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Index of Microcirculatory Resistance as a Tool to Characterize Microvascular Obstruction and to Predict Infarct Size Regression in Patients With STEMI Undergoing Primary PCI

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ABSTRACT

OBJECTIVES This study aimed to compare the value of the index of microcirculatory resistance (IMR) and microvascular obstruction (MVO) measured by cardiac magnetic resonance (CMR) in patients treated for and recovering from ST-segment elevation myocardial infarction.

BACKGROUND IMR can identify patients with microvascular dysfunction acutely after primary percutaneous coronary intervention (pPCI), and a threshold of >40 has been shown to be associated with an adverse clinical outcome. Similarly, MVO is recognized as an adverse feature in patients with ST-segment elevation myocardial infarction. Even though both IMR and MVO reflect coronary microvascular status, the interaction between these 2 parameters is uncertain.

METHODS A total of 110 patients treated with pPCI were included, and IMR was measured immediately at completion of pPCI. Infarct size (IS) as a percentage of left ventricular mass was quantified at 48 h (38.4 ± 12.0 h) and 6 months (194.0 ± 20.0 days) using CMR. MVO was identified and quantified at 48 h by CMR.

RESULTS Overall, a discordance between IMR and MVO was observed in 36.7% of cases, with 31 patients having MVO and IMR ≤40. Compared with patients with MVO and IMR ≤40, patients with both MVO and IMR >40 had an 11.9-fold increased risk of final IS >25% at 6 months ($p = 0.001$). Patients with MVO and IMR ≤40 had a significantly smaller IS at 6 months ($p = 0.001$), with significant regression in IS over time (34.4% [interquartile range: 27.3% to 41.0%] vs. 22.3% [interquartile range: 16.0% to 30.0%]; $p = 0.001$).

CONCLUSIONS Discordant prognostic information was obtained from IMR and MVO in nearly one-third of cases; however, IMR can be helpful in grading the degree and severity of MVO. (J Am Coll Cardiol Img 2018;■:■–■)

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ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

IMR = index of microcirculatory resistance

IQR = interquartile range

IS = infarct size

MVO = microvascular obstruction

pPCI = primary percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

Immediate coronary revascularization by primary percutaneous coronary intervention (pPCI) is the gold standard treatment for patients with ST-segment elevation myocardial infarction (STEMI) (1). Unfortunately, despite optimal interventional therapy, some patients have a suboptimal result from pPCI, with impaired myocardial perfusion. Immediate assessment of suboptimal myocardial reperfusion could enable the prompt identification of high-risk patients who could potentially benefit from additional therapy (2,3).

Cardiac magnetic resonance (CMR) is regarded as the gold standard for detection and quantification of infarct size (IS), and evidence of microvascular obstruction (MVO) is recognized as a strong predictor of adverse clinical outcomes after STEMI (4). However, because of the inherent time delay, CMR is hampered by logistic difficulties in the very early stage after myocardial revascularization.

For this reason, invasive indices of coronary physiology have been reconsidered (5). These parameters provide an early, "in the cath lab" assessment of post-pPCI microvascular function. Among these parameters, the index of microcirculatory resistance (IMR) has considerable appeal because it is readily performed (6), which provides assessment of coronary microvascular status early after pPCI (7). This index has been validated against CMR (8), with higher IMR values reported in STEMI patients with MVO on CMR (8). Moreover, IMR has been identified as a predictor of change in left ventricular ejection fraction and IS at 6 months after STEMI (9). Higher values indicate greater degrees of microvascular dysfunction, and an IMR <25 is accepted as a reflection of normal microvascular function (10). In STEMI, a post-stenting IMR >40 reflects severe microvascular impairment and is associated with worse clinical outcomes in terms of death, myocardial infarction, and readmission for heart failure (11,12).

Even though it has been validated against CMR, the actual reported relationship between IMR and MVO extension is unclear, and it appears that there are cases in which CMR findings and IMR values could be surprisingly discordant (13). The meaning of this discordance between presence of MVO on CMR and post-procedural IMR has never been specifically investigated.

In the current study, we aimed to understand coronary microvasculature injury post-pPCI by measuring how often IMR and MVO provide concordant or discordant assessment of the microvasculature and to define the clinical implications of these measures at follow-up.

METHODS

Patients with STEMI admitted to the Oxford Heart Centre for pPCI were prospectively considered for enrollment in the OxAMI (Oxford Acute Myocardial Infarction) study (Research Ethics Committee number 10/H0408/24) from January 2011 until December 2016. Details about the OxAMI study have been reported previously (14). The current study represents a retrospective analysis of patients prospectively enrolled. The study protocol was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki.

STEMI was defined as the occurrence of ongoing chest pain for at least 30 min associated with ST-segment elevation >2 mm in at least 2 contiguous leads. pPCI was performed according to international guidelines (1,15). All patients were loaded with double-antiplatelet therapy (aspirin 300 mg and clopidogrel 600 mg or ticagrelor 180 mg). Periprocedural anticoagulation was achieved by use of weight-adjusted unfractionated heparin or bivalirudin. Decisions about stenting technique (direct vs. nondirect), thrombectomy, and glycoprotein IIb/IIIa inhibitor adoption were left to the operator's discretion.

IMR MEASUREMENT. At the end of pPCI, IMR was measured with a thermodilution technique as described previously (16). Briefly, a standard pressure wire (Certus, St. Jude Medical, St. Paul, Minnesota) was calibrated, equalized, and advanced toward the distal third of the infarct-related artery. After intracoronary injection of 250 μg of isosorbide dinitrate, the following parameters were measured both at baseline and after hyperemia was induced with intravenous infusion of adenosine at a rate of 140 μg/kg/min: 1) mean aortic pressure; 2) mean distal pressure; and 3) mean transit time. Mean transit time was calculated as the average of 3 transit time measurements during 3 separate injections of 3 ml of room temperature 0.9% saline solution. IMR was then calculated as mean distal pressure at hyperemia multiplied by mean transit time at hyperemia.

CARDIAC MAGNETIC RESONANCE. Cardiac magnetic resonance scans were performed at 48 h (38.4 ± 12.0 h) after pPCI and at 6 months (194.0 ± 20.0 days) using a 3.0-T scanner (either MAGNETOM TIMTrio or MAGNETOM Verio, Siemens Healthcare, Munich Germany). The protocol included steady-state free precession cine imaging, T2-weighted (T2W) imaging, native shortened modified Look-Locker inversion

recovery T1 mapping, T2* mapping, and late gadolinium enhancement. Sequence acquisition was performed as described previously (17) (Online Appendix).

