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Clinical associations of microvascular obstruction and intramyocardial hemorrhage on cardiovascular magnetic resonance in patients with acute ST segment elevation myocardial infarction (STEMI)

An observational cohort study

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Abstract

Acute myocardial infarction (AMI) is recognized as being a life-threatening event. Both microvascular obstruction (MVO) and intramyocardial hemorrhage (IMH) have been recognized as poor prognostic factors in myocardial infarct (MI) since they adversely affect left ventricular remodeling. MVO refers to small vessels changes that prevent adequate tissue perfusion despite revascularization whereas IMH is a severe form of MVO. A limited number of studies have demonstrated the segmental intervention time and the clinical factors in the presence of MVO and IMH. Therefore, we aimed in this study to determine the correlations of the intervention-associated and clinical indexes with malignant cardiovascular magnetic resonance (CMR) signs in patients with AMI.

Sixty-three patients with STEMI who underwent primary percutaneous coronary intervention (PPCI) within 12 hours were included in this study. A 3.0-T CMR scan was prescribed, and the subsequent image analysis was conducted by researchers blinded to the clinical index results. Late-gadolinium enhancement (LGE) and T2* sequences were mainly used for MVO and IMH identification and quantification.

Patients exhibiting both MVO and IMH had the highest level of LGE ($P < .001$) and were significantly more frequently assigned to a pre-PPCI thrombolysis in myocardial infarction (TIMI) flow class of 0 (n=25, 89.3%). The MVO size correlated positively with the IMH size ($r = 0.81$, $P < .01$). A pre-PPCI TIMI flow class of 0 was found to reliably predict the presence of IMH ($P < .001$). Patients who received the intervention 4 to 6 hours after MI onset were more likely to exhibit MVO and IMH, although this trend was not statistically significant.

We showed in our study that both MVO and IMH correlated with the degree of AMI and the pre-PPCI coronary flow, and both tended to occur more frequently in cases involving an interval of 4 to 6 hours between the onset of MI and the intervention. CMR is a reliable method for assessing MVO and IMH and its imaging features following gadolinium administration are characteristic. These findings stress the importance of using CMR in evaluating and improving the outcome of the medical management.

Abbreviations: AMI = acute myocardial infarction, CMR = cardiaovascular magnetic resonance, IMH = intramyocardial hemorrhage, LAD = left anterior descending branch, LAX = long axis view, LCX = left circumflex branch, LGE = late gadolinium enhancement, LV = left ventricular, LVR = left ventricular remodeling, MVO = microvascular obstruction, PPCI = primary percutaneous coronary intervention, RCA = right coronary artery, SAX = short axial view, STEMI = ST segment elevation myocardial infarction, TIMI = Thrombolysis In Myocardial Infarction.

Keywords: cardiovascular magnetic resonance imaging, intramyocardial hemorrhage, microvascular obstruction, STEMI

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1. Introduction

Acute myocardial infarction (AMI) is a life-threatening disease that affects the human populations in the worldwide scale.[1] Although early successes and optimal primary percutaneous coronary intervention (PPCI) myocardial reperfusion have effectively reduced the mortality of myocardial infarction (MI),[2] the substantial patients still have continued to experience the poor clinical outcomes due to the insufficient restoration of microvascular function and the suboptimal myocardial perfusion, which have been referred to as the "no-reflow" phenomenon. Accurate detection of "no-reflow" is crucial on account of that it is independently associated with adverse ventricular remodelling (LVR) and the clinical prognosis.[3] Therefore, cardiaovascular magnetic resonance (CMR) provides the most comprehensive assessment of MVO and IMH.

In previous CMR studies, microvascular obstruction (MVO) or "no-reflow," which refers to the small vessel changes that prevent adequate tissue perfusion despite revascularization and an open epicardial coronary artery,[4] and intramyocardial hemorrhage (IMH), which is caused by prolonged ischemia/reperfusion injury[3] were believed to be independent predictor of major clinical adverse events.[5,6] They elicited considerable scientific interests,[7] especially IMH which has been increasingly recognized as a stronger poor prognostic indicator[8] as well as a marker of adverse in LVR.[9]

Many previous studies have only focused on the prognostic values of MVO[10,11] and IMH[12] among patients with AMI; however, a limited number of studies have demonstrated the potential effects of PPCI strategies, especially the segmental intervention time, as well as the pre-PPCI clinical factors on the presence of MVO and IMH, including HeartScore and laboratory parameters (e.g., platelet to lymphocyte ratio, neutrophil to lymphocyte ratio). Accordingly, we hypothesized that the mentioned pre-PPCI clinical indexes and PPCI related strategies may have an impact on the re-perfusion conditions of AMI patients' blood vessels, and thus play a predicting role for the presence of MVO and IMH.

2. Methods

2.1. Study population

This prospective single-center study consecutive enrolled patients with acute ST segment elevation myocardial infarction (STEMI) who were admitted to the chest pain center and underwent angiography and PPCI at our institution from September 2016 to March 2017. Patients younger than 75 years and those who experienced an interval from the time of symptom onset to PPCI of ≤12 hours were considered for inclusion. The main STEMI diagnostic criteria were based on the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) and European Society of Cardiology (ESC) definitions.[13]

The exclusion criteria included a previous history of cardiac shock, defined as a systolic blood pressure<90 mm Hg and the use of inotropic agents, an implant intra-aortic balloon pump (IABP), or extracorporeal membrane oxygenation (ECMO); thrombolysis; previous MI; valvular disease; coronary artery bypass grafting (CABG); cardiomyopathy; congenital heart disease; malignant arrhythmia; renal dysfunction, defined as a glomerular filtration rate of <30 mL/min, 73 m^2; chronic obstructive pulmonary disease (COPD); pregnancy; and a contraindication to CMR imaging (e.g., pacemaker, claustrophobia). 63 first-attack STEMI patients remained. Basic clinical

data of each patient were recorded. The HeartScore was computed after summarizing the 5 baseline indexes including history, electrocardiogram, age, risk factors, and initial troponin following the guidelines from the ESC.

