Acute Microvascular Impairment Post-Reperfused STEMI Is Reversible and Has Additional Clinical Predictive Value

A CMR OxAMI Study

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ABSTRACT

OBJECTIVES This study sought to investigate the clinical utility and the predictive relevance of absolute rest myocardial blood flow (MBF) by cardiac magnetic resonance (CMR) in acute myocardial infarction.

BACKGROUND Microvascular obstruction (MVO) remains one of the worst prognostic factors in patients with reperfused ST-segment elevation myocardial infarction (STEMI). Clinical trials have focused on cardioprotective strategies to maintain microvascular functionality, but there is a need for a noninvasive test to determine their efficacy.

METHODS A total of 64 STEMI patients post–primary percutaneous coronary intervention underwent 3-T CMR scans acutely and at 6 months (6M). The protocol included cine function, T2-weighted edema imaging, pre-contrast T1 mapping, rest first-pass perfusion, and late gadolinium enhancement imaging. Segmental MBF, corrected for rate pressure product (MBFcor), was quantified in remote, edematous, and infarcted myocardium.

RESULTS Acute MBFcor was significantly reduced in infarcted myocardium compared with remote MBF (MBFinfarct 0.76 ± 0.20 ml/min/g vs. MBFremote 1.02 ± 0.21 ml/min/g, \( p < 0.001 \)), but it significantly increased at 6M (MBFinfarct 0.76 ± 0.20 ml/min/g acute vs. 0.85 ± 0.22 ml/min/g at 6M, \( p < 0.001 \)). On a segmental basis, acute MBFcor had incremental prognostic value for infarct size at 6M (odds of no LGE at 6M increased by 1.4:1 \( [p < 0.001] \) for each 0.1 ml/min/g increase of acute MBFcor) and functional recovery (odds of wall thickening >45% at 6M increased by 1.38:1 \( [p < 0.001] \) for each 0.1 ml/min/g increase of acute MBFcor). In subjects with coronary flow reserve >2 or index of myocardial resistance <40, acute MBF was associated with long-term functional recovery and was an independent predictor of infarct size reduction.

CONCLUSIONS Acute MBF by CMR could represent a novel quantitative imaging biomarker of microvascular reversibility, and it could be used to identify patients who may benefit from more intensive or novel therapies. (J Am Coll Cardiol Img 2019;12:1783–93) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
Despite the improvement in mortality rates following the introduction of primary percutaneous coronary intervention (PPCI), the incidence of heart failure post-myocardial infarction (MI) remains persistently high. Microvascular impairment despite successful restoration of epicardial coronary artery patency is associated with poor long-term recovery and outcome (1, 2). There is a recognized lack of innovative medical therapy targeting the microcirculatory function, partly because of an insufficient understanding of the underpinning pathophysiological mechanisms (3). Invasive coronary measurements such as the index of microvascular resistance (IMR) have emerging clinical utility for patients’ stratification at the time of PPCI, with abnormal values being more likely associated with microvascular obstruction (MVO) (4).

Although standard cardiac magnetic resonance (CMR) techniques such as late gadolinium enhancement (LGE) allow anatomic volumetric quantification of MVO and intramyocardial hemorrhage (IMH) as biomarkers of severe microvascular disease (5), they do not provide any insight into microvascular function. Currently there is no noninvasive imaging method to stratify patients at risk of developing MVO or to determine the dynamic changes in microvascular impairment at the time of PPCI.

First-pass perfusion (FPP) by CMR for assessment of myocardial blood flow (MBF) (6) has been extensively used to estimate abnormal perfusion in patients with chronic artery disease (7), but a systematic investigation of MBF in acute STEMI is lacking.

By using MBF CMR, we sought to investigate: 1) the degree of microvascular impairment and its longitudinal changes in relation to the severity of ischemic injury; and 2) the extent to which the acute microvascular dysfunction predicts 6-month (6M) infarct size (IS) and myocardial functional recovery. This may help establish CMR as a clinically useful tool to determine the crucial role played by the microvascular function in the MI healing process and potentially provide novel and specific imaging biomarkers to assess the clinical efficacy of cardioprotective strategies.

