Characterization of Microvascular Dysfunction After Acute Myocardial Infarction by Cardiovascular Magnetic Resonance First-Pass Perfusion and Late Gadolinium Enhancement Imaging

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ABSTRACT

Purpose: While both first-pass perfusion and late gadolinium enhancement by cardiovascular magnetic resonance (CMR) can assess coronary microvascular status in acute myocardial infarction (AMI), there are only limited data on their respective diagnostic utility. We aim to evaluate: the utility of first-pass perfusion and late gadolinium enhancement imaging in the detection and quantification of microvascular dysfunction after reperfused acute myocardial infarction, using TIMI frame count (TIMI FC) as the reference standard of microvascular assessment; and their relationship with infarct size and ventricular function. Methods: First-pass perfusion and late gadolinium enhancement imaging were performed in 25 consecutive AMI patients (84% men, age 58 ± 10) within 72 h of successful reperfusion. We assessed the myocardial extent of microvascular dysfunction using the size of the perfusion defect on first-pass perfusion (PD%) and the hypoenhanced core region within late gadolinium enhancement (MDEcore%). PD%, MDEcore%, and TIMI FC were analyzed independently of each other and with blinding to clinical data. We adjusted PD% and MDEcore% to the myocardial mass subtended by the infarct-related artery according to the 16-segment model. Results: Median infarct size involved 13.9% (interquartile range: 8.5 to 22.2%) of the left ventricle and median left ventricular ejection fraction was 52% (interquartile range: 43 to 61%). PD% demonstrated evidence of microvascular dysfunction more frequently (84% vs. 36% of patients, p < 0.002) and involved a larger myocardial extent (23.5 ± 17.5% vs. 3.5 ± 7.7%, p < 0.001) compared to MDEcore%. PD% had strong correlations with TIMI FC (Spearman ρ = 0.62, p < 0.001) and infarct size (ρ = 0.64, p < 0.001), and a moderate correlation with LVEF (ρ = −0.39, p = 0.055). MDEcore% also correlated with TIMI FC (ρ = 0.54, p = 0.005) and infarct size (ρ = 0.52, p < 0.01) but not with LVEF (ρ = NS). Conclusions: PD% appeared to provide a stronger noninvasive assessment of the microvascular function than MDEcore% and correlated well with prognostic markers such as left ventricular ejection fraction and infarct size. Future studies should consider quantitative analyses of both first-pass perfusion and late gadolinium enhancement imaging in the evaluation of novel therapies targeted to the microvasculature of the infarct-related artery.

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INTRODUCTION

The primary goal of treatment for acute myocardial infarction (AMI) is the prompt and sustained restoration of myocardial tissue perfusion. Although current reperfusion strategies focus on re-establishing patency of the epicardial infarct-related artery, the importance of the coronary microvasculature has been increasingly recognized (1, 2). The no-reflow phenomenon, which refers to sluggish and abnormal blood flow after relief of coronary occlusion, is at least in part related to microvascular damage (1, 2). Several validated angiographic methods have been used to evaluate this important pathophysiologic process. The Thrombolysis in Myocardial Infarction Frame Count (TIMI FC), for example, is an objective and precise index of coronary blood flow that also predicts adverse clinical outcome after reperfused AMI (3-5).

Cardiovascular magnetic resonance (CMR) is a promising technique to assess the myocardial microvasculature in AMI (6). In animal models of AMI, CMR can reliably detect the altered wash-in and wash-out kinetics of gadolinium in microvascular dysfunction (7–10). Despite successful reperfusion therapy, patients with microvascular dysfunction detected by CMR have larger infarcts (11–13), more adverse ventricular remodeling (12–14), less myocardial functional recovery (12–17), and worse clinical outcomes (12, 13). Although both first-pass perfusion and late gadolinium myocardial enhancement imaging have been used to evaluate microvascular dysfunction (11–17), there are only limited data on their comparative diagnostic utility in relation to angiographic measures of coronary microvascular flow. Furthermore, it is uncertain whether the quantitative assessments of the extent of first-pass perfusion defects (PD) and the hypoenhanced core within myocardial late gadolinium enhancement (MDEcore) reflect the degree of microvascular dysfunction. Accordingly, we sought to determine the utility of first-pass perfusion and late gadolinium enhancement imaging in the detection and quantification of microvascular dysfunction, using TIMI FC as the angiographic reference standard, and their relationship with infarct size and ventricular function in patients with reperfused AMI.

