

Peri-Infarct Ischemia Determined by Cardiovascular Magnetic Resonance Evaluation of Myocardial Viability and Stress Perfusion Predicts Future Cardiovascular Events in Patients with Severe Ischemic Cardiomyopathy

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ABSTRACT

Background: We assessed whether cardiovascular magnetic resonance imaging (CMR) of peri-infarct ischemia provides prognostic information in severe ischemic cardiomyopathy (ICM) patients referred for revascularization. **Methods:** Twenty-one patients with severe ICM were recruited prospectively for combined stress adenosine perfusion, late gadolinium enhancement, and rest perfusion studies. The patients were followed for in-hospital and post-discharge cardiovascular events. **Results:** During 12 ± 9.8 months follow-up, 67% of the patients with peri-infarct ischemia and 13% of the patients without peri-infarct ischemia had cardiovascular events ($p = 0.03$). **Conclusion:** In severe ICM patients, the presence of peri-infarct ischemia was associated with a higher incidence of cardiovascular events.

INTRODUCTION

Congestive heart failure (CHF) has become a widespread public health concern with approximately 5 million patients in the United States. Over 550,000 new cases and 300,000 deaths are reported annually (1). The most common cause of CHF is coronary artery disease with the highest mortality rate seen in patients with severe left ventricular (LV) dysfunction (2).

The high morbidity and mortality of CHF have been associated with the incidence of ventricular arrhythmia and LV remodeling (3, 4). The post-infarction LV remodeling provides an important substrate for triggering high-grade ventricular arrhythmia (5). Peri-infarct ischemia has been recognized as a trigger for ventricular arrhythmias, and studies have demonstrated that revascularization of ischemic territories result in lower incidence of ventricular arrhythmias (4–9). In addition, peri-infarct ischemia has been related to pathological remodeling. Revascularization of ischemic region has significantly reduced LV dilatation in patients with severe ischemic cardiomyopathy (ICM) (10). Although peri-infarct ischemia determined by technetium-99m sestamibi tomography has demonstrated increased cardiovascular events and death, this imaging modality is limited by temporal and spatial resolutions (11). Therefore, this study was conducted to determine whether peri-infarct ischemia can be detected by cardiovascular magnetic resonance imaging (CMR) and also predict the future cardiovascular events in high-risk patient population with severe ICM.

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Table 1. Patient characteristics

	All (n = 21)	Revascularization (n = 4)	No revascularization (n = 17)	p
Age, years	54 ± 11	55 ± 7.8	54 ± 12	NS
Gender, male/female	19/2	4/0	15/2	NS
Risk factors, n (%)				
Hypertension	4(19)	1 (25)	3 (18)	NS
Hypercholesterolemia	11(52)	3 (75)	8 (47)	NS
Diabetes	4(19)	2 (50)	2 (12)	NS
Smoking	10(48)	3 (75)	7 (41)	NS
Coronary anatomy, n (%)				
2 vessel (include P-LAD or LMT)	9(43)	0 (0)	9 (53)	
3 vessel disease	12(57)	4 (100)	8 (47)	
Scar volume, cm ³	25 ± 19	26 ± 25	25 ± 19	NS
Scar % of myocardium volume,%	17 ± 13	16 ± 17	18 ± 13	NS
LVEF, %	23 ± 12	19 ± 4.3	25 ± 13	NS
Cardiovascular events, n (%)	6 (29)	2 (50)	4 (24)	NS

Values are expressed as a mean ±SD. LVEF = left ventricular ejection fraction; P-LAD = proximal left anterior descending artery; LMT = left main trunk.

Materials AND METHODS

Patient population

Twenty-one patients (19 men, 2 women, age 54 ± 11, range 36 to 74 years) with severe coronary artery disease (three vessel, left main trunk, or two vessel with proximal left anterior descending artery) and severe LV dysfunction scheduled to undergo medical therapy +/- implantable cardiac defibrillator (ICD) placement were recruited prospectively for CMR. All patients underwent diagnostic coronary angiography before MR examination. Coronary artery stenosis was defined as a lumen diameter narrowing of more than 50%. The baseline characteristics of the patient population are given in Table 1. After MR examination, 4 patients underwent CABG, 17 patients received medical therapy +/- ICD placement.