All patients were administered 300 mg of oral aspirin and 300 mg of clopidogrel or 180 mg of ticagrelor before revascularization. The prescriptions of anticoagulants, glycoprotein IIb/IIIa inhibitors, and thrombus aspiration via an Export aspiration device (Medtronic, Inc., Dublin, Ireland) were left to the physician's discretion. Subsequently, all patients received a dual-antiplatelet drug (aspirin, clopidogrel or ticagrelor), β-blocker agent, angiotensin-converting enzyme inhibitor (ACEI), and or angiotensin receptor (ARB) blockers and statins per the standard of care, in accordance with the current guideline[14] and individual characteristics. All 63 patients underwent an initial CMR scan at 3.0 ± 1.1 days post-PPCI, and all the patients follow-up 1 year after PPCI.

The study protocol was reviewed and approved by the institutional ethics committee of West China Hospital (Ethical approval No. 2016 (337)), and all patients provided written informed consent to participate. All procedures were conducted in accordance with the Declaration of Helsinki, 2000 revision.

2.2. Image acquisition

All patients were examined in the supine position using a 3.0-T whole-body scanner with an18-element body phased arraycoil (Skyra; Siemens Medical Solutions, Erlangen, Germany). The manufacturer's standard ECG-triggering device and the breath-hold technique were used to monitor the individuals' ECG values and breathing, respectively. Standard 2-, 3, and 4-chamber cine images were acquired using a TrueFISP sequence with a slice thickness of 8 mm. Gadolinium (Gadodiamide, GE Healthcare, Ireland) was injected at a dose of 0.1 mL/kg body weight, and late gadolinium-enhanced (LGE) images were acquired after 10–15 minutes (repetition time [TR]/echo time [TE], 512/1.24 ms; field of view [FOV], 380 mm × 320 mm; flip angle, 40°).

2.3. Image data analysis

The image data were analyzed using commercially available software (cvi^{42}; Circle Cardiovascular Imaging, Inc., Calgary, Canada). Two experienced observers (MXY and YZ) who were blinded to the clinical data independently and sequentially evaluated the regional myocardial dysfunction, infarct distribution and size, MVO, and IMH using images from each patient. Discrepancies between the 2 observers were referred to another trained radiologist (KYD). The analysis was conducted according to previously published guidelines[15] and was based on the 16 AHA segmentation in the form of a bulls-eye plot.[16]