Matching short-axis slices covering the left ventricle were analyzed with cvi42 software (Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada) by 2 expert independent operators blinded to clinical, procedural, and coronary physiology data. Disagreement was resolved by consensus. Left ventricular end-diastolic volume, end-systolic volume, and ejection fraction were assessed on cine images. Area at risk and IS were quantified as percentage of left ventricular mass on T2W (or native T1 if T2W was not available) and late gadolinium enhancement, respectively, by placing a reference region of interest in remote myocardium and setting the signal intensity threshold at 2 and 5 SDs above the mean intensity of the reference region of interest, respectively (18-20).

Myocardial salvage index was calculated as described previously (19) as: [(area at risk - IS) / area at risk] × 100. MVO was defined as hypointense area within the hyperenhancement region on late gadolinium enhancement and manually contoured (18). Presence of hemorrhage was first assessed visually on T2* maps or T2W imaging by identifying a hypointense core inside the hyperenhanced region (12,13) and was then quantified on T2W imaging, with the signal intensity threshold set at 2 SDs below the average intensity of the reference region of interest in the periphery of the area at risk (13).

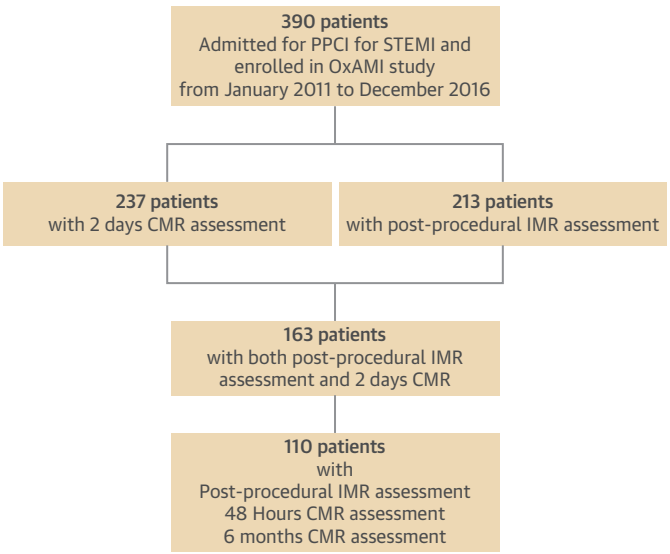
GROUP DEFINITIONS. Patients were identified according to final IMR and presence of MVO. A cutoff of 40 was adopted for IMR based on previous published reports (11,12) and a pre-specified sensitivity analysis to predict 6-month IS (Online Figure 1). We anticipated 4 groups: 1) patients with IMR ≤40 and no MVO; 2) patients with IMR >40 and no MVO; 3) patients with IMR ≤40 and MVO; and 4) patients with IMR >40 and MVO.

STATISTICAL ANALYSIS. After normal distribution was verified by use of the Shapiro-Wilk test, variables were expressed as mean ± SD or as median and interquartile range (IQR), as appropriate. Frequencies were compared with chi-square test or Fisher exact test, as appropriate. Continuous variables were compared with Student's *t*-test or analysis of variance with Scheffé post hoc comparisons, as appropriate. Student's *t*-test or Wilcoxon test was used as appropriate for paired samples. Non-normally distributed continuous variables were compared with the Mann-Whitney *U* test or Kruskal-Wallis test, as appropriate. Correlations between variables were expressed with Pearson r or Spearman rho coefficients as appropriate.

In the subgroup of patients with evidence of MVO on CMR, a binary logistic regression model was used to calculate the odds ratio for post-stenting IMR >40 to predict 6-month IS >25% (21). In the same subgroup of patients, a linear regression model was also considered to predict extent of IS at 6 months using the same covariates, after verifying that the assumptions for collinearity, independence of residuals, homoscedasticity, and normality of residuals distribution were all met. In both binary logistic and linear regression models, covariates with $p < 0.05$ in the univariate model were included in the multivariate model.

Statistical analysis was performed with SPSS version 22.0 (IBM Corporation, Armonk, New York), and $p < 0.05$ was considered statistically significant.

FIGURE 1 Study Flow Chart



CMR = cardiac magnetic resonance; IMR = index of microcirculatory resistance; OxAMI = Oxford Acute Myocardial Infarction study; PPCI = primary percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

RESULTS

CLINICAL AND PROCEDURAL CHARACTERISTICS. A total of 110 patients were included in the current analysis who had complete data for post-procedural IMR and 48-h and 6-month CMR (**Figure 1**). Clinical and procedural characteristics are reported in **Tables 1 and 2**.

CORRELATION OF IMR WITH IS AND MVO. A significant correlation was observed between post-procedural