Patients with recent infarction, unstable angina pectoris, asthma, pulmonary disease, severe valvular disease, or contraindications to the MR examination were excluded. To ensure a maximal vasodilatory response to adenosine, patients were instructed to refrain from smoking and drinking tea or coffee for 24 hours before the examination. The study protocol was approved by the Human Subjects Committee at Stanford University.

Imaging protocols

All images were acquired on a 1.5-Tesla whole-body scanner (Signa, GE, Milwaukee, WI, USA) with the patient in a supine position using a 8-element phased-array radiofrequency coil with breath-holding and cardiac gating. Stress myocardial perfusion images (Fast Gradient Echo-Echotrain, repetition time (TR) 6.6 ms, echo time (TE) 1.2 ms, inversion-recovery time 180 ms, flip angle (FA) 25°, field of view (FOV) 32 to 40 cm, matrix 128 × 128, in-plane resolution 2.5 to 3.1 × 2.5 to 3.1 mm, slice thickness 10 mm, 4 to 6 slices) were acquired during adenosine infusion (140 mcg/kg/min for 4 minutes) in 22 patients to

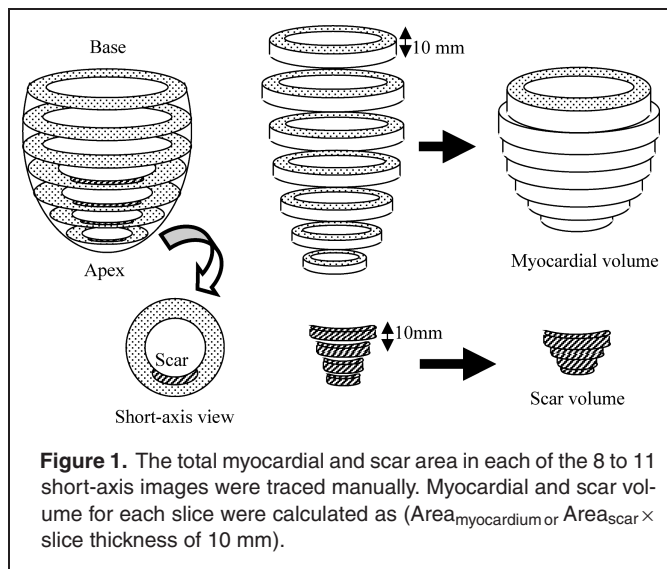
assess peri-infarct ischemia with 0.05 mmol/kg Gadolinium-DTPA bolus (Gd-DTPA, Magnevist®, Schering AG, Germany) injected at 3 mL/sec. Cine images of the LV in short and long axes were acquired using steady-state free precession sequence (SSFP, TR 3.8 ms, TE 1.6 ms, FA 45°, slice thickness 10mm, slice gap 0). Late gadolinium enhancement images (segmented *k*-space inversion recovery sequence, TR 7.1 ms, TE 3.1 ms, TI 200-250 ms, FA 20°, FOV 32 to 40 cm, slice thickness 10mm, slice gap 0) were performed with 16 segments acquired every cardiac cycle resulting in a breath-hold duration of 16 heart beats throughout the entire LV starting at 20 min following administration of a total of 0.2mmol/kg Gd-DTPA. The inversion time set to null the signal of normal myocardium after Gd-DTPA administration was adjusted during the course of the scan as necessary. Rest perfusion study was performed using 0.1 mmol/kg Gd-DTPA bolus at the end of the study (12). At least 30 minute intervals follow the stress myocardial perfusion study. The higher dose of Gd-DTPA was used for the resting myocardial perfusion study to obtain better signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) due to the residual Gd-DTPA in the myocardium from the previous stress and late gadolinium enhancement study.

Image analysis

Two observers blinded to patient information performed myocardial volume measurement and myocardial perfusion analysis before reviewing the late gadolinium enhancement images. Any disagreement between the two blinded observers was resolved by consensus.

Myocardial volume

The calculation of LVEF was performed by automatic tracing with manual adjustment of endocardial and epicardial borders from the short-axis images using the MASS analysis software



(MASS Analysis Plus Version 5.1, Leiden University, The Netherlands) as shown in Fig. 1.