Infarct myocardium was defined as an area of LGE; this was detected using a computer-aided threshold of >5 standard deviations (SDs) from the remote myocardium and adjusted manually (Fig. 1), and quantified using the multiple short-axis slice view. MVO was defined as the core area of nonenhancement within an LGE region,[17] and was determined semiautomatically in accordance with previous studies. IMH was defined as a hypointense lesion (<20 ms) within the MVO region on a T2* sequence. All the above measurements results were expressed both in mass (g) and percentage of the left ventricle (%) since no standard, or preferred scenario had been decided for this quantification and considering comparison convenience with
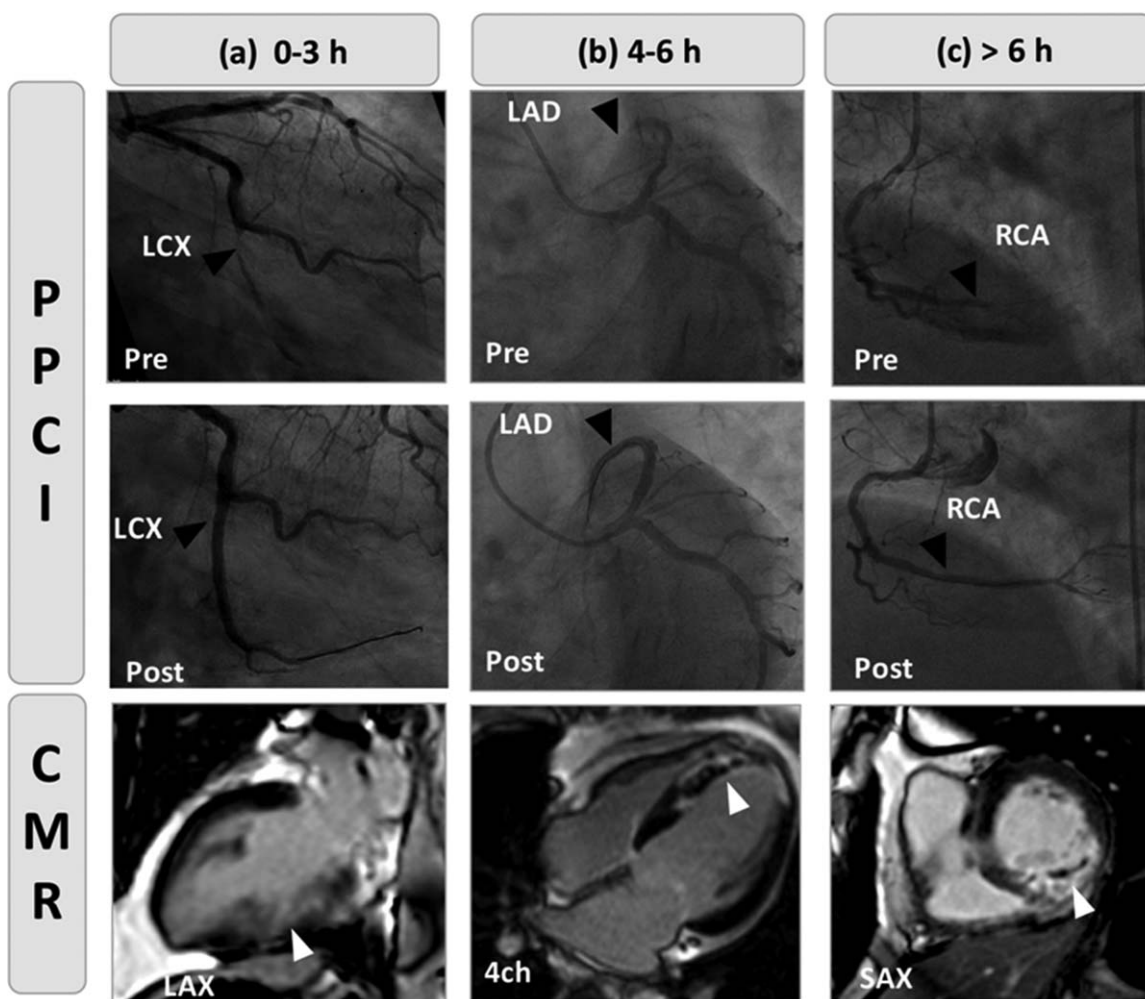
Figure 1. Representative images of PPCI and the corresponding cardiovascular magnetic resonances. (A) In Case 1, a 61-year-old man was admitted to the hospital 1 hours after symptom onset. The culprit artery was the LCX, and his pre-and post-PPCI TIMI flow statuses were II and III, respectively. Post-PPCI CMR revealed LGE (+) at the inferior wall of the LV, without MVO and IMH. (B) In Case2,a 50-year-old man was admitted to the hospital 4 h after symptom onset. The culprit artery was the LAD, and his pre- and post-PPCI TIMI flow statuses were I and III, respectively. Post-PPCI CMR revealed a lesion and both MVO (+) and IMH (+) on the anterior wall of the LV. (C) In Case3, a 64-year-old man was admitted to the hospital 9 hours after symptom onset. Here the culprit artery was the RCA. His pre-and post-PPCI TIMI flow statuses were 0 and III, respectively. Post-PPCI CMR revealed a lesion that was MVO (+) but IMH (−) on the inferior wall of the LV. All culprit arteries are identified with black triangles, and the infarction regions identified on CMR are marked with white triangles. 4ch=4 chamber view, CMR=cardiovascular magnetic resonance, IMH=intramyocardial hemorrhage, LAD=left anterior descending branch, LAX=long axis view, LCX=left circumflex branch, LGE=late-gadolinium enhancement, LV=left ventricular, MVO=microvascular obstruction, PPCI=primary percutaneous coronary intervention, RCA=right coronary artery, SAX=short axial view, TIMI=thrombolysis in myocardial infarction.

other studies, we record both. Cardiac function analysis of the left ventricle was performed as previously described.[18]

3. Statistical analysis

Continuous and categorical data are presented as means ± SDs and frequencies, respectively. Nonparametric variables are expressed as medians with interquartile ranges. The Wilcox and Chi-square tests were applied where appropriate. Comparisons between 3 groups were made using an analysis of variance. Single and multiple linear regression analyses were conducted to evaluate correlations between continuous data, and a logistical regression analysis was used to calculate the increased log-odds in favor of the events of interest according to a per unit increase in the related factor, and the results and corresponding interquartile ranges were subsequently transferred. Density plots were used to demonstrate within-group differences, and bubble plots were used to illustrate the possibilities predicted by the multivariate logistic regression model. A P value of $<.05$ was considered statistically significant, and the Bonferroni P value adjustment was applied when further comparisons between the 2 groups were intended. All statistical analyses were conducted using R statistical software (v. 3.3.1; R Project for Statistical Computing, Vienna, Austria).

4. Results

4.1. Patient baseline characteristics

The baseline characteristics of the subjects are presented in Table 1. The 63 first-attack STEMI patients included 57 men and 6 women with a mean age of 55.2 ± 9.3 years (median age, 54 [36–74] years) in this study. As anticipated, our experiments demonstrated that 35 (55.6%) and 28 (44.4%) patients

Table 1

Baseline clinical and laboratory characteristics of STEMI study participants.