METHODS

PATIENT STUDY GROUP. Survivors of acutely reperfused STEMI post-PPCI were prospectively recruited between October 2010 and March 2015. The study protocol was approved by the local ethics committee, and all patients gave written informed consent. Acute clinical management reflected contemporary practice and guidelines (Supplemental Appendix).

CORONARY PHYSIOLOGY. Transit time at rest (Tmn) and after hyperemia, coronary flow reserve (CFR), and IMR measurements were performed at the time of primary percutaneous coronary intervention (PPCI) in the infarct-related artery, as previously described (8) (Supplemental Appendix).

CMR PROTOCOL. CMR was performed on a 3-T magnetic resonance scanner (either MAGNETOM TIMTrio or MAGNETOM Verio, Siemens Healthcare, Erlangen, Germany), acutely (1 to 3 days post-PPCI) and at 6M. The CMR protocol (details of the sequences can be found in the Supplemental Appendix) included functional cine imaging, tissue characterization techniques such edema T2-prepared steady-state free precession (SSFP) imaging (T2-weighted [T2W]), native shortened modified Look-Locker inversion recovery (ShMOLLI) TI mapping, FPP at rest, and LGE. To track the first pass of a gadolinium-based contrast agent, 0.03 mmol/kg gadoterate meglumine (Dotarem, Guerbet, Villepinte, France) was injected at rest. LGE images were collected 10 to 15 min after the administration of an additional 0.1 mmol/kg of contrast agent. The inversion time was adjusted for nulling of remote normal myocardium. Matching short-axis images covering the entire left ventricle were acquired using all techniques except for FPP, which was limited to 3 to 5 matching short-axis slices.

CMR IMAGING ANALYSIS. CMR analysis is described in detail in the Supplemental Appendix.

Both global and segmental analyses were performed on anonymized images using cvi42 software (Circle Cardiovascular Imaging Inc., Calgary, Canada) by 3 experienced operators (A.B., D.V., A.B.); all of the images were reviewed by an experienced CMR cardiologist (E.D.A). Apical slices affected by partial volume effects and slices where the outflow tract was visible were excluded from the study in all sequences. For segmental analyses, short-axis images were divided into 6 equiangular segments with the right ventricle–left ventricle junction as the reference point. The wall thickening (WT) analyses at follow-up were performed by an operator (A.B.) without knowledge of the baseline analyses. Functional
Quantification of T2W edema and IS, both acutely and at 6M, was performed using a signal intensity threshold of 2 SD and 5 SD above the mean intensity of the remote reference region of interest (ROI), respectively, as previously described (10). When present, MVO and/or IHM were included in the measurements of left ventricular (LV) infarct or edema volume. Segmental tissue state was defined as remote if negative to LGE and on T2W, edematous if positive on T2W and negative to LGE, infarcted if positive to both (with a distinction between LGE 1% to 50% and LGE 51% to 100%), MVO (including segments with LGE >75% and MVO), and MVO in combination with IMH (including segments with LGE >75% with MVO and IMH) on the basis of acute LGE images. IS reduction was calculated as follows: 

\[
\text{IS reduction} = \left( \frac{\text{acute IS} - \text{6M IS}}{\text{acute IS}} \right) \times 100\%.
\]

MC-ROI (Interactive Data Language, version 6.1, Exelis Visual Information Solutions, Boulder, Colorado). Quantitative perfusion analysis to derive absolute MBF (ml/min/g) was performed using an in-house MatLab software, as previously described (6,7) (Figures 1A to 1L). MBF values were corrected for the heart rate–blood pressure product by dividing resting MBF by heart rate (in beats/min) × systolic blood pressure (mm Hg) / 10,000 (MBF corrected [MBF$_{\text{corr}}$]). A per subject index of MBF (average MBF in the culprit territory [MBF$_{\text{culprit}}$]) was calculated averaging segmental MBF$_{\text{corr}}$ of the culprit coronary artery territory.