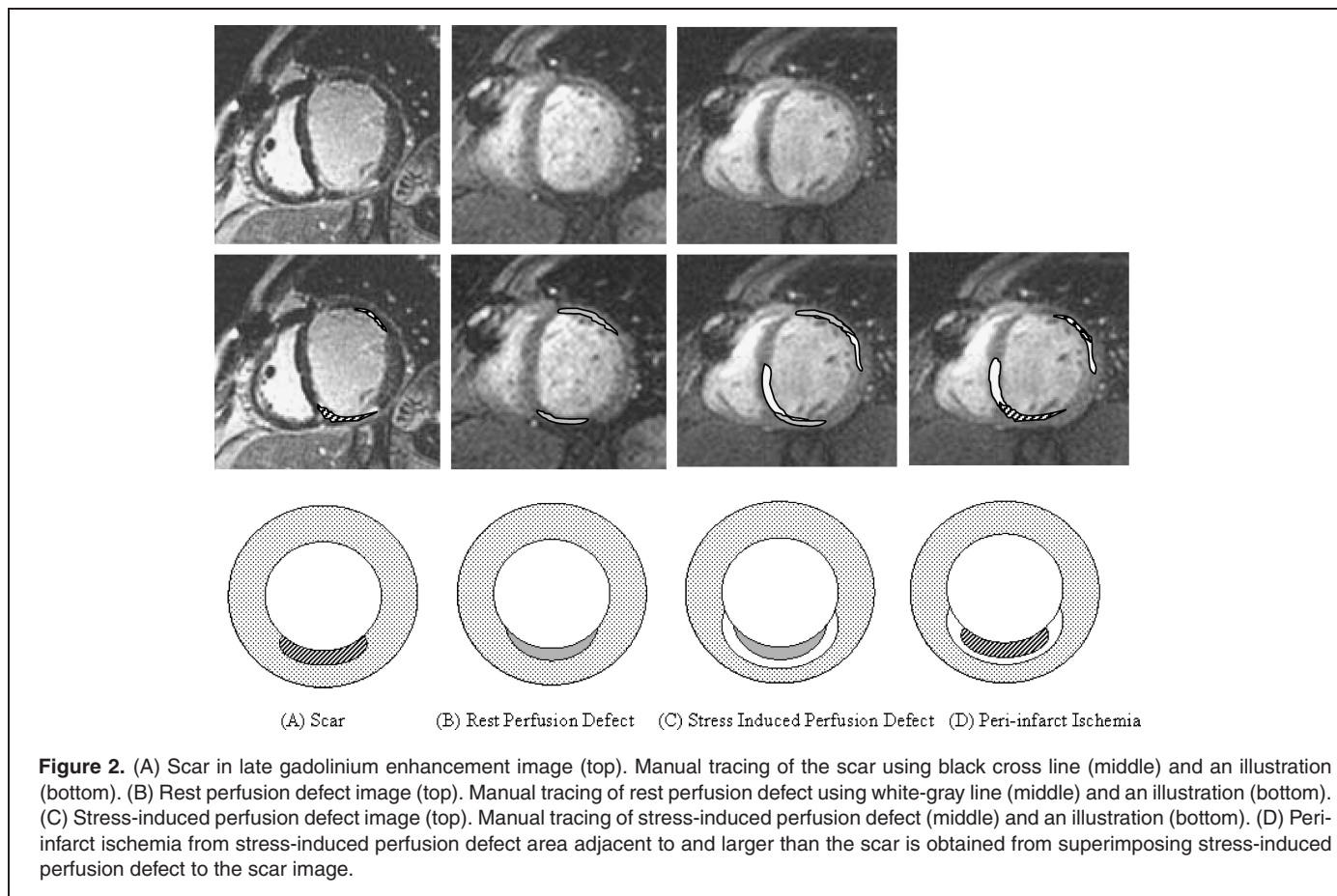
Myocardial perfusion

A myocardial perfusion defect was defined as delayed or absence of signal enhancement during Gd-DTPA infusion. The

definition of the myocardial defects (reversible, irreversible, and artifacts) was classified with 2×2 table in Fig. 3A as the following: normal—area of normal resting perfusion and normal stress perfusion; reversible defect—area of normal resting perfusion and stress perfusion defect and also larger area of stress perfusion defect in the peri-infarct area compared to resting perfusion defect; scar—area of stress perfusion defect matching with area of resting perfusion defect; artifact—area of resting perfusion defect and normal stress perfusion. It was necessary to obtain and analyze the resting perfusion images to rule out imaging artifacts in the stress perfusion images. The perfusion defect area per sector was traced manually as shown in Fig. 2 B,C. The peri-infarct ischemia was defined as a stress-induced perfusion defect area adjacent to and larger than the scar area as shown in Fig. 2 D. Sample images of peri-infarct ischemia in the anterior and inferior (left anterior descending artery and right coronary artery) region of a patient are shown in Fig. 2.