Characteristic	Mean ± SDs or frequencies
Age, years (mean ± SD)	55.2 ± 9.3
Male sex, n (%)	57 (90.5%)
BMI, kg/m²	25.1 ± 3.4
Risk factors, n (%)	
Smoking	50 (79.4%)
Hypertension	29 (46.0%)
Dyslipidemia	13 (20.6%)
Diabetes mellitus	10 (15.9%)
HeartScore	7.8 ± 0.9
Infarct-related coronary artery, n (%)	
LAD	35 (55.6%)
LCX/RCA/LCX+RCA	28 (44.4%)
Pre-PCI TIMI flow grade, n (%)	
TIMI flow 0 and I	51 (81.9%)
TIMI flow II	8 (12.7%)
TIMI flow III	3 (4.8%)
Post-PCI TIMI flow grade, n (%)	
TIMI flow 0 and I	0 (0%)
TIMI flow II	1 (1.6%)
TIMI flow III	62 (98.4%)
Pain onset to reperfusion (hour, mean ± SD)	4.7 ± 2.4
Door-to-device time (min, mean ± SD)	49.5 ± 14.8
Concomitant medication, n (%)	
Aspirin	65 (100%)
Clopidogrel or prasugrel	65 (100%)
ACEI/ARB	16 (25.4%)
β-Blocker	26 (41.3%)
Statins	65 (100%)
Initial results in admission	
Hemoglobin, g/L	149.4 ± 16.3
cTnT, ng/L	57.5 (14.6–154.7)
Leukocyte cell count (×10⁹/L)	11.0 ± 3.7
Neutrophil (%)	78.9 ± 10.2
Lymphocyte cell count (×10⁹/L)	1.63 ± 0.8
Platelet count, (×10⁹/L)	179.5 ± 121.1
Plasma glucose, mmol/L	8.7 ± 3.0
SBP, mm Hg	121.4 ± 21.5
DBP, mm Hg	78.2 ± 16.0
LVEF (%)	54.2 ± 9.1
PPCI procedure data	
Stent width, mm	3.1 ± 0.4
Stent length, mm	28.0 ± 0.8
Stent type, PE/GuReater (%)	51 (81.0%)/12 (19.0%)
Number of stents	1.2 ± 0.5
Thrombectomy, n (%)	18 (28.6%)
MVO/IMH present	
MVO⁺, n (%)	38 (60.3%)
IMH⁺, n (%)	27 (42.9%)
Baseline CMR scan, days	3.0 ± 1.1

Data were presented as mean ± SD, median (IQR), or n (%) as appropriate.

presented with anterior and nonanterior MI, respectively. Significantly, 50 (79.4%) patients reported a smoking history, hypertension (n=29, 46.0%), dyslipidemia (n=13, 20.6%) and diabetes mellitus (n=10, 15.9%), which were the most common comorbidities. Those included patients had an average HeartScore of 7.8 ± 0.9.

Regarding the PPCI procedure, we found that the average time of pain onset to reperfusion and door-to-device intervals were 4.7 ± 2.4 hours and 49.5 ± 14.8 minutes, respectively. All patients

received the dual antiplatelet therapy and statin therapy, while 16 (25.4%) and 26 (41.3%) patients were prescribed ACEIs and β-blocker therapies, respectively. PROMUS Element Plus (PE) stents were used in 81.0% of the patients, while and Co-Cr sirolimus-eluting coronary stents (GuReater) were used in 19.0% of the patients, with mean stent widths and lengths of 3.1 ± 0.4 mm and 28.0 ± 0.8 mm, respectively. Around 51 (81.9%) patients experienced a severe coronary occlusion and were classified as having a pre-PPCI thrombolysis in myocardial infarction (TIMI) flow of 0 or I, and 62 patients achieved a post-PPCI TIMI flow of III. Moreover, it was interesting to note that 18 patients underwent thrombectomy during the intervention.

4.2. CMR analysis

The mean interval time between PPCI and the subsequent CMR examination was 3.0 ± 1.1 days. At this time, patients were further divided into 3 groups on the basis of the presence of MVO and/or IMH (Fig. 2). In this study, 40 patients (63.5%) presented with MVO and 28 patients (44.4%) presented with IMH. The frequency of patients with a pre-PPCI TIMI flow class of 0 was higher among patients who exhibited both MVO and IMH, compared to patients without MVO, although this difference was not statistically significant (P=.08251) (Fig. 3C). Furthermore, the LGE size significantly differed in the 3 groups (P<.001), although the MVO (−) and MVO (+) groups did not differ. No significant differences between intergroups were observed in any of the baseline characteristics, the clinical routine laboratory investigation findings, the door-to-device time, and the CMR-assessed cardiac function (Table 2).

A linear regression model analysis revealed positive correlations of the MVO size with the IMH size (r=0.81, P<.001) and LGE size (r=0.67 for IMH (−) and r=0.45 for IMH (+)) (Fig. 3A and B). Furthermore, there were significant predictors of the MVO size (r=0.91, P<.001) included age, HeartScore, history of hyperlipidemia, smoking status, platelet to lymphocyte ratio, LGE size, and IMH size in a multivariate linear regression analysis (Fig. 3C).

Additionally, a logistic regression model analysis identified the MVO size (odds ratio: 1.28, 95% confidence interval [CI]: 1.07–1.63, P=.018), the LGE size (odds ratio: 1.07, 95% CI: 1.03–1.11, P<.001), and a pre-PPCI TIMI flow class of 0 (odds ratio: 1.51, 1.17–1.94, P<.001) as reliable predictors in the presence of IMH. Meanwhile, a multivariate model analysis of IMH predictors revealed discernible differences in both the LGE size and the MVO size, and the corresponding bubble plot is presented in Figure 3D.

