronary pressure by the mean aortic pressure during maximal hyperemia.

After the procedure, the distance from the ostium of the vessel to the position of the pressure sensor was measured and recorded by fastening the torque device to the wire at the hub of the Y-connector with the wire still down the vessel and then measuring the amount of wire pulled out of the catheter to position the pressure sensor at the ostium of the vessel. Knowing the distance may be important, given that the mean transit time is affected by large differences in sensor distance.

Other measures of microvascular function. The Thrombolysis In Myocardial Infarction (TIMI) myocardial perfusion grade (TMPG) was assessed from the final recorded cine images after completion of the procedure as previously described (2). If necessary, the view was adjusted so that the culprit vessel territory was not superimposed on noninfarcted regions. The duration of cine filming was prolonged at least 3 cardiac cycles to make sure that the entire washout phase was included. The TMPG was assessed during the

same phase of the cardiac cycle. The images were analyzed offline independently by 2 interventional cardiologists blinded to the IMR result. Any discrepancies were resolved by consensus. The corrected Thrombolysis In Myocardial Infarction frame count (cTFC) was defined as the number of frames necessary for the dye to reach standardized distal landmarks, as previously described (11). The left anterior descending coronary artery frame counts were corrected by dividing by 1.7.

An electrocardiogram was obtained immediately before the procedure and within 1 h after completion of the procedure. The ST-segment elevation was summed from all of the infarct-related leads on the baseline electrocardiogram and from the same leads on the after-procedure electrocardiogram. The resolution of the sum of ST-segment elevation (ST-segment resolution) was expressed as a percentage from baseline, as previously described (12).

Total creatine kinase (CK) was measured every 8 h after presentation until the total CK began to decline. Peak CK was defined as the highest CK measured.

Echocardiographic analysis. A transthoracic echocardiogram was obtained within 24 h of presentation. Follow-up echocardiography was performed approximately 3 months after the acute event. A wall motion score (WMS) was determined by an experienced echocardiographer blinded to the IMR results using a 16-segment model as previously described (13). Each segment was visually analyzed and scored from 1 to 5 (1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic, and 5 = aneurysm). The final WMS was arrived at by adding the points for each segment. A lower score implies better left ventricular function. The percent change in WMS was calculated by subtracting the follow-up WMS from the baseline WMS, dividing by the baseline WMS, and multiplying by 100%.

Statistics. Data are presented as mean \pm SD. The Wilcoxon signed-rank test and the Mann-Whitney test were used for paired and unpaired comparisons, respectively. Measures of microvascular function and other clinical features listed in Table 1 were compared to peak CK, 3-month WMS, and the percent change in WMS using linear regression analysis. The three strongest univariate predictors were entered into a multivariate model to determine independent predictors. A p value <0.05 was considered statistically significant.

Abbreviations and Acronyms

| | |
|--------------|--|
| CFR | = coronary flow reserve |
| CK | = creatine kinase |
| cTFC | = corrected Thrombolysis In Myocardial Infarction frame count |
| FFR | = fractional flow reserve |
| IMR | = index of microcirculatory resistance |
| PCI | = percutaneous coronary intervention |
| STEMI | = ST-segment elevation myocardial infarction |
| TIMI | = Thrombolysis In Myocardial Infarction |
| TMPG | = Thrombolysis In Myocardial Infarction myocardial perfusion grade |
| WMS | = wall motion score |

| Table 1 Clinical Characteristics and Measures of Microvascular Function | |
|---|----------------|
| Variable | Total (n = 28) |
| Age (yrs) | 62.2 |
| Male gender (%) | 64 |
| Diabetes (%) | 15 |
| Hypertension (%) | 50 |
| Hypercholesterolemia (%) | 54 |
| Tobacco use (%) | 29 |
| IMR | 39 ± 26 |
| CFR | 2.0 ± 1.1 |
| FFR | 0.88 ± 0.12 |
| TIMI flow grade 3 (%) | 89 |
| cTFC | 23 ± 10 |
| TMPG (%) | |
| 0/1 | 11 |
| 2 | 46 |
| 3 | 43 |
| ST-segment resolution (%) | 66 |
| Baseline WMS | 28 ± 7 |
| Medication at discharge (%) | |
| Beta-blocker | 86 |
| ACE inhibitor | 89 |
| Statin | 93 |

ACE = angiotensin-converting enzyme; CFR = coronary flow reserve; cTFC = corrected Thrombolysis In Myocardial Infarction frame count; FFR = fractional flow reserve; IMR = index of microcirculatory refraction; TIMI = Thrombolysis In Myocardial Infarction; TMPG = Thrombolysis In Myocardial Infarction myocardial perfusion grade; WMS = wall motion score.