TABLE 1 Clinical Characteristics

	Overall (N = 110)	No MVO and IMR ≤40 (n = 42)	No MVO and IMR >40 (n = 9)	MVO and IMR ≤40 (n = 31)	MVO and IMR >40 (n = 28)	p Value
Age, yrs	61.3 ± 9.6	60.8 ± 9.4	63.3 ± 9.6	60.6 ± 9.7	62.2 ± 10.0	0.82
Male	94 (85.4)	36 (85.7)	8 (88.9)	23 (74.2)	27 (96.4)	0.11
Hypertension	56 (50.9)	22 (52.4)	3 (33.3)	16 (51.6)	15 (53.6)	0.74
Hypercholesterolemia	44 (40.0)	14 (33.3)	4 (44.4)	16 (51.6)	10 (35.7)	0.08
Active smoker	53 (48.2)	21 (50.0)	4 (44.4)	17 (54.8)	11 (39.3)	0.67
Diabetes mellitus	43 (39.1)	11 (26.2)	3 (33.3)	15 (48.4)	14 (50.0)	0.13
Family history of CAD	61 (55.4)	22 (52.4)	6 (66.7)	21 (67.7)	12 (42.8)	0.23
Previous history of CAD	37 (33.6)	11 (26.2)	3 (33.3)	13 (41.9)	10 (35.7)	0.56
Ischemic time, min	169.5 (128.2-275.7)	168.5 (121.5-302.7)	177.0 (155.0-299.5)	147.0 (130.0-190.0)	175.5 (120.2-347.0)	0.24
Ischemic time groups						
<3 h	60 (54.5)	21 (50.0)	5 (55.5)	20 (64.5)	14 (50.0)	0.85
≥3 h and <6 h	28 (25.4)	12 (28.6)	3 (33.3)	6 (19.3)	7 (25.0)	
≥6 h	22 (20.1)	9 (21.4)	1 (11.2)	5 (16.2)	7 (25.0)	
Culprit vessel						
LAD	59 (53.6)	18 (42.8)	6 (66.7)	18 (58.1)	17 (60.7)	0.42
LCx	8 (7.3)	2 (4.8)	1 (11.2)	2 (6.4)	3 (10.7)	
RCA	43 (39.1)	22 (52.4)	2 (22.1)	11 (35.5)	8 (28.6)	
TIMI flow grade at presentation						
0	93 (84.6)	35 (83.3)	6 (66.7)	28 (90.3)	24 (85.8)	0.09
1	5 (4.5)	0 (0.0)	2 (22.1)	1 (3.3)	2 (7.1)	
2	8 (7.3)	5 (11.9)	1 (11.2)	0 (0.0)	2 (7.1)	
3	4 (3.6)	2 (4.8)	0 (0.0)	2 (6.4)	0 (0.0)	
Number of vessels diseased						
1	85 (77.3)	35 (83.3)	8 (88.8)	24 (77.4)	18 (64.3)	0.34
2	17 (15.4)	5 (11.9)	0 (0.0)	6 (19.3)	6 (21.4)	
3	8 (7.3)	2 (4.8)	1 (11.2)	1 (3.3)	4 (14.3)	
SYNTAX score	7.0 (4.0-11.0)	6.5 (4.0-9.0)	5.5 (4.0-10.5)	5.0 (4.0-10.0)	12.0 (4.0- 16.0)	0.12
Creatinine, μmol/ml	74.5 (66.0-88.0)	72.5 (66.0-87.0)	83.0 (69.5-101.0)	69.0 (61.0-79.0)	78.0 (72.2-95.2)	0.02
eGFR, ml/min/1.73 m^2	93.9 ± 19.5	96.1 ± 22.6	84.7 ± 17.8	97.5 ± 12.8	89.7 ± 20.4	0.18
Periprocedural medication						
Aspirin	108 (98.2)	41 (97.6)	9 (100.0)	31 (100.0)	27 (96.4)	0.73
Clopidogrel	107 (97.3)	41 (97.6)	9 (100.0)	30 (96.8)	27 (96.4)	0.94
Ticagrelor	3 (2.7)	1 (2.4)	0 (0.0)	1 (3.2)	1 (3.6)	0.94
Heparin	41 (37.3)	10 (23.8)	3 (33.3)	16 (51.6)	12 (42.8)	0.09
Bivalirudin	69 (62.7)	32 (76.2)	6 (66.7)	15 (48.4)	16 (57.2)	0.09
GP IIb/IIIa inhibitors	43 (39.1)	11 (26.2)	3 (33.3)	16 (51.6)	13 (46.4)	0.12
Medications at discharge						
Aspirin	108 (98.2)	41 (97.6)	9 (100.0)	31 (100.0)	27 (96.4)	0.73
Clopidogrel	79 (71.8)	29 (69.0)	7 (77.8)	22 (71.0)	21 (75.0)	0.93
Ticagrelor	32 (29.1)	14 (33.3)	2 (22.2)	9 (29.0)	7 (25.0)	0.85
Statin	110 (100.0)	42 (100.0)	9 (100.0)	31 (100.0)	28 (100.0)	1.00
Beta-blockers	109 (99.1)	41 (97.6)	9 (100.0)	31 (100.0)	28 (100.0)	0.65
ACE inhibitors	104 (94.5)	38 (90.5)	9 (100.0)	29 (93.5)	28 (100.0)	0.31
Sartans	2 (1.8)	2 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	0.35
Calcium-channel blockers	1 (0.9)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0.65
Diuretic agents	6 (5.4)	2 (4.8)	0 (0.0)	1 (3.2)	3 (10.7)	0.50
Nitrates	97 (88.2)	35 (83.3)	8 (88.9)	28 (90.3)	26 (92.8)	0.64
Anticoagulant	1 (0.9)	0 (0.0)	0 (0.0)	1 (3.2)	0 (0.0)	0.46

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IMR and IS at 48 h (rho = 0.21, p = 0.03) (Figure 2A), IS at 6 months (rho = 0.43, p = 0.001) (Figure 2B), and MVO extent (rho = 0.29, p = 0.002) (Figure 2C). Moreover, a significantly higher IMR value was confirmed in patients with evidence of MVO than in those without (35.6 [IQR: 24.5 to 56.5] vs. 26.6 [IQR: 19.0 to 37.0]; p = 0.001) (Figure 2D).

IMR AND MVO DISCORDANCE. Discordance between IMR and presence of MVO was observed in 40 of 110 patients, accounting for 36.4% of the entire cohort

TABLE 1 Continued

	Overall (N = 110)	No MVO and IMR ≤40 (n = 42)	No MVO and IMR >40 (n = 9)	MVO and IMR ≤40 (n = 31)	MVO and IMR >40 (n = 28)	p Value
Medications at 6 months						
Aspirin	107 (97.3)	41 (97.6)	9 (100.0)	30 (96.8)	27 (96.4)	0.94
Clopidogrel	79 (71.8)	29 (69.0)	7 (77.8)	22 (71.0)	21 (75.0)	0.93
Ticagrelor	32 (29.1)	14 (33.3)	2 (22.2)	9 (29.0)	7 (25.0)	0.85
Statin	109 (99.1)	41 (97.6)	9 (100.0)	31 (100.0)	28 (100.0)	0.65
Beta-blockers	106 (96.4)	41 (97.6)	8 (88.9)	31 (100.0)	26 (92.8)	0.29
ACE inhibitors	106 (96.4)	40 (95.2)	9 (100.0)	29 (93.5)	28 (100.0)	0.52
Sartans	1 (0.9)	0 (0.0)	0 (0.0)	1 (3.2)	0 (0.0)	0.46
Calcium-channel blockers	4 (3.6)	2 (4.8)	1 (11.1)	0 (0.0)	1 (3.6)	0.43
Diuretic agents	3 (2.7)	1 (2.4)	0 (0.0)	1 (3.2)	1 (3.6)	0.94
Nitrates	101 (91.8)	36 (85.7)	7 (77.8)	31 (100.0)	27 (96.4)	0.05
Anticoagulant	1 (0.9)	0 (0.0)	0 (0.0)	1 (3.2)	0 (0.0)	0.46

Values are mean ± SD, n (%), or median (interquartile range).