**Statistical Analysis.** Statistical analyses were performed using IBM SPSS Statistics software (version 22.0, IBM Corporation, Armonk, New York) and the R statistical environment (version 3.4.1, R Project, Vienna, Austria). Normally distributed continuous variables are expressed as mean ± SD, and not
TABLE 1 Baseline Patient Characteristics (N = 64)

| Age, yrs | 60 ± 9 |
|----------|--------|
| Sex, male:female | 50:14 |

Risk factors
- Current smoker: 18 (30)
- Diabetes: 4 (7)
- Dyslipidemia: 17 (28)
- Hypertension: 22 (36)
- Family history of CHD: 25 (41)
- Peak troponin I (mg/ml): 65 (41-158)
- Pain to balloon time (min): 119 (137-239)
- Time from PPCI to CMR (days): 2 (1-3)

Culprit coronary artery
- LAD: 29 (45)
- RCA: 29 (45)
- LCx: 6 (10)

No. of vessels diseased
- 1: 41 (67)
- 2: 15 (25)
- 3: 5 (8)

TIMI flow pre-PPCI
- 0: 50 (78)
- 1: 6 (9)
- 2: 7 (11)
- 3: 1 (2)

TIMI flow post-PPCI
- 0: 0 (0)
- 1: 0 (0)
- 2: 4 (6)
- 3: 60 (94)

Medications during PPCI
- GP Iib/IIa inhibitor: 8 (13)
- Bivalirudin: 42 (66)
- Heparin: 39 (61)
- Clopidogrel: 10 (16)

Medications post-PPCI
- Beta-blockers: 61 (95)
- ACE inhibitors: 62 (97)
- Statins: 64 (100)
- Aspirin: 61 (95)
- Diuretic: 4 (8)
- Nitrates: 53 (83)
- Clopidogrel: 53 (83)
- Ticagrelor: 11 (22)

Invasive measurements post-PPCI (n = 53)
- IMR: 32 (20-46)
- CFR: 1.7 (1.3-2.3)
- T90 (ms): 0.8 (0.4-1.2)

TABLE 2 CMR Findings

| | Acute (n = 64) | 6 Months (n = 64) | p Value |
|---|---|---|---|
| EF (%) | 47 ± 9 | 54 ± 9 | <0.001 |
| EDV (ml) | 153 ± 41 | 164 ± 42 | 0.001 |
| ESV (ml) | 83 ± 31 | 76 ± 31 | 0.002 |
| LGE, 5 SD (LV%) | 25 (14-32) | 12 (8-19) | <0.001 |
| Edema, 2 SD (LV%) | 40 (33-48) | 0 (0-0) | <0.001 |
| MSI (%) | 41 (31-60) | 68 (58-78) | <0.001 |
| MVO patients | 40 (63) | — | — |
| MVO (g) | 0.8 (0-2.6) | — | — |
| IMH patients | 31 (48) | — | — |
| IMH (g) | 0 (0-2.9) | — | — |
| MBFculprit (ml/min/g) | 0.78 ± 0.14 | 0.87 ± 0.16 | <0.001 |
| Heart rate (beats/min) | 67 ± 12 | 57 ± 8 | <0.001 |
| Systolic blood pressure (mm Hg) | 113 ± 15 | 119 ± 18 | 0.002 |
| Rate pressure product (beats/min mm Hg/1e4) | 0.75 ± 0.15 | 0.68 ± 0.15 | <0.001 |