Results

Twenty-nine patients were enrolled in the study. In 1 patient, accurate thermodilution mean transit time measurements could not be obtained. One patient died before follow-up echocardiographic data could be obtained, and 1 patient was lost to follow-up. The clinical features and measures of microvascular function of the 28 included patients are outlined in Table 1. The culprit vessel was the left anterior descending in 12 cases, the right coronary in 12 cases, and the left circumflex in 4 cases. Neither the door-to-balloon time (136 ± 114 min) or the symptom-onset-to-balloon time (287 ± 138 min), defined as the onset of persistent symptoms until the first balloon inflation, correlated with IMR. Removing the 3 patients who received fibrinolytic therapy from the analysis did not significantly change the correlation between IMR and peak CK or WMS.

The mean IMR was 39 ± 26 U with a median value of 32 U. As a point of reference, in a study including patients with stable coronary disease and no obvious microvascular dysfunction, the mean IMR was 22 U (5). There were 3 left anterior descending infarcts, 7 right coronary artery infarcts, and 4 circumflex infarcts with an IMR below the median. The average distance of the pressure sensor down the vessel was 9.4 ± 1.7 cm. The mean peak CK was 2,164 ± 1,627 ng/ml. The mean WMS at the time of the STEMI was 28 ± 7. At approximately 3-month follow-up (85 ± 32 days), the mean WMS had improved to 24 ± 7 (p = 0.006).

The left ventricular ejection fraction at the time of the STEMI was 48 ± 11%. At approximately 3-month follow-up, the left ventricular ejection fraction had improved to 52 ± 11% (p = 0.05).

The IMR correlated significantly with peak CK (R = 0.61, p = 0.0005), whereas cTFC, TMPG, CFR, and ST-segment resolution did not (Table 2). The IMR also correlated with peak CK-MB (R = 0.67, p < 0.0001); however, in 6 patients the peak CK-MB fraction was reported as >300 ng/ml and not further quantified by our laboratory. Because of this limitation, we used peak CK as our primary biomarker measure of infarct size. In patients in whom the IMR was greater than the median value of 32 U, the average peak CK was significantly higher than in those patients in whom the IMR was less than or equal to the median value (3,128 ± 1,634 ng/ml vs. 1,201 ± 911 ng/ml, p = 0.002) (Fig. 1). A similar significant difference was found when comparing patients above and below the mean value of IMR (3,641 ± 1,332 ng/ml vs. 1,209 ± 943 ng/ml, p < 0.0001). The only other univariate predictors of peak CK were baseline WMS (R = 0.55, p = 0.002) and the absence of hyperlipidemia (R = 0.49, p = 0.009). On multivariate analysis including these 2 variables and IMR, IMR was the strongest independent predictor of peak CK (p = 0.002). The absence of hyperlipidemia was no longer a significant predictor (p = 0.33), and baseline WMS was a weak predictor (p = 0.02). The correlation between IMR and peak CK was similar if only left anterior descending infarcts (R = 0.55, p = 0.07) or only right coronary artery infarcts (R = 0.68, p = 0.01) were included.

The IMR correlated significantly with the echocardiographic WMS at 3 months (R = 0.59, p = 0.002), whereas cTFC, TMPG, CFR, and ST-segment resolution did not (Table 2). The IMR also correlated with left ventricular ejection fraction at 3 months (R = 0.55, p = 0.004). In patients in whom the IMR was greater than the median value of 32 U, the average WMS at 3 months was significantly worse than in those patients in whom the IMR was less than or equal to the median value (27.9 ± 6.8 vs. 19.5 ± 3.6, p = 0.001) (Fig. 2). A similar significant difference was found when comparing patients above and below the mean value of IMR (29 ± 7 vs. 21 ± 5, p = 0.004). The only other significant predictors of 3-month WMS were the baseline WMS (R = 0.58, p = 0.002) and

| Table 2 Correlation (R Value) Between Measures of Microvascular Function and Peak CK and 3-Month WMS | | |
|--|---------|-------------|
| Variable | Peak CK | 3-Month WMS |
| IMR | 0.61* | 0.59† |
| TMPG | 0.05 | 0.12 |
| CFR | -0.32 | -0.35 |
| ST-segment resolution | -0.35 | -0.34 |
| cTFC | -0.02 | 0.06 |

*p = 0.0005, †p = 0.002, p = NS for all others.
Abbreviations as in Table 1.