ACE = angiotensin-converting enzyme; CAD = coronary artery disease; eGFR = estimated glomerular filtration rate; GP = glycoprotein; IMR = index of microvascular resistance; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; MVO = microvascular obstruction; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction.

(Figure 3). Forty-two patients (38.2%) had IMR ≤40 and no MVO and 28 (25.4%) had IMR >40 and MVO on CMR. Conversely, in the context of a discordant pattern between IMR and MVO, most patients (31 of 40 [77.5%]) had IMR ≤40 and evidence of MVO, whereas a minority of cases (9 of 40) had IMR >40 without evidence of MVO (Figure 3).

IMR-MVO DISCORDANCE AND FINAL IS. Table 3 reports coronary physiology and CMR features for the entire cohort and after stratification into the 4 groups according to IMR and MVO. At 6-month follow-up, patients with both MVO and higher values of IMR had a significantly larger IS than all other groups. Similarly, patients with both low IMR and no MVO

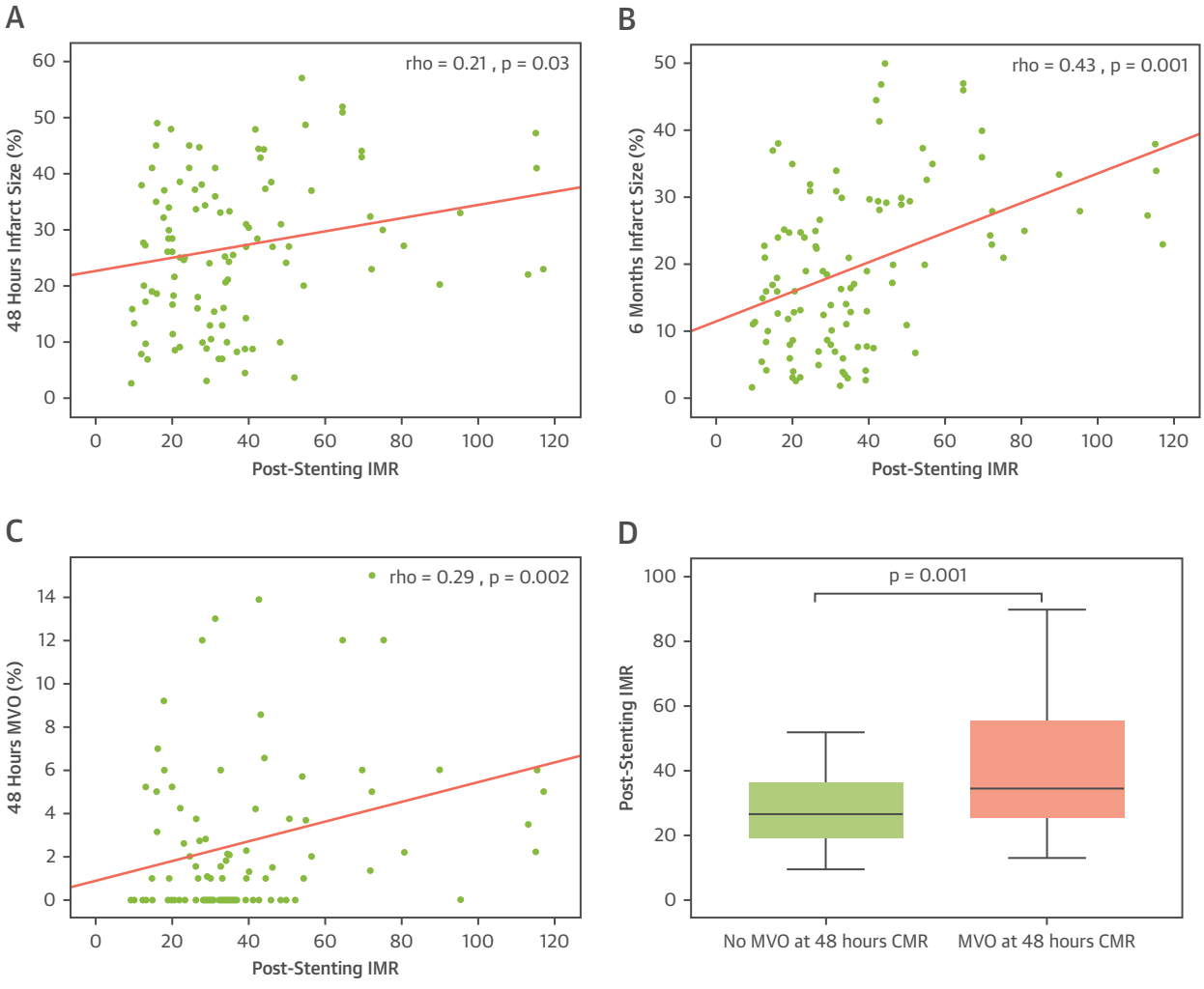
TABLE 2 Procedural Characteristics

	Overall (N = 110)	No MVO and IMR ≤40 (n = 42)	No MVO and IMR >40 (n = 9)	MVO and IMR ≤40 (n = 31)	MVO and IMR >40 (n = 28)	p Value
Thrombus aspiration	97 (88.2)	36 (85.7)	8 (88.9)	28 (90.3)	25 (89.3)	0.94
Pre-dilation	105 (95.4)	39 (92.8)	8 (88.9)	31 (100.0)	27 (96.4)	0.38
Maximum balloon diameter, mm	2.5 ± 0.2	2.5 ± 0.3	2.7 ± 0.2	2.5 ± 0.2	2.5 ± 0.3	0.21
Drug-eluting stent	95 (86.4)	36 (85.7)	7 (77.8)	26 (83.9)	26 (92.8)	0.63
Number of stents						
1	90 (81.8)	35 (83.3)	7 (77.8)	26 (83.9)	22 (78.6)	0.99
2	12 (10.9)	4 (9.5)	1 (11.1)	3 (9.7)	4 (14.3)	
3	8 (7.3)	3 (7.2)	1 (11.1)	2 (6.4)	2 (7.1)	
Total stent length, mm	29.7 ± 15.4	29.0 ± 15.2	29.5 ± 15.9	28.4 ± 11.7	32.5 ± 19.3	0.75
Stent diameter, mm	3.5 ± 0.4	3.5 ± 0.5	3.5 ± 0.4	3.5 ± 0.5	3.4 ± 0.3	0.90
Post-dilation	77 (70.0)	32 (76.2)	8 (88.9)	19 (61.3)	18 (64.3)	0.28
Maximum balloon diameter, mm	3.8 ± 0.5	3.8 ± 0.6	3.7 ± 0.3	3.8 ± 0.4	3.6 ± 0.4	0.62
Final TIMI flow grade						
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0.05**
1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
2	16 (14.5)	2 (4.8)	1 (11.1)	5 (16.1)	8 (28.6)	
3	94 (85.5)	40 (95.2)	8 (88.9)	26 (83.9)	20 (71.4)	
Myocardial blush grade						
0–1	22 (20.0)	1 (2.4)	2 (22.2)	5 (16.1)	14 (50.0)	**0.001**
2	32 (29.0)	10 (23.8)	3 (33.3)	11 (35.5)	8 (28.6)	
3	56 (51.0)	31 (73.8)	4 (44.5)	15 (48.4)	6 (21.4)	
Incomplete ∑STR (<70%)	38 (34.5)	5 (11.9)	3 (33.3)	13 (41.9)	17 (60.7)	**0.001**