4.3. Intervention time analysis

A density plot revealed a tendency toward higher prevalence rates of both MVO and IMH among patients who were referred to PCI within 4 to 6 hours after the onset of MI (Fig. 4). All patients (100%) referred within this interval were LGE (+), with a mean LGE of 31.3 g corresponding to 28.5% of the LV volume. Furthermore, 72.4% and 51.7% had patients an MVO and IMH, respectively. Despite the observed differences, however, no significant difference was identified between the patients referred within 3 h and those referred beyond >6 hours with respect to the above-mentioned indexes (Table 3). Further comparison between the patients with different onset-to-PPCI time interval showed no significantly clinically associated differences.
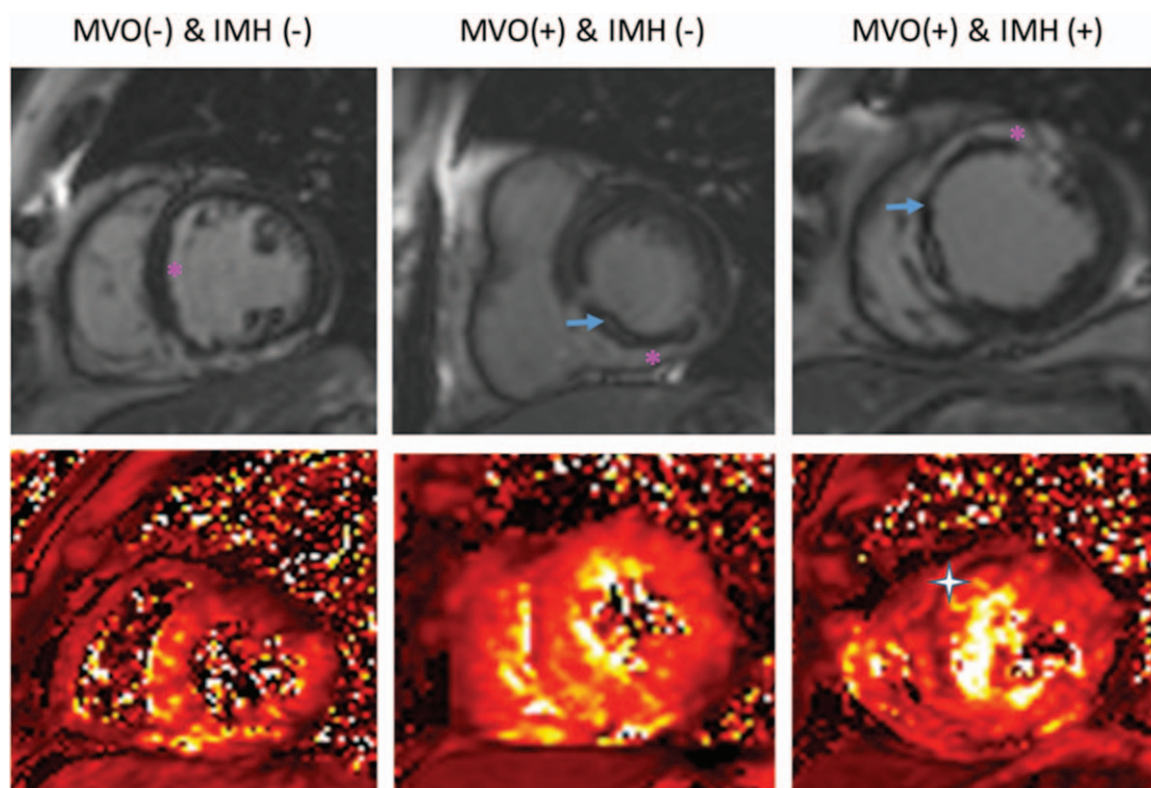
Figure 2. Representative CMR images of patients stratified by the presence of MVO and IMH. All images depict the SAX view at the middle of the left ventricle. The upper 3 scans were obtained with the LGE sequence, and the lower 3 depict the color-maps yielded byT2* scans. Purple asterisks indicate myocardium with LGE, blue arrows indicate regions with MVO, and white 4-pointed stars indicate regions with IMH, which appeared as areas of low signal on T2*sequences. CMR = cardiovascular magnetic resonance, IMH = intramyocardial hemorrhage, LGE = late-gadolinium enhancement, MVO = microvascular obstruction, PPCI = primary percutaneous coronary intervention, SAX = short axial view.

5. Discussion

In this single-center study, which prospectively recruited 63 continuous first-time STEMI patients with an interval from symptom onset to PPCI of <12 hours, we demonstrated a moderate correlation between current MI-related CMR evaluation indexes. Compared with previous studies, the patients enrolled in our study tended to be younger, although the incidences of MVO[19] and IMH[20] were comparable. In fact, our recruited population also contained a considerably higher percentage of male patients, which we primarily attribute to the more frequent exclusion of female STEMI patients who more often experience difficulty with completing the CMR examinations.[12] We noted couple of clinical risk factors including the commonly body mass index, the high percentage of current smokers, and cardiovascular comorbidities such as hypertension, diabetes, and dyslipidemia, which were similar with the group of patient recruited in the previous studies in this field. Other laboratory indexed of our patients showed identical level to prior studies.