Segmental analysis
- WT (%)
  - WTremote (n = 276): 85 ± 34
  - WTedema (n = 228): 68 ± 29
  - WTinfarct (n = 406): 36 ± 27
  - WTmvo (n = 36): 20 ± 17
  - WTMBF <36 (n = 56): 15 ± 13
- T1 (ms)
  - T1remote (n = 150): 1,190 ± 55
  - T1edema (n = 152): 1,258 ± 64
  - T1infarct (n = 306): 1,351 ± 86
  - T1mvo (n = 31): 1,340 ± 70
  - T1MBF <36 (n = 47): 1,386 ± 82
- MBFcor (ml/min/g)
  - MBFremote (n = 276): 1.02 ± 0.21
  - MBFedema (n = 228): 0.97 ± 0.18
  - MBFinfarct (n = 406): 0.76 ± 0.20
  - MBFMBF <36 (n = 36): 0.69 ± 0.16
  - MBFMBF <36 (n = 56): 0.59 ± 0.11

Values are mean ± SD, median (first to third quartile), or n (%). *Values were not normally distributed, and the p values then pertain to a paired Wilcoxon test.

Shapiro-Wilk test. For normally distributed variables, comparison among groups were performed with unpaired Student’s t-tests, and comparisons within each group of follow-up versus baseline used paired Student’s t-tests. For variables such as %LGE (% of LV mass) that are not normally distributed, we used Wilcoxon rank sum and signed rank tests.

The lme4 package (11) for the R statistical environment was used to build linear models with mixed effects (LME) for the analysis of segmental MBFcor acutely and over 6M follow-up (details in the Supplemental Appendix).
To investigate the predictive value of acute rest MBF_{cor} for LGE, WT at 6M, and WT<45% at 6M, we used Generalized Additive Models for Location Scale and Shape (GAMLSS) using acute rest MBF_{cor}, LGE and MVO as predictors (details in the Supplemental Appendix). Spearman correlation coefficients were used to assess any relationships among segmental MBF_{cor}, WT, and LGE and MBF_{culprit} with invasive measurements and 6M myocardial functionality. Receiver-operating characteristic (ROC) analysis was performed to assess the diagnostic performance of MBF_{culprit}, LGE, and invasive measurements in the acute setting in predicting LV dysfunction (ejection fraction [EF] <50%) at 6M in patients with IMR <40 or CFR >2. Independent predictors of IS reduction from acute to 6M, in the same subgroup of patients, were assessed by adopting linear regression models. Variables with a p value <0.10 at univariable analysis were then entered into the multivariable models. The p values ≤0.05 were considered statistically significant.

RESULTS

Of 104 patients with STEMI who consented, 40 were excluded because of claustrophobia or technical issues (n = 12), bystander cardiomyopathy (n = 6), poor-quality image (n = 10), and declined follow-up scan (n = 12). A total of 64 patients underwent acute and follow-up scan. The measurement of IMR, CFR, and T_{mn} was feasible in 53 of 64 patients. Clinical and demographic baseline characteristics are shown in Table 1.

CMR FINDINGS. The CMR findings are reported in Table 2. Acutely, all patients had positive edema, and only 1 had negative LGE; of 40 patients (63%) with MVO, 31 had also IMH. In 10 patients (i.e., 41 segments), myocardial edema persisted at 6M. Longitudinal native T1 changes relative to the degree of injury are also reported in Table 2 and Supplemental Figure 1A.

LONGITUDINAL MBF_{cor} CHANGES FOLLOWING ACUTE MI. Acute MBF_{cor} decreased with worsening ischemic injury (p < 0.001) (Table 2, Supplemental Figure 1B), with the lowest MBF_{cor} values observed in infarcted segments with MVO and IMH. Over 6M, MBF_{cor} improved significantly in all segment classes, including the groups of segments with LGE and/or MVO. In segments with IMH, MBF_{cor} did not change significantly over time (p = 0.08) (Figure 2).