Late gadolinium enhancement

The short-axis late gadolinium enhancement images were evaluated for the presence of scar and traced manually to measure total scar volume as shown in Fig. 2 (A). Myocardial and scar volume were calculated as $(Area_{myocardium} \times slice\ thickness)$ or $(Area_{scar} \times slice\ thickness)$. The scar percentage of myocardial



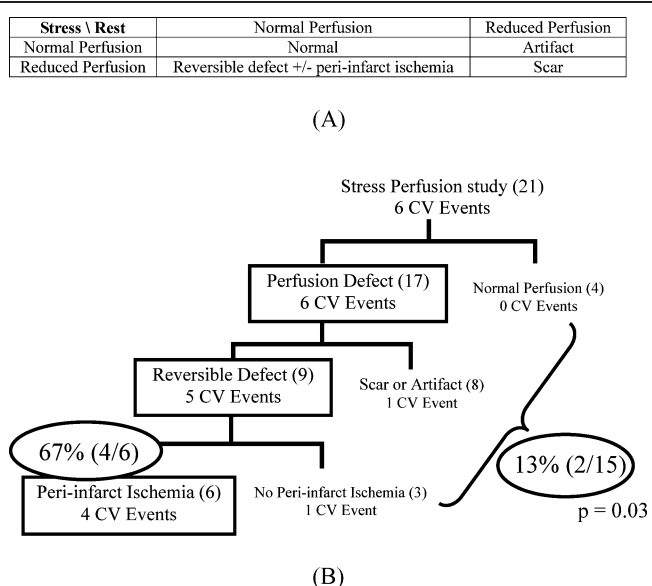


Figure 3. (A) Normal: area of normal resting perfusion and normal stress perfusion. Reversible defect: area of normal resting perfusion and stress perfusion defect and also larger area of stress perfusion defect in the peri-infarct area compared to resting perfusion defect. Scar: area of stress perfusion defect matching with area of resting perfusion defect. Artifact: area of resting perfusion defect and normal stress perfusion. (B). Twenty-one patients underwent stress myocardial perfusion using CMR. Perfusion defect was seen in 17 patients and of which 9 patients demonstrated a reversible defect indicative of ischemia. Of the 9 patients with ischemia, 6 had peri-infarct ischemia. Four of the 6 patients (67%) with peri-infarct ischemia had cardiovascular events while 2 of the 15 patients (13%) without peri-infarct ischemia had cardiovascular events ($p = 0.03$).

volume was also expressed as percentage of the total myocardial volume ($\text{Volume}_{\text{scar}}/\text{Volume myocardium} \times 100$) as shown in Fig. 1.

Event follow-up

Clinical follow-up was obtained in all patients for a period up to 31 months (mean of 12 ± 9.8 months, range 1 to 31 months). Cardiovascular events were defined as cardiac death, incidence of ventricular arrhythmia (ventricular tachycardia or fibrillation) or hospitalization due to unstable angina, myocardial infarction, worsening CHF. Survival status and occurrence of cardiovascular events were obtained by telephone contact with the patients, their relatives, or the referring physician and from review of inpatient or clinic records. The mean period and ranges of clinical follow-up for patients with and without events were 14 ± 9.8 months (5 to 31 months) and 10 ± 10 months (1 to 28 months), respectively. The mean period and ranges of clinical follow-up for patients with and without peri-infarct ischemia were also 9.8 ± 6.6 months (1 to 17 months) and 12 ± 11 months (1 to 31 months), respectively.

Statistical analysis

Data are expressed as the mean value $\pm$ SD. The comparisons between groups were performed with Student's t test, χ^2 or Fisher's exact tests. A p value <0.05 was considered significant.