Our findings were in accordance with the gold-standard rescue time for AMI patients (<3 hours). Meanwhile, our analysis suggested that intervention would be required pay special attention during a slightly later time interval. According to postulations regarding the development of microvascular injuries,[21] MVO can be attributed to compression from swelling cardiomyocytes in response to ischemic injury, as well as to substances produced by unstable atherosclerotic plaques, platelet microthrombi, and neutrophils or other recruited vasomotor and thrombogenic substances in response to later reperfusion injury. Consequently interventions should give special attention to the particular problem during the period when the injured myocardium is most susceptible to reperfusion injury, in order to maximize therapeutic benefits while minimizing reperfusion harm. According to our density plot, patients treated within 4 to 6 hours after symptom onset exhibited a definite tendency toward an increased risk of MVO. Although this difference was not statistically significant, this might be an effect of the small number of recruited patients. Furthermore, no differences were observed for the clinically associated indexes such as pre-TIMI flow, HeartScore and others which showed significant associations with the presence of MVO and IMH. Surprisingly, it also gave a clue that the different tendency in the presence of MVO and IMH might be attributed to the time differences. Further studies would be needed to confirm whether or not patients at this time window need to take special measures for the performance of PPCI.

As expected, CMR analyses were conducted at an average of 3 days after PPCI, in accordance with reports describing the relatively stable stage with respect to MVO and IMH.[20] Our CMR findings suggest a strong correlation between IMH and the MVO area, and our subgroup analysis revealed a more significant correlation between the LGE size and MVO size in IMH-negative cases. This latter finding supports the non-negligible effects of IMH on the myocardial size quantified by LGE, in accordance with previously published results, and confirms the need to establish the MVO and IMH statuses when evaluating the myocardial injury.[19–22] We noted that previous studies also
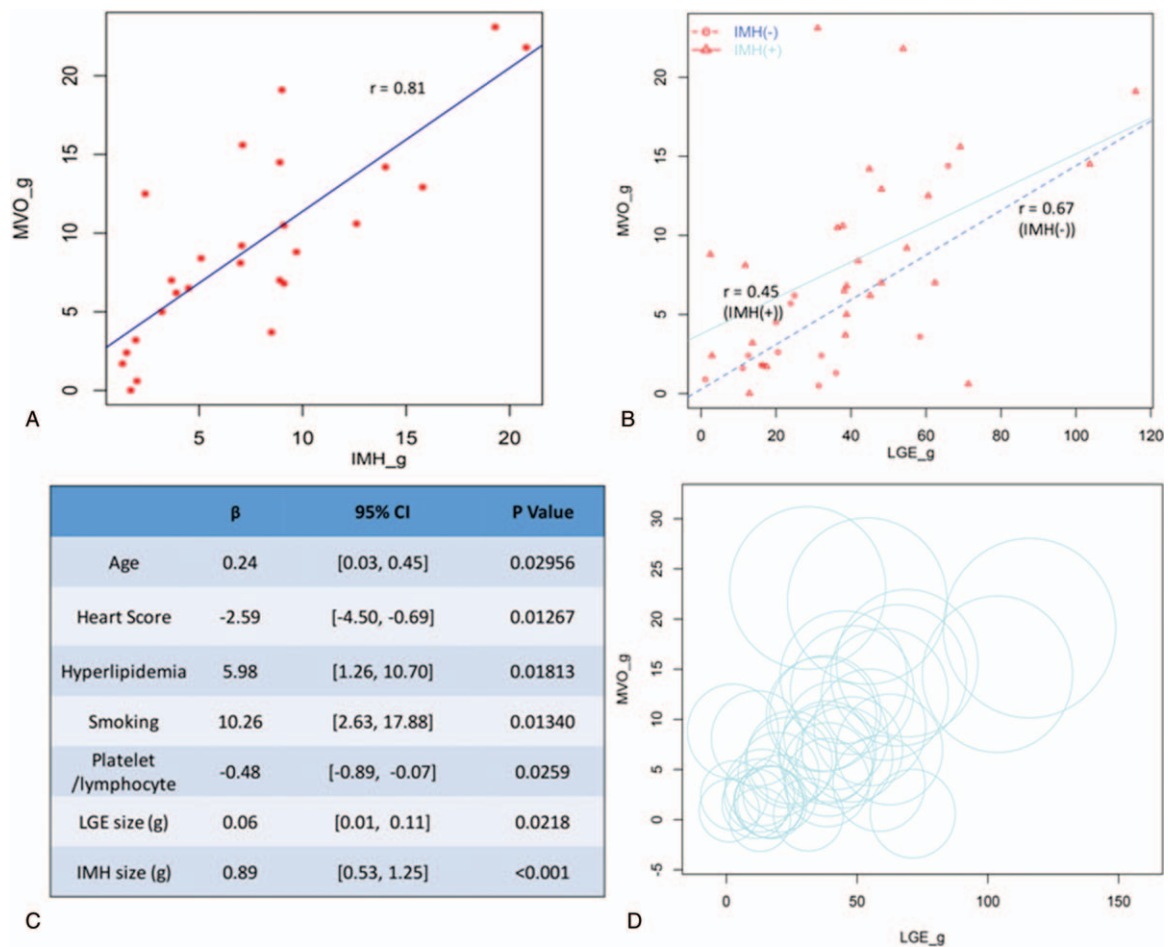
Figure 3. The results of linear regression and multivariate regression analyses. (A) Linear regression analysis of the sizes of IMH and MVO (*r* = 0.81). (B) Linear regression analysis of the sizes of MVO and LGE in the presence or absence of IMH. (C) Multivariate regression analysis. (D) Bubble plot demonstrating the potential use of 2 quantitative factors, the sizes of MVO and LGE, to predict the presence of IMH. IMH = intramyocardial hemorrhage, LGE = late-gadolinium enhancement, MVO = microvascular obstruction.

reported the pre-PPCI flow grade as a risk factor for the presence of MVO and IMH.[23] In our study, although we observed no significant difference in the pre-PPCI TIMI flow grade distribution, logistic regression analysis identified this parameter as a predictor of MVO and IMH.