Values are n (%) or mean ± SD. **Bold** p values indicate significance.

∑STR = ST resolution; other abbreviations as in Table 1.

FIGURE 2 **Correlations Between IMR, Infarct Size, and MVO**



(A) Scatterplot showing correlation between IMR and 48-h infarct size. **(B)** Scatterplot reporting correlation between IMR and 6-month infarct size. **(C)** Scatterplot showing correlation of IMR with microvascular obstruction (MVO) at 48 h. **(D)** Boxplots reporting median IMR values in patients with and without MVO on cardiac CMR. Abbreviations as in Figure 1.

had a significantly smaller IS than all other groups (Figure 4A). Notably, among patients with MVO, those with concordant IMR >40 had a significant larger IS than did those with IMR ≤40 ($p < 0.001$) (Figure 4A).

When change in IS over time was analyzed, presence of a lower IMR was associated with a regression in IS at 6 months. Indeed, among patients without MVO, significant regression in IS was observed only in those patients with IMR ≤40 (16.1% [IQR: 9.0% to 25.3%] vs. 9.3% [IQR: 4.1% to 14.3%]; $p = 0.001$) and not in those with IMR >40 (28.6% [IQR: 9.4% to 40.8%] vs. 28.2% [IQR: 9.2% to 29.7%]; $p = 0.26$) (Table 4). Similarly, among patients with MVO, IS was unchanged for those with concordant IMR >40 (34.7% [IQR: 23.0% to 44.4%] vs. 31.2% [IQR: 25.0% to 39.5%]; $p = 0.19$) whereas significant regression was evident in the group with IMR ≤40 (34.4% [IQR: 27.3% to 41.0%] vs. 22.3% [16.0% to 30.0%]; $p = 0.001$) (Table 4).

These data are supplemented by the lack of difference in terms of MVO extent (4.6% [IQR: 2.0% to 6.4%] vs. 2.8% [IQR: 1.6% to 5.4%]; $p = 0.26$) (Figure 4C) or presence of intramyocardial hemorrhage (75.0% vs. 51.6%; $p = 0.10$) (Table 3) when patients with MVO and high IMR were compared with those with MVO and low IMR. However, a significantly greater extent of intramyocardial hemorrhage was observed in patients with MVO and increased

IMR (3.0% [IQR: 1.0% to 6.0%) vs. 1.0% [IQR: 0.0% to 3.2%); p = 0.004) (Figure 4D).

In the multivariable model, in patients with MVO and an IMR >40, there was an 11.9-fold increased chance of final IS at 6 months >25% (odds ratio: 11.9; 95% confidence interval: 2.8 to 51.3; p = 0.001, model R^2= 0.30) (Table 4) with an increase of a single unit of IMR, which resulted in a 0.28% increase in final IS (beta coefficient = 0.28; p = 0.003) (Table 4).

DISCUSSION

In the present study, the correlation between IMR and MVO was explored in patients after STEMI. We observed the following: 1) IMR and MVO are related, but when a threshold of 40 is adopted for IMR, there is a discordance in the information obtained between IMR and MVO in one-third of cases; 2) in patients with MVO and higher IMR, a larger IS is observed than in those in whom MVO is associated with IMR ≤40; and 3) patients with MVO but IMR ≤40 have evidence of significant regression of IS at 6 months, whereas no significant change in IS extent is observed in patients with MVO and higher IMR.

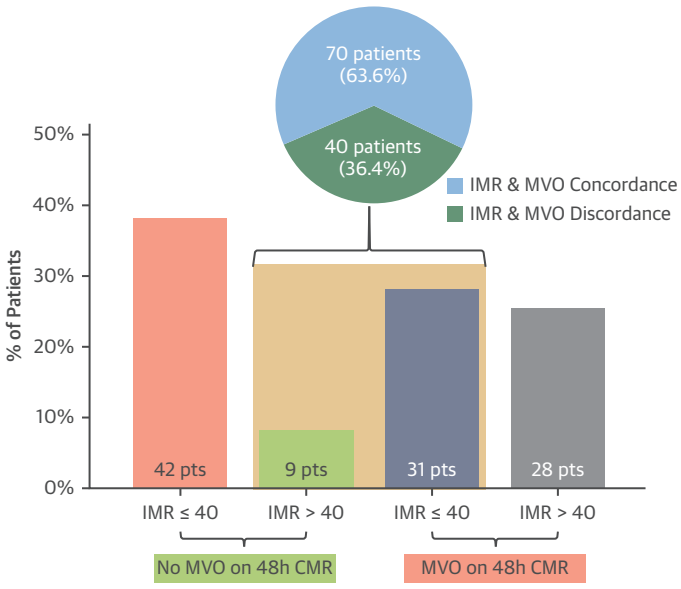
CMR is considered to be the gold standard for accurate assessment of the status of the coronary microvasculature post pPCI; however, invasive indices of coronary physiology have recently been proposed to facilitate early, "in the cath lab" diagnosis of post-procedural coronary microvascular injury (22). In this context, IMR is the most investigated invasive index of coronary physiology in STEMI because of its ease of use (6). IMR has been shown to be significantly related to long-term clinical outcomes and to predict IS and MVO on CMR (8,12), with most studies reporting higher occurrence of MVO when IMR is above a predefined threshold (8,12,23). However, when the actual correlation between IMR and extent of MVO is assessed, results across studies have been less consistent. Indeed, Patel et al. (24) failed to show a strong correlation between MVO extent and IMR in a small cohort of 34 STEMI patients, whereas Payne et al. (13) reported a significant but modest correlation of 0.38 between IMR and MVO extent in a larger cohort of 108 patients. Consequently, we conducted an in-depth investigation of the relationship between IMR and MVO.