RESULTS

Patient characteristics and angiographic findings

During the follow-up period, 6 of the 21 patients (29%) had cardiovascular events: 1 cardiac death, 4 ventricular arrhythmias, 1 recurrent CHF. In addition, patient characteristics were compared between revascularization (CABG) and no revascularization groups (medical therapy $\pm$ ICD placement). There was no significant difference in the incidence of cardiovascular events between the two groups (Table 1). All patients underwent diagnostic coronary angiography before CMR examination. Nine of the 21 patients (43%) had 2 vessel disease (Left main trunk, or two vessel with proximal left anterior descending artery), and 12 of the 22 patients (57%) had 3 vessel disease.

Relationship between peri-infarct ischemia and cardiovascular events

Perfusion defect was seen in 17 patients, 9 of which demonstrated reversible defect indicative of ischemia. Of the 9 patients with ischemia, 6 had peri-infarct ischemia. Four of the 6 (67%) patients with peri-infarct ischemia had cardiovascular events while 2 of the 15 (13%) without peri-infarct ischemia had cardiovascular events ($p = 0.03$) as demonstrated in Fig. 3. There was no difference in the occurrence of cardiovascular events between the presence of reversible or non-reversible perfusion defect groups. In addition, LVEF, age, and severity of coronary artery disease did not correlate with cardiovascular events (Table 2).

Table 2. Stress myocardial perfusion, late gadolinium enhancement study and cardiovascular events

	Events (+) (n = 6)	Events(-) (n = 15)	p
Peri-infarct ischemia, n (%)	4 (67)	3 (13)	0.03
Scar volume, cm ³	31 ± 19	21 ± 19	NS
Scar % of myocardial volume, %	21 ± 13	16 ± 13	NS
LVEF, %	24 ± 4.1	23 ± 13	NS
Age, years	51 ± 12	54 ± 11	NS
Coronary anatomy, n (%)			NS
2 vessel (include P-LAD or LMT)	3 (50)	6 (40)	
3 vessel disease	3 (50)	9 (60)	
Treatment, n (%)			NS
Revascularization (n = 4)	2 (50)	2 (50)	
Non-revascularization (n = 17)	4 (24)	13 (76)	

Values are expressed as a mean $\pm$ SD. LVEF = left ventricular ejection fraction, P-LAD = proximal left anterior descending artery, LMT = left main trunk.

Relationship between myocardial viability and cardiovascular events

All 21 patients underwent myocardial viability using CMR. The scar volume was $31 \pm 19 \text{ cm}^3$ in patients who suffered cardiovascular events, and $21 \pm 19 \text{ cm}^3$ in those without cardiovascular events ($p = 0.38$). The scar percentage of myocardial volume was $21 \pm 13\%$ in patients who suffered cardiovascular events, and $16 \pm 13\%$ in those without cardiovascular events ($p = 0.18$). The total scar volume and the scar percentage of myocardial volume did not demonstrate statistical significant correlation with cardiovascular events as shown Table 2. High intraobserver and interobserver correlations were found in the measurement of scar volume with $r = 0.997$ ($p = 0.0002$) and $r = 0.991$ ($p = 0.001$), respectively.

Comparison between resting perfusion and myocardial viability

Myocardial scar was seen by late gadolinium enhancement MRI in all patients. While resting perfusion image could detect perfusion defect in 17 of 21 patients. Resting perfusion was rather insensitive than delayed enhancement to detect scar.

DISCUSSION

CHF is the leading diagnosis associated with hospital admissions resulting in approximately 300,000 deaths annually (1). Over the last several decades, advances in medical and surgical interventions provided significant improvement in the treatment of ischemic cardiomyopathy (ICM). However, the average 5-year survival today remains at a dismal 50% (13). To date, prognostic information and clinical decision in this patient population are based mostly on the evaluation of coronary anatomy (14, 15), LVEF (2, 14, 17) and comorbidities (14).

This is the first study to investigate whether CMR assessment of peri-infarct ischemia through comprehensive evaluation of myocardial perfusion and viability will predict the occurrence of cardiovascular events in ICM patients with severe LV dysfunction. In order to address this issue, we conducted this study to determine whether peri-infarct ischemia can be detected reliably and whether prognostic information can be generated from detection of peri-infarct ischemia. We found that the presence of peri-infarct ischemia determined by CMR was associated with higher incidence of cardiovascular events in patients with severe ICM. However, age, LVEF and the severity of coronary artery disease did not correlate with the occurrence of cardiovascular events in this high risk patient population. In addition, the measurement of scar volume and the scar percentage of myocardial volume did not demonstrate statistically significant correlation with cardiovascular events. The assessment of peri-infarct ischemia may provide a more sensitive measure to predict future cardiovascular events in this high risk patient population than the assessment of myocardial viability or traditional assessment of LVEF or severity of coronary artery disease.