METHODS

Study design and patient population

We prospectively recruited 25 consecutive patients hospitalized for a first AMI. We diagnosed AMI based on elevated serum creatine kinase-MB or troponin levels with typical ischemic symptoms and electrocardiographic changes. All patients had restored coronary flow of the epicardial infarct-related artery (fibrinolysis n = 1; primary percutaneous coronary intervention n = 23; spontaneous restoration of epicardial coronary flow n = 1) as evidenced by angiographic patency with < 50% residual stenosis. Patients with a history of coronary artery bypass surgery, hemodynamic instability, or contraindications to CMR examination (such as pacemaker and metallic devices) were excluded. The institutional review board approved the study protocol, and all patients provided written informed consent.

CMR acquisition

CMR examination was performed within 72 hours of reperfusion therapy, using a 1.5 T scanner (Signa CV/i, General Electric, Milwaukkee, WI, USA) and a 4-channel cardiac phased-array coil. Images were acquired during repeated breath-holds with the patient in supine position. Cine images covering the entire left ventricle were obtained using a ECG-gated steady state free precession pulse sequence, with the following imaging parameters: TR 3.8 ms, TE 1.5 ms, flip angle 45°, matrix size 192 × 160, field of view 28–34 cm, slice thickness 8 mm with no gap, views per segment 16, number of excitation 1.

After cine imaging was completed, an intravenous bolus dose of 0.1 mmol/kg gadolinium-DTPA (Magnevist, Berlex, Montville, NJ, USA) was administered at a rate of 5 mL/s by a power injector. First-pass perfusion imaging was performed simultaneously with contrast injection for the first 50 heart beats, using a saturation recovery interleaved fast gradient echo-echo planar pulse sequence at a temporal resolution equal to one or two cardiac cycles depending on heart rate, in order to acquire at least 3 short-axis slices. The imaging parameters were as follows: TR 6.6 ms, TE 1.3 ms, flip angle 20°, echo train length 4, matrix size 128 × 96, field of view 28–34 cm, phase field of view 0.75, slice thickness 10 mm, notched saturation pulse 90°, and an inversion time of 142 ms.

Following first-pass perfusion imaging, the patients received a second dose (0.10 mmol/kg) of gadolinium-DTPA (cumulative dose of 0.20 mmol/kg). Delayed images were acquired 10 minutes later with an inversion-recovery prepared segmented fast gradient echo pulse sequence. The following imaging parameters were used: TR 7.2 ms, TE 3.2 ms, flip angle 20°, matrix size 256 × 128, field of view 28–34 cm, slice thickness 8 mm with no spacing, inversion time 250–350 ms (adjusted to null normal myocardium), and a views per segment of 16–24.

CMR analysis

We analyzed the CMR images off-line using a commercially available software package (CineTool 2.9.4, General Electric). For each slice location, the end-diastolic and end-systolic cine frames were defined as the ones showing the largest and smallest left ventricular cavity, respectively. The endocardial border was manually traced, and the end-diastolic and end-systolic volumes were the sums of left ventricular cavity sizes across all continuous slices in the corresponding phase of the cardiac cycle. Stroke volume was calculated as the difference between end-diastolic and end-systolic volumes, and ejection fraction as stroke volume divided by end-diastolic volume and multiplied by 100%.