We report a correlation between post-procedural IMR and IS at 48-h and 6-month follow-up. Although higher IMR was observed more frequently in patients with MVO, the correlation between IMR and MVO was relatively weak (rho = 0.29). However, by applying a clinically relevant threshold of 40 for IMR (11), we observed a concordance between IMR and MVO in 73.6% of cases, with discordance in the remaining 36.4%. In this regard, previous studies have suggested that Doppler-derived hyperemic microvascular resistance might show a better concordance with MVO (25), even though its greater technical complexity and lower reproducibility make its application more challenging in clinical practice.

Patients with MVO and abnormal IMR had a significantly larger IS, and patients with no MVO and IMR ≤40 had the best outcome, with a significantly lower IS at 6-month follow-up. Importantly, patients with MVO but IMR ≤40 had a significantly smaller final IS than patients with both MVO and IMR >40. This observation was further corroborated by the fact that a significant regression in IS at 6 months was only seen in patients with MVO and IMR ≤40 and not in those with evidence of MVO and higher IMR.

These data illustrate an additive insight from measuring IMR in the assessment of infarct healing and prognosis. MVO on CMR is essentially an anatomic observation with no direct insight into the function of the coronary microvasculature. Together

FIGURE 3 IMR and MVO Discordance



Frequency of IMR-MVO discordance and distribution in the 4 groups stratified according to MVO and IMR. Pts = patients; other abbreviations as in Figures 1 and 2.

TABLE 3 Invasive Coronary Physiology and Cardiac Magnetic Resonance Imaging Parameters

	Overall (N = 110)	No MVO and IMR ≤40 (n = 42)	No MVO and IMR >40 (n = 9)	MVO and IMR ≤40 (n = 31)	MVO and IMR >40 (n = 28)	p Value
Post-stenting coronary physiology indices						
Baseline						
Pa_{mean}, mm Hg	93.9 ± 17.0	92.0 ± 20.2	92.5 ± 7.9	92.7 ± 10.9	94.7 ± 17.9	0.42
Pd_{mean}, mm Hg	86.0 ± 15.9	86.3 ± 19.0	88.4 ± 10.0	84.1 ± 13.1	87.0 ± 15.5	0.85
Transit time, s	0.75 (0.43-1.06)	0.57 (0.33-0.90)	1.00 (0.95-1.21)	0.71 (0.35-0.86)	0.99 (0.66-1.49)	**0.001**
Pd/Pa	0.95 ± 0.04	0.95 ± 0.05	0.96 ± 0.03	0.95 ± 0.04	0.94 ± 0.04	0.88
Hyperemia						
Pa_{mean}, mm Hg	79.8 ± 15.4	78.5 ± 15.6	78.9 ± 20.0	81.5 ± 14.3	79.8 ± 15.4	0.89
Pd_{mean}, mm Hg	73.4 ± 13.3	72.4 ± 13.0	70.9 ± 16.4	75.6 ± 13.2	73.2 ± 13.3	0.71
Transit time, s	0.40 (0.26-0.66)	0.30 (0.23-0.43)	0.62 (0.42-0.92)	0.34 (0.23-0.46)	0.86 (0.57-1.18)	**0.001**
FFR	0.93 ± 0.06	0.92 ± 0.06	0.94 ± 0.03	0.93 ± 0.05	0.92 ± 0.07	0.82
CFR	1.7 (1.2-2.2)	1.8 (1.3-2.4)	1.8 (1.1-2.8)	2.0 (1.4-2.4)	1.2 (1.0-1.6)	**0.004**
IMR	31.3 (20.0-44.1)	21.3 (14.4-32.5)	48.2 (42.4-50.9)	26.0 (17.7-31.3)	60.5 (44.1-74.5)	**0.001**
48-h CMR						
Time to CMR scan, h	38.4 ± 12.0	38.4 ± 7.2	38.4 ± 3.6	38.4 ± 7.2	38.4 ± 8.4	0.80
EDV, ml	161.6 ± 41.9	158.2 ± 42.2	162.5 ± 52.1	153.4 ± 40.3	176.2 ± 38.0	0.19
ESV, ml	88.1 ± 31.6	81.6 ± 28.5	91.0 ± 39.6	85.2 ± 28.4	100.2 ± 30.6	0.11
Stroke volume, ml	74.3 ± 19.5	77.1 ± 21.8	72.2 ± 12.3	69.3 ± 21.7	76.4 ± 14.2	0.35
Ejection fraction, %	47.0 ± 9.3	48.9 ± 8.2	49.1 ± 15.9	45.2 ± 8.4	45.5 ± 9.0	0.26
Area at risk, % of LV mass	41.2 (34.0-52.0)	36.6 (29.1-45.1)	45.0 (31.2-52.7)	47.8 (36.0-54.5)	49.0 (38.0-58.6)	**0.001**
Infarct size, % of LV mass	27.0 (16.1-37.5)	16.1 (9.0-25.3)	28.6 (9.4-40.8)	34.4 (27.3-41.0)	34.7 (23.0-44.4)	**0.001**
MVO, % of LV mass	3.7 (1.7-6.0)	-	-	2.8 (1.6-5.4)	4.6 (2.0-6.4)	0.26
Myocardial salvage index, %	36.1 (24.2-54.7)	52.8 (37.4-68.0)	31.1 (25.5-70.0)	28.0 (813.9-37.9)	28.8 (18.0-39.0)	**0.001**
Hemorrhage occurrence	37 (33.6)	-	-	16 (51.6)	21 (75.0)	0.10
Hemorrhage extent, %	2.0 (0.0-5.0)	-	-	1.0 (0.0-3.2)	3.0 (1.0-6.0)	**0.004**
6-month CMR						
Time to CMR scan, days	194.0 ± 20.0	195.6 ± 17.8	193.9 ± 21.6	192.7 ± 23.3	193.7 ± 21.0	0.73
EDV, ml	164.4 ± 41.3	157.3 ± 35.6	167.1 ± 44.0	157.0 ± 40.5	182.5 ± 45.7	**0.05**
ESV, ml	75.9 ± 31.6	67.1 ± 23.6	77.0 ± 31.4	77.2 ± 27.4	87.1 ± 40.0	0.08
Stroke volume, ml	85.8 ± 19.7	90.2 ± 20.2	90.0 ± 11.0	79.7 ± 22.4	84.6 ± 16.4	0.13
Ejection fraction, %	53.4 ± 10.7	57.9 ± 8.4	56.1 ± 10.4	51.6 ± 9.1	47.8 ± 12.7	**0.001**
Infarct size, % of LV mass	19.0 (10.1-29.3)	9.3 (4.1-14.3)	28.2 (9.2-29.7)	22.3 (16.0-30.0)	31.2 (25.0-39.5)	**0.001**