Dose of Gd-DTPA at perfusion study

In previous studies, the dose of gadolinium contrast administered in the studies varied 6-fold, with doses ranging from 0.025 to 0.15 mmol/kg (12, 18, 19). Different dosages performed differently depending on type of data analysis, i.e., quantitative (at lower dosage [19]) versus semi-automatic quantitative stress-only analyses (at higher dosage, [20]). The multicenter dose-ranging study has been reported that a low dose of 0.05mmol/kg gadolinium contrast media was at least as efficacious as higher doses (19). At this time no general recommendation can be made regarding the dosage when both myocardial perfusion and late gadolinium enhancement study will be performed at the same time. In this investigation, we performed stress myocardial perfusion study with 0.05mmol/kg Gd-DTPA first, and rest myocardial perfusion study with 0.10 mmol/kg Gd-DTPA. We used different dose of Gd-DTPA to obtain a better resting perfusion signal from myocardium because of the residual Gd-DTPA in the circulation and myocardium as a result from the previous stress perfusion and late gadolinium enhancement studies.

Prognostic value of stress-induced peri-infarct ischemia

Myocardial perfusion can be assessed reliably with CMR at rest and stress. This approach has been reported to be highly sensitive for the detection of myocardial ischemia with a sensitivity of 88% and specificity of 90% (18). Furthermore, recent studies have also demonstrated reliable imaging of myocardial infarction (21, 22). The advantages of CMR over other conventional imaging modalities consist of comprehensive characterization of the myocardial tissue including myocardial perfusion and viability through exquisite tissue contrast mechanism and high temporal and spatial resolution (23). There were several studies that combined perfusion and viability studies by CMR. Previous studies reported that late gadolinium enhancement image is more accurate than resting perfusion at differentiating normal from nonviable myocardium (24, 25). In the present study, resting perfusion image could not also detect perfusion defect in 4 of 21 patients with scar. Resting perfusion might be rather insensitive than late gadolinium enhancement to detect scar. This study was designed to exploit such features of CMR to diagnose peri-infarct ischemia detected by the presence of stress-induced perfusion defect adjacent to and larger than the scar. This capability has been tested clinically to determine the prognosis in severe ICM patients in whom therapeutic options are frequently limited. This investigation demonstrated that significantly higher number of patients with peri-infarct ischemia developed cardiovascular events.

Prognostic value of viability

The CMR late gadolinium enhancement study can distinguish between viable and non-viable myocardium independent of wall motion through evaluation of the transmural extent of infarction (26, 27). The transmural extent of infarction determined by late gadolinium enhancement study has been found to predict

future recovery of contractile function in patients undergoing coronary revascularization (21, 28). However correlation between the transmural extent of infarction and future cardiovascular events have not been well demonstrated. In this investigation, the measurement of scar volume and the scar percentage of myocardial volume in patients with cardiovascular events did not demonstrate any statistical significant correlation although this may have been due to the limited sample size and end-stage nature of patients with severe ICM.

Study limitations

The small sample size of patients in this study is mainly due to difficulty in recruiting patients with severe coronary artery disease and LV dysfunction. Since a highly selected patient population was enrolled, the results of this study are applicable only to those with extensive coronary artery disease and advanced LV dysfunction considered for possible revascularization. In previous studies, LVEF, severity of coronary disease and scar volume had been shown to be associated with patient outcome (29,31). However, this study did not generate these findings most likely due to the highly selected patient population. Future studies may evaluate the efficacy of peri-infarct ischemia to predict the incidence of cardiovascular events between patients undergoing revascularization versus medical therapy.

CONCLUSION

Patients with severe ICM demonstrating peri-infarct ischemia are pre-disposed to a higher risk of developing cardiovascular events. CMR may enable accurate prognostication in this high-risk patient population to help guide appropriate therapeutic decision.

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