However, our study obtained mixed results with respect to the relationships between clinical factors and quantitative imaging results. First, no significant difference was observed in this study regarding the clinical indexes, although patients with MVO and IMH exhibited a visually reduced left ventricular ejection fraction; On the other hand, a multivariate linear regression conducted in our study identified the age, HeartScore, history of hyperlipidemia, smoking status, platelet to lymphocyte ratio, LGE size, and IMH size as significant predictors of the MVO size. Those negative results were evident with an earlier study by Bekkers et al,[22] however, a more previous study regarding the blood test indexes by Carrick et al.[20] reported noticeable differences in the leukocyte and neutrophil counts among patients categorized into different groups according to CMR signs. The Carrick and colleagues acquired the CMR images used in their study on the second day post-MI, when the MVO and IMH were still plastic, although these differences might be attributable to the small number of recruited patients. For the multivariate analysis, HeartScore had been identified as a significant index for high risk

and a HeartScore > 7 had been proven to predict major adverse cardiovascular event for AMI patients.[24,25] Our study reported the predictive value of this index on MVO size, in agreement of the clinical significance of HeartScore considering that MVO size was also proven to be a positive predictor of the significant adverse cardiovascular event for AMI patients.

As is well known, various CMR sequences to detect MVO and IMH, we still preferred LGE and T2*-weighted sequences in the present study. We found that the MVO was more stable on the LGE sequence and better correlated with follow-up LV remodeling, as suggested for clinical use,[27] although another study reported that LGE underestimated the final MVO size relative to first-pass perfusion (FFP).[26] Furthermore, a 3-slice short-axis FFP scan does not provide complete coverage of the left ventricle, and its use has inevitably been responsible for more deviations, compared with the LGE.[28] For IMH detection, a T2* sequence is preferable, given its advantageous ability to more sensitively detect subacute hemorrhages when compared with hypointense T2 mapping core or T1-weighted sequences, as well as its reported insensitivity to myocardial edema.[29] Our results additionally demonstrated a lower incidence of IMH and a smaller detected IMH size relative to the MVO size, in accordance with the postulation that the IMH occurs subsequently to MVO.[30]

Table 2

Cardiac magnetic resonance findings.

Characteristic	Symptom onset to PCI time			P value
	0–3 hours, n = 22	4–6 hours, n = 29	>6h, n = 12	
Age	53.1 ± 8.9	54.8 ± 9.0	60.1 ± 10.0	.1089
BMI	24.6 ± 3.5	25.6 ± 3.5	24.7 ± 2.9	.5277
Risk factors				
HTN, n (%)	7 (31.8%)	15 (51.7%)	7 (58.3%)	.2348
DM, n (%)	6 (27.3%)	4 (13.8%)	0 (0%)	.1054§
Hyperlipidemia, n (%)	2 (9.1%)	10 (34.5%)	1 (8.3%)	.04296§
Smoking, n (%)	18 (81.8%)	25 (86.2%)	7 (58.3%)	.1255§
Clinical index				
PLT/Lymph	13.9 ± 7.2	12.5 ± 6.2	12.7 ± 5.9	.7403
Neu/Lymph	7.7 ± 5.4	6.3 ± 4.4	6.3 ± 3.4	.5071
Heart Score	7.5 ± 1.0	8.0 ± 0.9	8.1 ± 0.8	.105
LVEF, (%)	52.7 ± 10.6	50.0 ± 11.3	51.4 ± 10.4	.6912
Pre-TIMI				.3599§
TIMI flow 0	14 (63.6%)	19 (65.5%)	11 (91.7%)	
TIMI flow I	2 (9.1%)	6 (20.7%)	0 (0.0%)	
TIMI flow II	4 (18.2%)	3 (10.3%)	1 (8.3%)	
TIMI flow III	2 (9.1%)	1 (3.4%)	0 (0.0%)	
CMR findings				
LGE present, n (%)	21 (95.5%)	29 (100%)	11 (91.2%)	.3457
MVO present, n (%)	13 (59.1%)	21 (72.4%)	6 (50.0%)	.3461
IMH present, n (%)	8 (36.4%)	15 (51.7%)	5 (41.7%)	.5375

BMI = body mass index, DM = diabetes mellitus, HTN = hypertension, LGE = late gadolinium enhancement, LVEF = left ventricle ejection fraction, Lymph = lymphocyte, MVO = microvascular obstruction, Neu = neutrophil, PLT = platelet, Pre-TIMI = the TIMI score evaluated before percutaneous coronary intervention.

§ Chisq-test might be incorrect for these items because of not even distribution of the tests numbers.

6. Study limitations

We are aware that our research may have several limitations. First, this was a single-center study with a relatively small sample, and the inherent bias could have affected the accuracy and efficacy of our statistical analysis. However, this trial implemented rigorous inclusion criteria to reduce the risk of confounding bias. Moreover, few studies have been reported in this area, which can contribute to the value of our research. Second, we initially included patients with the unstable post-PPCI status (e.g., higher Killip class; cardiogenic shock; need to implant IABP and/or ECMO), who comprise the highest-risk group. Accordingly, our study interpretation should be considered in light of low- and moderate-risk STEMI patients. Third, the intervention time categories were not pre-specified, which might also have led to the bias existed. Experimental studies are needed to confirm these findings in the future. Last, we failed to determine the exact corresponding slices for the comparison of interested lesions on various sequences when we were limited by the scanning features of the CMR methods. However, our study warrants the continuation of our research to include future assessments, such as prognosis analyses, in hopes of providing a more comprehensive evaluation.