TISSUE STATE AND SEVERITY OF INJURY BY T1 MAPPING AS DETERMINANTS OF 6M MBF_{cor} CHANGES. To determine the effect of tissue state on MBF_{cor} changes between the acute phase and 6M, we used a mixed-effects model for MBF_{cor}, with tissue state and time point (acute, 6M), and their interaction as independent predictors. At the acute stage, edema, LGE, and LGE in combination with MVO were

**FIGURE 2** MBF_{cor} Changes Over 6M in Acutely Infarcted Myocardium

Myocardial blood flow corrected (MBF_{cor}) improves significantly at 6 months (6M) in all segments, with the exception of segments with an acute presentation with microvascular obstruction (MVO) and intramyocardial hemorrhage (IMH). Bars are SEM. Mean values in the bars are reported with SD. *p < 0.001. LGE = late gadolinium enhancement.

**TABLE 3** Estimated Effect in Mixed-Effects Model for Mean Resting MBF_{cor}, Acutely and at 6M

| Linear mixed-effect model for MBF with tissue state as predictors | Coefficient ± SE | p Value |
|------------------------------------------------------------------|------------------|---------|
| (Intercept)                                                      | 1.00 ± 0.017     | <0.001  |
| Edema, acute                                                     | -0.03 ± 0.016    | 0.053   |
| LGE                                                              | -0.18 ± 0.015    | <0.001  |
| LGE + MVO acute                                                  | -0.38 ± 0.020    | <0.001  |
| 6M                                                               | 0.04 ± 0.013     | <0.001  |
| Edema 6M                                                         | 0.00 ± 0.075     | 0.989   |
| LGE with edema 6M                                                | -0.11 ± 0.037    | 0.002   |
| LGE 6M                                                           | -0.19 ± 0.013    | <0.001  |

**TABLE 3** Estimated Effect in Mixed-Effects Model for Mean Resting MBF_{cor}, Acutely and at 6M

| Linear mixed-effect model for MBF_{cor} with T1 as predictor | Coefficient ± SE | p Value |
|---------------------------------------------------------------|------------------|---------|
| (Intercept)                                                   | 0.90 ± 0.02      | <0.001  |
| T1 (100-ms change)                                            | -0.09 ± 0.007    | <0.001  |
| 6M                                                            | 0.01 ± 0.01      | 0.409   |
| T1: 6M                                                        | -0.05 ± 0.016    | 0.001   |

A 100-ms change of T1 rather than a 1-s change, was used here to estimate the effect size because it is of the same order of magnitude as the T1 differences at the acute stage between remote myocardium and regions with ischemic injury. 6M = 6 months; other abbreviations as in Table 2.
associated with a significant reduction of MBF\textsubscript{cor} by 0.03 ml/min/g (p = 0.05), 0.18 ml/min/g (p < 0.001), and 0.38 ml/min/g (p < 0.001), respectively (Table 3). These model predictions are in close agreement with the differences in acute MBF\textsubscript{cor} among tissue states that can be inferred from Table 2. At 6M, there was a significant, albeit small, overall improvement in MBF\textsubscript{cor} (0.04 ml/min/g, p < 0.001), independent of tissue state. 6M LGE with edema had a by 0.11 ml/min/g worse effect than acutely (p = 0.002).

Next, we investigated the association between MBF\textsubscript{cor} and native T1 as quantitative marker of severity of injury. Acutely, a 100-ms increase in myocardial T1 was associated with a significant MBF\textsubscript{cor} reduction of 0.10 ± 0.007 ml/min/g, whereas at 6M, an increase in native T1 by 100 ms was associated with a further MBF\textsubscript{cor} reduction by 0.05 ± 0.02 ml/min/g (p = 0.001) (Table 3, Figure 3). We found a negative association between MBF\textsubscript{cor} and T1 for all segments independent of the tissue state (Figure 3). Notably, if regression coefficients for the effect of native T1 on MBF are estimated for each tissue state, the association between MBF and native T1 is significant only in the acute phase for late gadolinium enhancement with edema, and at 6 months (6M) for edema, late gadolinium enhancement (LGE), and late gadolinium enhancement with edema. MVO = microvascular obstruction.