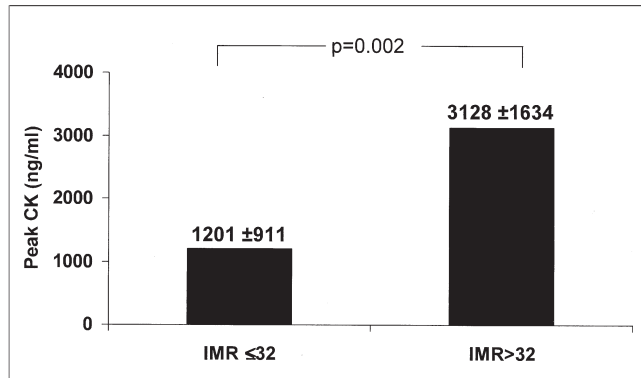


Figure 1 Peak CK With Low Versus High IMR

A comparison of the average peak creatine kinase (CK) in patients presenting with an index of microcirculatory resistance (IMR) less than or equal to the median value with those presenting with an IMR greater than the median value.

the absence of hyperlipidemia, which, curiously, predicted a worse WMS ($R = 0.69$, $p = 0.0001$). On multivariate analysis including these 2 variables and IMR, IMR was the strongest independent predictor of 3-month WMS ($p = 0.003$). Baseline WMS was no longer a significant predictor ($p = 0.11$), and the absence of hyperlipidemia was a weak predictor ($p = 0.01$).

The IMR was the only significant predictor of recovery of left ventricular function based on the percent change in WMS ($R = 0.50$, $p < 0.01$). In patients with an $IMR \leq 32$ U, the WMS improved significantly from 25.4 ± 6.6 at baseline to 19.5 ± 3.6 ($p = 0.002$) at 3 months. In patients with an $IMR > 32$ U, the WMS did not change significantly from baseline to 3 months (29.9 ± 7.0 vs. 27.9 ± 6.8 , $p = 0.44$) (Fig. 3).

The IMR correlated weakly with CFR ($R = 0.38$, $p = 0.06$) but did not correlate with TMPG ($R = 0.26$, $p = 0.18$), $cTFC$ ($R = 0.26$, $p = 0.18$), or ST-segment resolution ($R = 0.13$, $p = 0.50$).

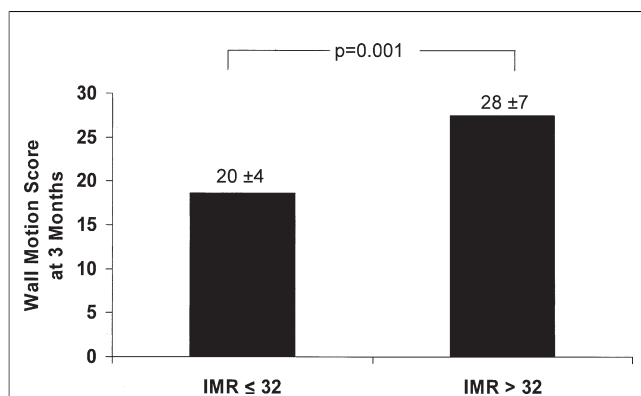


Figure 2 Three-Month Wall Motion Score With Low Versus High IMR

A comparison of the wall motion score at 3 months in patients presenting with an IMR less than or equal to the median value with those presenting with an IMR greater than the median value. Abbreviations as in Figure 1.

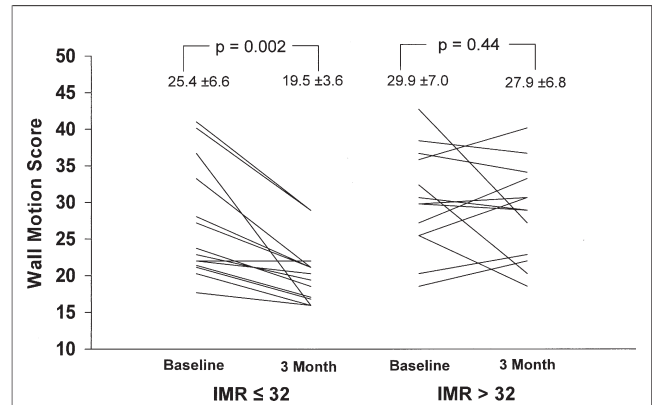


Figure 3 Relation Between Change in WMS and IMR

A comparison of recovery of left ventricular function based on the change in wall motion score (WMS) from baseline to 3 months in patients presenting with an IMR less than or equal to the median value with those presenting with an IMR greater than the median value. Abbreviations as in Figure 1.

Discussion

The main findings of this study are that IMR, an invasive wire-based, quantitative measure of microvascular function, correlates with peak CK in patients undergoing PCI for acute STEMI. The IMR, measured immediately after primary PCI, predicts left ventricular function as assessed by measuring a WMS from echocardiography at 3-month follow-up. The IMR also predicted recovery of left ventricular function at 3-month follow-up. Compared to standard techniques for assessing microvascular dysfunction, such as TMPG, CFR, and ST-segment resolution, IMR was the strongest and only significant independent predictor of peak CK and WMS at 3 months.