We analyzed all first-pass perfusion and late gadolinium enhancement images in short-axis planes (16 segments) according to the standard American Heart Association/American College of Cardiology model, with each segment assigned to a coronary artery territory (18). For first-pass perfusion, three slices (basal, mid, and apical) were assessed, and the frame demonstrating peak signal enhancement in the remote normal myocardium.
was chosen for quantification of the myocardial extent of the PD. Surface-coil intensity correction was applied to adjust for signal dropout relative to the distance from the surface coil. PD was assessed visually and defined as a hypoenhanced region compared to the normal adjacent myocardium. The PD was planimetered, and the size was normalized as a percentage (PD%) of the total left ventricular mass (area of the segments) subtended by the infarct-related artery.

In order to quantify the infarct size, we first manually traced the endocardial and epicardial borders of the left ventricle during end-diastole. Late gadolinium enhancement was detected and quantified by a semi-automated algorithm using a signal intensity threshold criteria of >2 SD above the mean signal intensity of the remote normal myocardium (19). On delayed imaging, microvascular dysfunction was considered to be present if there was subendocardial hypo-enhancement surrounded by hyper-enhanced regions (MDEcore). MDEcore was included in the measurement of the infarct size, which was expressed as a percentage of total left ventricular mass. The size of the hypoenhanced core (MDEcore%) was adjusted to the sum areas of the myocardial segments assigned to infarct-related artery.

First-pass perfusion and late gadolinium enhancement images were analyzed blinded to each other and to all clinical and angiographic data.

**Angiographic technique and analysis**

Coronary angiography was performed with a standard biplane system at a cine rate of 30 frames per second. TIMI FC is the number of cine-frames required for the contrast dye to reach standardized distal anatomic landmarks of the coronary artery (3). In the absence of dissection or residual stenosis in the open infarct-related artery, a higher TIMI FC indicates slower epicardial coronary blood flow due to more severe microvascular dysfunction (1–3). The decision to proceed with percutaneous coronary intervention, the use of stents and pharmacologic therapies, was at the discretion of the interventional cardiologist. TIMI FC was determined on coronary angiograms immediately after percutaneous coronary angioplasty or stenting; if intervention was not performed, TIMI FC was graded on the diagnostic angiogram. All angiographic data were analyzed by a blinded core laboratory.

**Statistical analysis**

Continuous data are summarized as median and interquartile range (IQR), and paired comparisons were made by Wilcoxon signed-rank test. Categorical variables are presented as percentage and compared by McNemar test for paired data. Correlations were evaluated by Spearman’s rank correlation coefficients ($\rho$). In addition, we calculated the areas under receiver-operating characteristics (ROC) curves for PD% and MDEcore% in the detection of microvascular dysfunction, defined as TIMI FC >40 (4, 5). We conducted statistical analysis using SPSS 12.0 (SPSS Inc, Chicago, Illinois, USA), and considered two-sided p values $\leq0.05$ to be statistically significant.

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**RESULTS**

Table 1 summarizes the baseline demographic and clinical characteristics of the study patients. All patients underwent successful percutaneous coronary intervention with stenting, except for one who was found to have a patent infarct-related artery involving small septal branch of the left anterior descending artery. After successful mechanical revascularization of the epicardial infarct-related artery, TIMI flow grade 3 was achieved in 21 patients (84%), and the remaining 4 patients had TIMI flow grade 2; the median TIMI FC was 32 (IQR: 20 to 46).

All patients demonstrated myocardial late gadolinium enhancement representing infarction in the territory of corresponding culprit artery. The median infarct size involved 13.9% (IQR: 8.5 to 22.2%) of the left ventricle, and the median left ventricular ejection fraction was 52% (IQR: 43 to 61%). Infarct size correlated with peak serum creatine kinase level (Spearman $\rho = 0.77$, p < 0.001).