7. Conclusions

The evidence from this study intimates that both MVO and IMH correlated strongly with the infarct sizes determined from CMR LGE sequences, as well as a clinical index that included the pre-PPCI TIMI flow, hyperlipidemia, smoking status, and platelet to lymphocyte ratio. Therefore, we have devised a methodology that both MVO and IMH are malignant imaging markers in patients with STEMI. Furthermore, our study indicated a higher occurrence of MVO and IMH among STEMI patients who received reperfusion therapy between 4 and 6 hours after symptom onset. The further investigations need to determine whether these extensive lesions are a consequence of differences in reperfusion time, and whether those patients can expect a poorer prognosis.

Author contributions

MM and DKY conceived of the study, and participated in its design and coordination and drafted the manuscript. GYK for help with designing the imaging protocol. YMX and ZY helped with the image analysis. ZY was responsible for the clinical data analysis. YZG and HY are both the study guarantors, had full access to the data in the study and take responsibility of the study design and the accuracy of the data analysis, and had the final responsibility to submit for publication. All authors read and approved the final manuscript.

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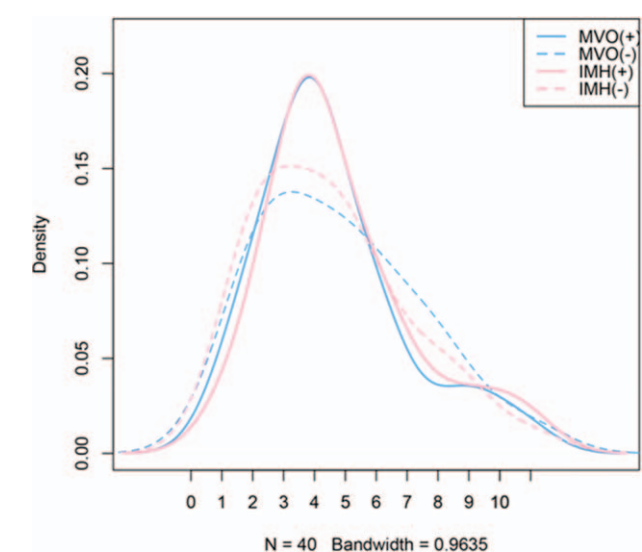**Project administration:** Min Ma, Zhi-gang Yang, Kai-yue Diao.
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Supervision: Zhi-gang Yang, Ying-kun Guo, Yong He.
Writing – original draft: Min Ma.

Figure 4. Density plot of the presence of MVO and IMH among patients admitted at different time intervals after symptom onset. IMH = intramyocardial hemorrhage, MVO = microvascular obstruction.

Table 3

MVO and IMH's.

Characteristic	MVO (−) and IMH (−) (n=23)	MVO (+) and IMH (−) (n=12)	MVO (+) and IMH (+) (n=28)	P value
Age	57.1±9.4	54.0±5.8	51.5±11.1	.4945
BMI	24.9±3.3	24.5±3.6	25.5±3.4	.6996
Risk factors				
HTN, n (%)	11 (47.8%)	8 (66.7%)	10 (35.7%)	.1934
DM, n (%)	5 (21.7%)	2 (16.7%)	3 (10.7%)	.5609
Hyperlipidemia, n (%)	3 (13.0%)	1 (8.3%)	9 (32.1%)	.1235
Smoking, n (%)	16 (69.6%)	11 (91.7%)	23 (82.1%)	.274
Clinical index				
PLT/Lymph	13.0±7.1	13.8±4.9	12.7±6.6	.5503
Neu/Lymph	7.9±5.4	7.0±3.3	5.8±4.3	.5670
Heart Score	8.0±0.8	7.9±0.7	7.7±1.0	.5368
Door to device, minutes	45.5±13.8	52.2±22.1	51.5±11.1	.1177
Thrombectomy	6 (24.0%)	1 (8.3%)	11 (42.3%)	.1318
Pre-TIMI				.08251
TIMI flow 0	10 (43.4%)	9 (75.0%)	25 (89.3%)	
TIMI flow I	5 (20.0%)	1 (8.3%)	2 (7.7%)	
TIMI flow II	6 (24.0%)	1 (8.3%)	1 (3.8%)	
TIMI flow III	2 (8.0%)	1 (8.3%)	0 (0.0%)	
CMR findings				
LGE, g	17.2±9.9	25.2±18.9	43.9±27.1**	<.001
LGE (%)	16.7±8.4	25.5±15.8	36.5±14.8*	<.001
MVO, g	–	3.8±3.8	9.2±6.2	<.01†
MVO (%)	–	3.6±2.6	6.8±4.0	<.01†
LVEF (%)	54.8±10.4	51.4±7.8	48.2±11.6	.2984

BMI = body mass index, DM = Diabetes mellitus, HTN = hypertension, LGE = late gadolinium enhancement, LVEF = left ventricle ejection fraction, Lymph = lymphocyte, MVO = microvascular obstruction, Neu = neutrophil, PLT = platelet, Pre-TIMI = the TIMI score evaluated before percutaneous coronary intervention.

* Significantly different from the MVO (−) group.

** Significantly different from both the MVO (−) and MVO (+) and IMH (−) group.

† Wilcox-test was performed for the 2 groups with MVO.

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