**TABLE 4** Predictive Value of Acute MBF\textsubscript{cor}, LGE, and MVO for 6M LGE and WT (GAMLSS Model)

| Multivariable Associations | Coefficient ± SE | t Value | p Value |
|----------------------------|-----------------|---------|---------|
| GAMLSS for LGE 6M          |                 |         |         |
| (Intercept)                | −1.7 ± 0.209   | −8.4    | <0.001  |
| Acute LGE (%)              | 0.025 ± 0.002  | 15.4    | <0.001  |
| Acute MBF\textsubscript{cor} (ml/min/g) | −0.564 ± 0.228  | −2.5    | 0.013   |
| MVO (%)                    | 0.017 ± 0.006  | 2.6     | 0.009   |
| GAMLSS for WT 6M           |                 |         |         |
| (Intercept)                | 74.147 ± 1.522 | 48.71   | <0.001  |
| Acute LGE (%)              | −0.377 ± 0.042 | −9.01   | <0.001  |
| Acute MBF\textsubscript{cor} (ml/min/g) (centered) | 60.066 ± 6.314 | 9.51 | <0.001 |
| MVO (%)                    | −0.944 ± 0.238 | −3.97   | <0.001  |
| Acute LGE: acute MBF\textsubscript{cor} | −0.360 ± 0.151 | −2.39 | 0.017   |

GAMLSS = Generalized Additive Models for Location Scale and Shape; other abbreviations as in Table 2 and 3.
independent of acute LGE and MVO ($p = 0.013$) (Table 4, Figures 4A and 4B). As an example of point estimates from the model summarized in Table 4, we note that for segments with LGE of 50% and acute MBF_{cor} of 0.3 ml/min/g, the predicted IS at 6M (34%) was ~6% larger than in segments with the same LGE and an acute MBF_{cor} of 0.8 ml/min/g (28% LGE at 6M) and ~11% larger than in segments with same LGE and an acute MBF_{cor} of 1.3 ml/min/g (23% LGE at 6M) (Figure 4A). There was no evidence of an interaction between acute LGE and MBF_{cor} for predicting 6M LGE.

In segments without LGE at 6M, 97% had no acute LGE, whereas the remaining 3% had a median acute LGE of 10.5%, which was resorbed over 6M. Conversely, 9% of segments without acute LGE showed a median LGE of 13% at 6M. The probability of no LGE at 6M varied significantly with acute MBF_{cor}...
and LGE, as shown in Figure 4B. The odds of no LGE at 6M increased by 1.4:1 for each 0.1 ml/min/g increase of acute MBFcor (95% confidence interval: 1.21 to 1.58; p < 0.001), independent of acute LGE. Each 10% increase of acute LGE decreased the odds of no LGE at 6M by 1:4.7 (p < 0.001).

**PREDICTIVE VALUE OF ACUTE MBFcor FOR 6M SEGMENTAL FUNCTIONAL RECOVERY.** Acute MBFcor and LGE are simultaneous, independent predictors of 6M WT (Table 4, Supplemental Figure 2B and 2C). Notably, our results show that in segments with intermediate LGE (Figure 4C), acute MBFcor can account for the relatively large variability of 6M WT independent of the level of acute LGE; segments with intermediate LGE (i.e., 50%) and MBFcor of 0.35 ml/min/g have a 15% reduction of WT 6M compared with segments with the same LGE and MBFcor of 0.7 ml/min/g, and a 28% reduction compared with segments with same LGE and normal MBFcor of 1.0 ml/min/g.

Acute MBFcor impairment decreases the likelihood of 6M functional recovery (Figure 4D), both in a univariate model that includes only MBFcor (p < 0.001) and in a multivariate model that also includes acute T1 (p = 0.001), acute LGE (p = 0.02), and MVO (p = 0.001) as additional predictors. In the multivariate model the odds of WT >45% at 6M increased by 1.38:1 (95% confidence interval: 1.29 to 1.48) for each 0.1 ml/min/g increase of acute MBFcor (Table 5).