Overall, PD on first-pass imaging was more prevalent than MDEcore on delayed imaging (84% vs. 36% of patients, respectively; p < 0.002). Table 2 shows the relationship between the

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<table>
<thead>
<tr>
<th>Table 1. Baseline demographic and clinical characteristics</th>
<th>N = 25</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong>$^*$</td>
<td>59 (52, 65)</td>
</tr>
<tr>
<td><strong>Male, %</strong></td>
<td>84</td>
</tr>
<tr>
<td><strong>Current smoker, %</strong></td>
<td>60</td>
</tr>
<tr>
<td><strong>Family history of premature coronary disease, %</strong></td>
<td>36</td>
</tr>
<tr>
<td><strong>Hypertension, %</strong></td>
<td>64</td>
</tr>
<tr>
<td><strong>Dyslipidemia, %</strong></td>
<td>68</td>
</tr>
<tr>
<td><strong>Diabetes, %</strong></td>
<td>12</td>
</tr>
<tr>
<td><strong>Previous angina, %</strong></td>
<td>8</td>
</tr>
<tr>
<td><strong>Peak serum creatine kinase, U/mL</strong></td>
<td>1048 (600, 1860)</td>
</tr>
<tr>
<td><strong>Infarct-related artery, %</strong></td>
<td></td>
</tr>
<tr>
<td>- Left anterior descending artery</td>
<td>32</td>
</tr>
<tr>
<td>- Left circumflex artery</td>
<td>24</td>
</tr>
<tr>
<td>- Right coronary artery</td>
<td>44</td>
</tr>
<tr>
<td><strong>Primary or rescue percutaneous coronary intervention, %</strong></td>
<td>96</td>
</tr>
<tr>
<td><strong>Time from symptom onset to percutaneous coronary intervention, h</strong></td>
<td>10 (3, 12)</td>
</tr>
</tbody>
</table>

$^*$median (interquartile range).

| Table 2. Presence or absence of perfusion defect (PD) on first-pass imaging versus hypoenhanced core with hyperenhancement (MDEcore) on delayed imaging |
|-----------------|-----------------|-----------------|
| **Microvascular dysfunction** | **PD** | **Total** |
| | Absent | Present | **Total** |
| MDEcore Absent | 3 | 13 | 16 |
| MDEcore Present | 1 | 8 | 9 |
| Total | 4 | 21 | 25 |

All data represent number of patients. McNemar test p < 0.002.
presence of PD versus MDE\textsubscript{core}. The size of PD (median PD\% = 23\%; IQR: 9.6 to 35.9\%) was also greater than that of MDE\textsubscript{core} (median MDE\textsubscript{core} \% = 0\%; IQR: 0 to 4.1\%) (p < 0.001). There was a significant positive correlation between MDE\textsubscript{core} \% and PD\% (Spearman \( \rho = 0.55, p = 0.005 \)). The scatter plot is depicted in Fig. 1.

Both PD\% (Spearman \( \rho = 0.62, p < 0.001 \)) and MDE\textsubscript{core} \% (Spearman \( \rho = 0.54, p = 0.005 \)) demonstrated positive correlations with TIMI FC. However, as illustrated in the scatter plot (Fig. 2), there was a relatively wide range of TIMI FC (8 to 72) among patients without any evidence of MDE\textsubscript{core} (MDE\textsubscript{core} \% = 0\%). In contrast, there was a more graded relationship between higher TIMI FC and increasing PD\%. The areas under the ROC curves to predict microvascular dysfunction (TIMI FC > 40) were 0.88 for PD\% and 0.75 for MDE\textsubscript{core} \%. When PD and MDE\textsubscript{core} were adjusted to the total left ventricular mass (the total area of all myocardial segments, instead of the area subtended by the infarct-related artery only), their positive correlations with TIMI FC remained unchanged (Spearman \( \rho = 0.56, p = 0.003 \) and Spearman \( \rho = 0.55, p = 0.004 \), respectively).