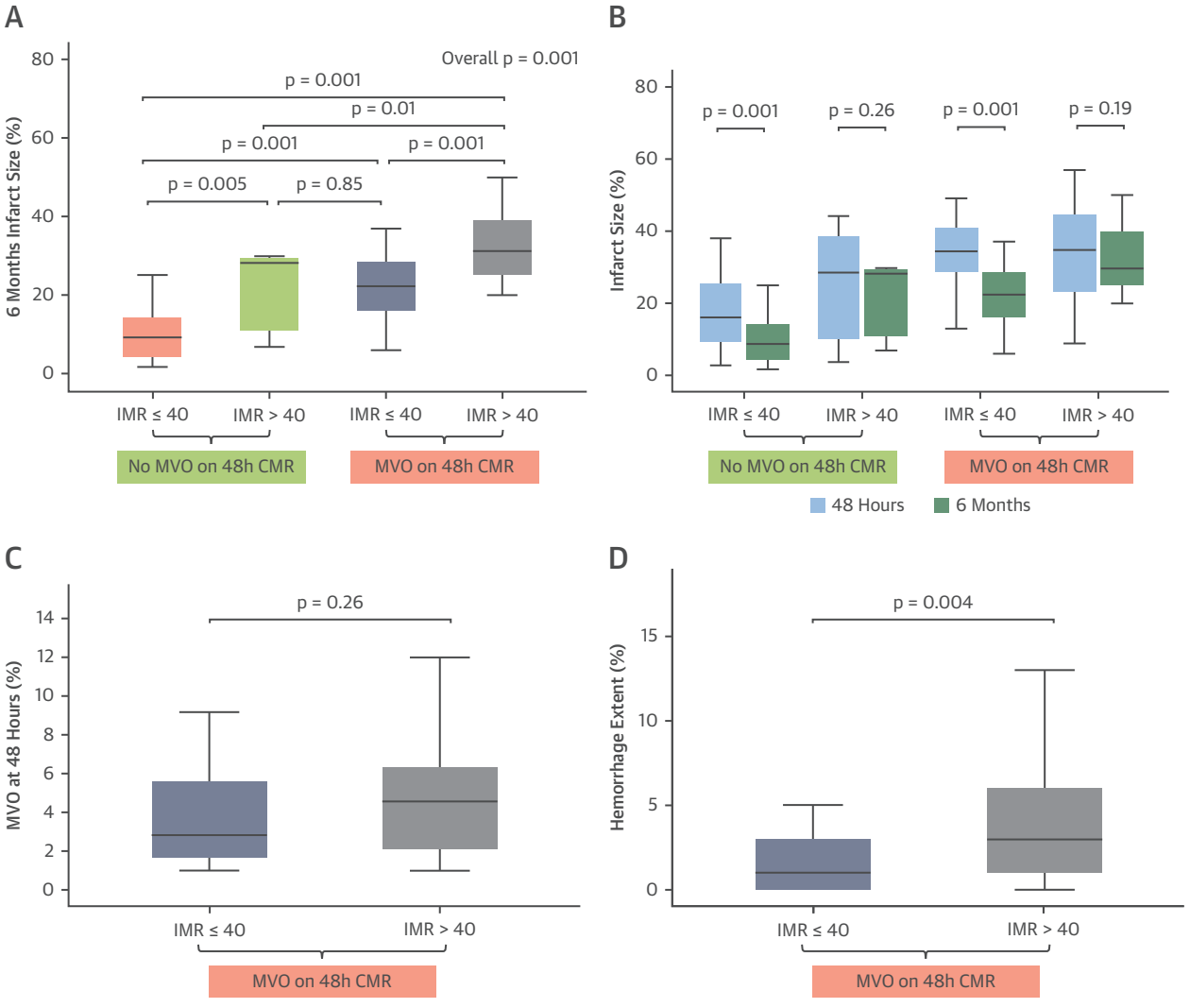
Values are mean ± SD or median (interquartile range). **Bold** p values areindicate significancet.

CFR = coronary flow reserve; CMR = cardiac magnetic resonance; EDV = end-diastolic volume; ESV = end-systolic volume; FFR = fractional flow reserve; LV = left ventricular; Pa = aortic pressure; Pd = distal pressure; other abbreviations as in Table 1.

with the presence of intramyocardial hemorrhage, it could be considered to be evidence of severe and potentially irreversible myocardial injury in that particular area. Conversely, IMR is a functional measure of the status and viability of coronary microvasculature within the entire distribution of the culprit vessel. Our data confirm the overlap between the anatomic microvascular impairment observed on CMR and the functional microvascular impairment depicted by IMR. However, these data also show that in nearly one-third of cases, there is a lack of concordance of these 2 parameters. When these circumstances occur, it is possible to assume that patients with MVO but IMR ≤40 are those in whom the ischemic or ischemic/reperfusion injury has been relatively small or partially contained, allowing for continued functional integrity of most of the coronary microvasculature. Additionally, by reflecting the status of the whole microvascular bed in the territory supplied by the culprit artery, IMR could be considered a marker of the integrity and viability of the watershed zones adjacent to the infarct core. Previous CMR and histopathology studies have shown how the integrity of the peri-infarct zone is ultimately responsible for the final extent of IS (26,27), and similarly, we observed that an IMR ≤40 was associated with a regression of IS at long-term follow-up even in the presence of MVO.