**ADDITIONAL PREDICTIVE VALUE OF MBF IN ADDITION TO INVASIVE MEASUREMENTS FOR 6M EF AND IS REDUCTION.** Results for CFR, IMR, and Tmn post-PPCI are summarized in Table 1. MBFculprit correlated positively with 6M EF (R = 0.506, p < 0.001) (Figure 5A). When EF was
simultaneously adjusted by acute LGE (p = 0.005) and acute EF (p < 0.001), the association remained significant (p = 0.02). In patients with IMR <40 or CFR >2 (N = 40), acute MBFCULPRIT and LGE were equally strong predictors of EF <50% at 6M (area under the curve: 0.843, p = 0.001 for MBFCULPRIT; and area under the curve: 0.838, p = 0.002 for LGE) (Figure 5B). MBFCULPRIT (p = 0.031) was independently associated with IS reduction (Table 6).

**DISCUSSION**

The microcirculation plays a crucial role in infarct healing as the main supply conduit of oxygen and nutrients and as a delivery path for pharmacological treatments. An impairment in microvascular function is associated with a poor prognosis (12). To the best of our knowledge, this is the first CMR study using absolute MBF quantification to systematically estimate the longitudinal changes in microvascular function and predict functional recovery following STEMI.

The main findings of the study are as follows: 1) the acute microvascular dysfunction is strongly associated with the extent of the ischemic injury; 2) it is reversible, depending on the severity of the acute injury; 3) acute MBFCOR, LGE, and MVO are simultaneous predictors of final IS; 4) MBFCOR has incremental predictive value for final IS and segmental recovery, compared with predictions that are based solely on acute LGE; and 5) in a lower-risk subgroup of patients (IMR <40 or CFR >2), acute rest MBF in the culprit territory may be superior to acute invasive measurements in predicting long-term recovery and may be an independent predictor of IS reduction. Taken together, these results suggest that quantifying myocardial blood at the acute stage leads to an improved prediction of segmental myocardial viability and wall motion at follow-up.

The lack of detailed understanding of the pathophysiological cascade leading up to irreversible microvascular damage in the context of ischemia-reperfusion injury has prevented adequate pharmacological treatment (3). Previous evidence by positron emission tomography or CMR stress testing demonstrated partial recovery of the vasomotor function over time (13,14); however, such studies were performed in a subacute phase post-MI, and MBF was assessed in the myocardium pertaining to the culprit artery, thus leading to values likely not fully representative of the severity of injury. For the first time, our findings clearly show that the progressive deterioration of the acute microvascular function following ischemic injury is reversible even in severely damaged tissue. MBF normalization in areas with intermediate degree of ischemic insult is in line with pre-clinical evidence showing reversible endothelial damage and increased permeability of the microvessels at the time of reperfusion (15,16).
TABLE 6 Multivariable Associations Among Clinical Characteristics, Invasive Measurements at the Time of PPCI, and Infarct Size Reduction at 6M in Patients With IMR < .40 or CFR > .2