As shown in Fig. 3, infarct size was also positively correlated with PD\% (Spearman \( \rho = 0.64, p < 0.001 \)) and with MDE\textsubscript{core} \% (Spearman \( \rho = 0.52, p < 0.01 \)). There was a trend toward an inverse correlation between left ventricular ejection fraction and PD\% (Spearman \( \rho = -0.39, p = 0.055 \)) (Fig. 4). A similar relationship was not observed between left ventricular ejection fraction and MDE\textsubscript{core} \% (p = NS).

**DISCUSSION**

In this prospective pilot study of 25 consecutive AMI patients, we found that both PD\% and MDE\textsubscript{core} \% correlated with angiographic measures of microvascular dysfunction in the reperfused infarct-related artery. PD\% also demonstrated correlations with other post-MI prognostic markers such as left ventricular ejection fraction and infarct size.

The pathogenesis of microvascular dysfunction is complex and multifactorial. Platelet microembolization, neutrophil plugging, thrombosis can lead to microvascular obstruction, while free radicals, neutrophil and complement activation cause reperfusion injury to endothelial cells (1, 2). Despite successful reperfusion therapy, microvascular dysfunction remains common and portends a worse clinical outcome. The “time dependent...
open artery and open microvascular hypothesis” represents a paradigm shift in the treatment of AMI, which is now targeted to restoring and maintaining myocardial tissue perfusion (1–3). Currently, therapeutic options may improve microvascular flow beyond maintenance of epicardial coronary patency are under active investigation (1, 2, 20–22). Although the TIMI FC has been widely used to assess the integrity of microvasculature and is a validated prognosticator (3), the risk of procedural complications, the exposure to radiation and the requirement for potentially nephrotoxic contrast agents pose serious problems in the serial monitoring of AMI patients and the evaluation of novel therapies. Therefore, the need for an accurate, safe and non-invasive imaging modality that can detect and quantify microvascular dysfunction is apparent. Because CMR provides excellent spatial resolution and is non-invasive, it holds great promise as such an ideal technique.

Over the past decade, the physiological basis of myocardial contrast enhancement has been elucidated (7–10), and both first-pass perfusion and late gadolinium enhancement imaging by CMR have been used to assess the microvascular status (11–17). In a seminal study of 44 AMI patients by Wu et al. (11), microvascular obstruction, defined as the presence of MDEcore, predicted more extensive scar formation, ventricular remodeling, and adverse cardiovascular events in follow-up, even after

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**Figure 3.** Relationship between infarct size, PD% and MDEcore%.

**Figure 4.** Relationship between left ventricular ejection fraction, PD% and MDEcore%.
adjusting for infarct size. More recent reports have also confirmed the prognostic significance of MDEcore and its association with persistent functional impairment in the long term (13, 14). Other investigators have utilized first-pass perfusion imaging to study the microvascular status. Rogers et al. studied 17 AMI patients and found that the myocardium with PD on first-pass imaging had limited recovery of mechanical function at 7 weeks, regardless of the pattern of delayed enhancement (15). Taylor and colleagues performed first-pass perfusion imaging to assess microvascular function in 20 AMI patients who had successful angioplasty (16). Severe delay of contrast wash-in (≥2 seconds compared to remote segments) and transmurality of infarct were both independent predictors of reduced regional systolic thickening at 3 months. In a study of 60 AMI patients, MDEcore was shown to have a sensitivity of 74% and a specificity of 95% in detecting microvascular obstruction when first-pass perfusion imaging was considered as the reference standard, but neither was validated against an independent technique (12). Finally, Gerber and others demonstrated that compared to normal first-pass perfusion, lack of late gadolinium enhancement had superior diagnostic accuracy for functional improvement after AMI (74% vs 49%, p < 0.001) (17). It should be noted that this conclusion was primarily based on the poorer sensitivity (19% vs 82%) of first-pass perfusion in predicting persistent systolic dysfunction, although its specificity was higher (89% vs. 64%). These results are in keeping with the notion that most infarcts demonstrated by late gadolinium enhancement are unlikely to recover mechanical function, but the presence of microvascular dysfunction, as evidenced by PD on first-pass imaging, further decreases the likelihood of any functional improvement. Moreover, there was no direct comparison between the predictive values of MDEcore and PD. Therefore, despite these important studies, the relationships between MDEcore and PD with angiographic and other post-infarction prognostic markers have not been well defined.