The importance of the coronary microvasculature has recently been highlighted (14). A number of techniques have been proposed as methods for evaluating the microcirculation in the setting of STEMI. Coronary flow reserve measured with a Doppler wire has been shown to predict left ventricular recovery after STEMI in one study, although another study found no correlation (15,16). In addition, CFR is not specific for the microcirculation but interrogates the epicardial vessel as well; CFR is affected by hemodynamic perturbations, and measuring CFR with a Doppler wire can be challenging (6,17,18). Other Doppler-derived measures of microvascular dysfunction, such as the diastolic deceleration time and systolic flow reversal, have been shown to correlate with recovery of left ventricular function after PCI for STEMI, but they may be difficult to calculate immediately and are dependent on an adequate Doppler signal (1).

The TMPG has been extensively evaluated as a determinant of microvascular function and found to be a predictor of outcomes in the setting of STEMI (2). However, the analysis is qualitative, and studies involving similar STEMI patient populations have shown wide variations in the

percentage of patients in each grade (19,20). Moreover, some investigators have questioned the usefulness of TMPG in studies with smaller sample sizes (19). Like TMPG, ST-segment resolution on the electrocardiogram is another simple and readily available method for assessing tissue-level perfusion after PCI for STEMI (21). This technique's limitations include the fact that ST-segment resolution is generally evaluated in a dichotomous fashion, which may mandate large populations to demonstrate significant differences between 2 groups.

We have recently validated IMR in an animal model and subsequently tested it in stable patients after PCI (3–5). Additionally, we have found that IMR, unlike CFR, is very reproducible and not affected by hemodynamic changes (6). We have also measured IMR in cardiac transplant recipients, where we have shown that in combination with FFR, IMR provides insight into the changes in microvascular function that occur early after transplantation and during longer term follow-up (7,22). This is the first report documenting the predictive value of measuring IMR in patients undergoing primary PCI for STEMI.

Study limitations. Although IMR is relatively easy to perform and interpret and does not add much time to the procedure, it has a number of limitations. Its invasive nature limits the ability to perform follow-up evaluations in the same patients. Moreover, it is inherently dependent upon the distance down the vessel that the sensor is positioned. In this study, we placed the sensor in the distal two-thirds of the culprit vessel. After the procedure, we measured how far down the vessel the sensor was placed. We found no correlation between sensor distance and IMR, suggesting that small differences in position likely do not have a major impact on IMR.

Another inherent limitation of IMR is that its simplified form (distal pressure multiplied by hyperemic mean transit time), which was used in this study, may overestimate true microvascular resistance if significant collaterals are present. This occurs because the hyperemic mean transit time, the method used to estimate flow, is a reflection of coronary flow and not myocardial flow (23). In the presence of significant collaterals, coronary flow underestimates myocardial flow, and resistance is overestimated. A more complex form of IMR that accounts for collateral flow can be calculated by measuring the coronary wedge pressure as outlined previously (4,5). Because IMR was measured at the end of the procedure, after removal of the epicardial obstruction, it is unlikely that significant collateral flow was present in this study. In addition, in calculating IMR, only distal coronary pressure was measured instead of calculating the pressure gradient across the microvasculature by subtracting venous pressure from distal coronary pressure. In patients with large myocardial infarctions in whom the venous pressure might be elevated, the IMR measured may have been falsely higher than it would have been if venous pressure had been taken into account.

A final inherent limitation of IMR is the fact that myocardial resistance varies depending on the amount of myocardium interrogated. Theoretically the IMR in the left anterior descending of a larger heart may be quite different from the IMR in the right coronary artery of a smaller heart. The fact that IMR remained an important predictor of acute and short-term myocardial damage suggests that this feature does not have a major impact when assessing IMR in the setting of STEMI.

This study is limited by its small numbers. However, IMR remained predictive of myocardial damage despite the size of the study. The small sample size may explain why the other measures of microvascular function did not correlate with myocardial damage in this study. Larger studies will be necessary to determine whether IMR can predict clinical outcomes. Ideally, Doppler-derived parameters of microvascular injury also would have been assessed and compared to IMR. **Clinical implications.** The ability to risk-stratify patients with STEMI at the time of primary PCI by measuring IMR may allow earlier application of pharmacologic intervention or stem-cell therapy to improve myocardial cell salvage in high-risk patients. By demonstrating the correlation between IMR and myocardial damage, this study helps to validate the use of IMR in assessing novel therapies, as was recently done (24) to evaluate adjunctive intracoronary fibrinolytic administration after primary PCI in patients with STEMI.

Conclusions

The IMR is an independent predictor of acute and short-term myocardial damage in patients undergoing primary PCI for STEMI.

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