These data translate into the observation that when the microvascular bed is damaged irreversibly, IMR is likely to be high, whereas a lower IMR reflects the potential for recovery. This concept that IMR can aid in the understanding and exploration of the MVO

FIGURE 4 **CMR Findings in 4 Groups Stratified According MVO and IMR**



(A) Difference in infarct size at 6 months between 4 groups derived after stratification according to MVO and IMR. **(B)** Time trend in infarct size in the 4 groups. **(C)** MVO extent in patients with IMR ≤40 and >40. **(D)** Comparison of intramyocardial hemorrhage extent in patients with IMR ≤40 and >40. Abbreviations as in Figures 1 and 2.

phenomenon is in line with previous reports in which indices of coronary physiology provided insights into the process of microvascular healing post STEMI (14,28). Notably, when both functional (high IMR) and anatomic (MVO on CMR) impairment is evident, the long-term prognosis is significantly worse. Conversely, a margin of improvement and recovery can be expected when MVO is associated with some preservation of microvascular function, defined by IMR ≤40.

After correcting for baseline IS and MVO extent, we observed that in the presence of MVO, IMR >40 increased the risk of having IS >25% at 6 months by more than 10-fold. This observation could provide some pathophysiological explanation for the results recently reported by de Waha et al (4). de Waha et al. (4) reported in a pooled analysis of 7 trials that not only the occurrence of MVO but also its severity was prognostically relevant, with an MVO extent >1.55% significantly associated with worse 1-year clinical outcome. In our study, the ability of IMR to define a more severe degree of MVO was also suggested by the observation that patients with MVO and IMR >40 had a larger extent of intramyocardial hemorrhage, thus extending the results of previous studies that also showed an association

TABLE 4 Effect of IMR on 6-Month IS in Subgroup of Patients With MVO at 48-h CMR

	Univariate Analysis		Multivariate Analysis	
	Odds Ratio (95% CI) or Beta Coefficient	p Value	Odds Ratio (95% CI) or Beta Coefficient	p Value
Binary logistic regression (6-month IS >25%)				
Post-stenting TIMI flow grade >2	0.42 (0.11–1.53)	0.19	-	-
Post-stenting MBG >1	0.46 (0.46–1.46)	0.19	-	-
Complete ∑STR	0.94 (0.34–2.63)	0.91	-	-
Post-stenting CFR <2.0	2.20 (0.72–6.72)	0.17	-	-
Post-stenting IMR >40	6.67 (2.08–21.36)	**0.001**	11.9 (2.8–51.3)	**0.001**
48-h IS >25%	5.10 (1.01–9.21)	**0.05**	4.6 (0.9–22.3)	0.06
48-h MVO >1.55%*	3.90 (1.01–12.26)	**0.05**	3.70 (0.7–19.8)	0.12
Linear logistic regression (6-month IS)				
Post-stenting TIMI flow grade	−0.15	0.26	-	-
Post-stenting MBG	−0.20	0.13	-	-
Complete ∑STR	0.05	0.72	-	-
Post-stenting CFR, U	−0.23	0.09	-	-
Post-stenting IMR, U	0.28	**0.04**	0.28	**0.003**
48-h IS, % U	0.65	**<0.001**	0.61	**0.001**
48-h MVO, % U	0.41	0.01	0.17	0.09

Bold p values indicate significance. *The cutoff of 1.55% was selected according to de Waha et al (4).
CI = confidence interval; IS = infarct size; MBG = myocardial blush grade; other abbreviations as in Tables 1 and 3.

of IMR >40 and the occurrence of intramyocardial hemorrhage (12,13).

In our study, we also observed a small group of patients with higher IMR without evidence of MVO. Because of the low number of cases in this group (n = 9), definitive evidence is not possible, but it is interesting that these patients with impaired IMR and no MVO had no significant IS regression at 6 months. This observation gives further emphasis to the value of IMR, which presumably reflects extensive microvascular stunning or severe and long-lasting functional microcirculatory impairment in these cases without anatomic microvascular injury (MVO) at 48 h (29).

Our study explored for the first time the relationship between IMR and the acute evidence of MVO on CMR, reporting a discordance between these 2 parameters in nearly one-third of cases. IMR assesses the status of the coronary microvasculature, with significant implications for both the clinical/imaging cardiologist and the interventional cardiologist. Indeed, when combined with CMR findings, IMR can be used to grade the severity of MVO and to identify those patients at highest risk who might require more aggressive therapeutic strategies at follow-up. Our data further confirm previous reports (11,12,30) that a final IMR ≤40 could represent a reasonable criterion for the interventional cardiologist to judge the efficacy of pPCI in STEMI, which would enable ad hoc myocardial treatment options for those patients with IMR >40 while still in the catheterization laboratory.

STUDY LIMITATIONS. This study is a retrospective analysis of patients prospectively enrolled within the OxAMI study, so selection bias is possible, even though the 4 groups were well balanced for clinical and procedural variables. Patients were enrolled over a long period of time, and only patients with a full dataset for IMR and CMR were included. In this regard, a 19.9% dropout rate was observed at 6-month follow-up, with 190 patients of 237 completing the protocol with 6-month CMR.

CONCLUSIONS

We report for the first time the potential of IMR to depict 2 main types of MVO (functional vs. anatomic); however, it should be acknowledged that only minimal insights into the mechanisms accounting for the discordance between IMR and MVO are provided. Potentially interesting insights into the role of glycoprotein IIb/IIIA inhibitors in the pathogenesis of MVO in STEMI were not possible because of the non-randomized nature of the study and different drug administration strategies (by intention vs. bailout).

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: A mismatch between anatomic and functional microvascular indices can appear in nearly one-third of STEMI patients. Even in the presence of MVO, an IMR ≤40 is significantly associated with a greater chance of IS regression at 6-month follow-up.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Although MVO remains the current gold standard to assess microvascular injury, IMR can be applied as a marker of the functional severity of microvascular injury and as a possible marker of viability of the peri-infarct zone. If applied in combination with CMR, IMR can be helpful in grading the severity of MVO on top of MVO extent or hemorrhage occurrence, enabling the identification of those patients who require more aggressive follow-up and medical management. At the same time, in line with previous reports, IMR ≤40 is confirmed as a reasonable criterion to assess the success and efficacy of pPCI, which enables early identification, in the catheterization laboratory, of high-risk patients who could benefit from ad hoc additional or alternative therapeutic strategies.

TRANSLATIONAL OUTLOOK: Additional studies are required to explore the efficacy of an IMR-guided approach for selecting high-risk STEMI patients who require more aggressive therapeutic strategies. Similarly, additional studies are needed to assess whether a combined approach that integrates IMR and MVO for risk stratification in STEMI is plausible and cost-effective.

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KEY WORDS index of microcirculatory resistance, microvascular obstruction, primary percutaneous coronary intervention, ST-segment elevation myocardial infarction

APPENDIX For an expanded Methods section as well as a supplemental figure, please see the online version of this paper.