In the present study, evidence of microvascular dysfunction was demonstrated more frequently by PD on first-pass imaging and involved a larger myocardial extent compared to MDEcore on delayed imaging. Using a canine model of AMI, Wu et al. had previously validated contrast-enhanced echocardiography against CMR delayed imaging and S-thioflavin staining in the quantification of microvascular obstruction (9). While both techniques correlated well with blood flow measurement by radioactive microspheres, MDEcore was significantly smaller and corresponded to regions with lower blood flow (<40% of remote myocardium) compared to PD demonstrated on echocardiography (blood flow <60% of remote myocardium). Although gadolinium is an extra-cellular contrast agent, first-pass perfusion imaging primarily reflects coronary flow rather than contrast diffusion into the interstitial space. Our observations are therefore consistent with the experimental findings by Wu et al. (9). We postulate that first-pass perfusion imaging by CMR may also be more sensitive in detecting lesser degrees of microvascular dysfunction, which may compromise but not completely abolish blood flow in the microvessels. In comparison, the presence of MDEcore on delayed imaging may be more specific for profound microvascular damage or obstruction—gadolinium fails to diffuse into the interstitium of the necrotic core even after a prolonged period of time. In other words, MDEcore may have a higher detection threshold than PD (Figs. 1 and 2). Nevertheless, their strong positive correlations with TIMI FC indicate that both first-pass perfusion and delayed imaging by CMR can effectively measure microvascular dysfunction and may provide complementary information. In addition to TIMI FC, the correlations with other established prognostic markers such as infarct size and left ventricular function after AMI imply that PD and MDEcore may be useful surrogate markers of adverse outcome. Finally, our study suggests that CMR may represent a valuable non-invasive alternative to serial coronary angiography in the clinical evaluation of new therapies targeted to the microvasculature in AMI.

**LIMITATIONS**

The present study has several limitations. The significant correlations demonstrated in this pilot study should be confirmed in larger patient populations. Due to the small sample size, we did not have adequate power to examine clinical endpoints and to directly compare the prognostic value of PD and MDEcore. However, the prognostic importance of TIMI FC has been well established (3–5). The size of PD was assessed qualitatively, although analysis of first-pass perfusion images was blinded to MDE and angiographic data. The temporal course of microvascular dysfunction in patients with AMI will need to be assessed by serial CMR examinations and cannot be adequately addressed in the present study. Follow-up CMR examinations were not routinely performed as part of the study for evaluation of functional recovery in segments showing PD and MDEcore, although this has been the subject of prior investigations (15–17). Finally, it is noteworthy that in contrast to late gadolinium enhancement imaging, first-pass perfusion images cannot be acquired throughout the entire left ventricle even with current parallel imaging techniques. In other words, localized microvascular dysfunction is more likely to be missed on first-pass perfusion imaging. This bias likely accounted for the small number of patients with evidence of MDEcore, but no apparent PD in the present study. Notwithstanding this inherent limitation, PD demonstrated equally good correlation overall with TIMI FC.

**CONCLUSION**

In conclusion, both PD on first-pass perfusion and MDEcore on delayed imaging correlate with angiographic measures of microvascular dysfunction after AMI. These techniques may reflect different aspects or severities of this critical pathophysiologic process, and together they provide complementary and useful information about the microvascular status. Furthermore, PD and MDEcore correlate with established prognostic markers after AMI. Therefore, CMR appears to be a promising non-invasive tool to characterize microvascular dysfunction and to evaluate novel therapies targeting the coronary microvasculature.
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