| IS Reduction From Acute to 6M | Univariable Analysis | Multivariable Analysis |
|-----------------------------|----------------------|------------------------|
|                             | Estimate Coefficient | p Value                |
|                             |                      |                        |
| Age (yrs)                   | -0.005               | 0.163                  |
| Male                        | 0.016                | 0.861                  |
| Diabetes                    | -0.144               | 0.266                  |
| Hypertension                | -0.161               | 0.026                  |
| Hypercholesterolemia        | -0.110               | 0.165                  |
| Active smoking              | 0.009                | 0.896                  |
| Family history of CHD       | 0.056                | 0.413                  |
| Pain to balloon time (min)  | 0.0001               | 0.152                  |
| LAD vs. non-LAD             | 0.108                | 0.116                  |
| TIMI pre                    | -0.038               | 0.131                  |
| TIMI post                   | 0.114                | 0.474                  |
| CFR PPCI                    | 0.095                | 0.041                  |
| IMR PPCI                    | -0.002               | 0.473                  |
| EDV (ml)                    | 0.000                | 0.710                  |
| ESV (ml)                    | 0.000                | 0.714                  |
| EF (%)                      | 0.001                | 0.733                  |
| Acute IS (%)                | -0.001               | 0.673                  |
| MBF_CULPRIT (ml/min/g)      | 0.350                | 0.071                  |
| MVO (yes/no)                | -0.141               | 0.037                  |
| IMH (yes/no)                | -0.105               | 0.124                  |
| IMH (%)                     | -0.008               | 0.388                  |

IS – infarct size; other abbreviations as in Table 1 to 3.

contrast, for areas with MVO, the underlying mechanisms promoting functional recovery and infarct reduction are less clear. The infarcted myocardium, once thought to be “dead,” is actually a dynamic tissue undergoing an extensive process of remodeling, ultimately forming a core of scar, surrounded by neoangiogenesis in the infarct border zone (17,18). No improvement in MBF was seen in infarcted areas with persistent edema at 6M. As shown recently, residual iron deposits at 6M following acute IMH resulted from severe acute microvascular impairment (19). Therefore, the correlation between persistent edema and microvascular dysfunction seems plausible and in line with putative mechanisms for edema in the presence of capillary leakage or hemorrhage.

In this study, we demonstrate for the first time the incremental role of microvascular function for final IS in segments with intermediate or lower LGE transmurality, independent of the extent of the acute LGE and MVO. The long-term prognostic value of even small amounts of LGE has been previously studied (20,21). Our results show that the probability of having no 6M LGE is significantly affected by acute microvascular function, a finding suggesting that measures to restore microvascular function after MI may have longer-term benefits. Unexpectedly, we found that a small fraction of segments without LGE acutely were positive to LGE at 6M. There are at least 3 potential explanations for this finding: 1) a mismatch of short-axis positions imaged at different time points; 2) lower diagnostic performance of standard CMR techniques such as \( T_2W \) and LGE compared with more accurate parametric maps to quantify ischemic techniques; and 3) late development of necrotic tissue within an area at risk.

Finally, our study shows that in patients with preserved microvascular function as assessed by invasive measurements post-PPCI (i.e., IMR < .40 or CFR > .2), acute MBF estimates of microvascular function could provide a tool to stratify patients and predict LV remodeling. The predictive relevance of the changes in microvascular function early after PPCI are known (8): CMR MBF assessment could represent a valid alternative to invasive repeated measurements.

STUDY LIMITATIONS. The results of this study should be interpreted in light of some limitations. In this study, continuous variables such as MBF and native \( T_1 \) represent averages for each myocardial segment. Any estimate of an effect modification of MVO in the relationship of native \( T_1 \) and MBF is likely not representative of MVO itself because MVO in most segments represented a relatively small subarea of a myocardial segment. Our IMR measurements (median 32; interquartile range: 20 to 46) are comparable to those in previous studies (4,22); however, we did not find a significant relationship between IMR and MVO/MBF_CULPRIT. There may be several reasons for this, including the small sample size and the assessment of resting perfusion rather than stress perfusion 3 days after the invasive coronary measurements (8). Further larger studies are needed to corroborate our findings.

CONCLUSIONS

Microvascular function estimated using CMR MBF has additional clinical and prognostic value beyond tissue characterization. In the context of novel potential therapeutic targets such as endothelial integrity, vascular permeability, or angiogenesis (23), MBF measurements could represent a useful noninvasive tool for risk stratification of patients with STEMI post-PPCI and to guide cardioprotective treatment.
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APPENDIX For an expanded methods section as well as supplemental figures and references, please see the online version of this paper.