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Functional Outcome after Revascularization in Patients with Chronic Ischemic Heart Disease: A Quantitative Late Gadolinium Enhancement CMR Study Evaluating Transmural Scar Extent, Wall Thickness and Periprocedural Necrosis

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ABSTRACT

In patients with chronic ischemic myocardial dysfunction, late gadolinium enhancement CMR (LGE-CMR) accurately depicts the regional extent of fibrosis and predicts functional recovery after revascularization. We hypothesized that the predictive accuracy of LGE-CMR could be optimized by not only taking into account the transmural extent of hyperenhancement but also the amount of residual, non-enhanced viable myocardium, and procedure related necrosis. We studied 45 patients with chronic ischemic left ventricular dysfunction, who underwent cine and LGE-CMR 1 month before and 3 months after surgical or percutaneous revascularization. Segmental and global function, scar, presence of a significant residual viable rim (defined as ≥4.5 mm), and procedure related necrosis were fully quantified using standardized methods and objective thresholds. Sixty percent of segments without hyperenhancement showed functional improvement at follow-up. No improvement was observed in segments with >75% segmental extent of hyperenhancement (SEH), while segments with 1–25%, 26–50%, and 51–75% SEH were 4, 8, and 20 times less likely to improve (multilevel analysis, p < 0.001). Thickness of the viable rim largely paralleled total wall thickness; therefore, the presence of a significant viable rim did not provide additional diagnostic value beyond SEH. Procedure related necrosis was found in 12 (27%) patients. The presence of procedure related necrosis was the only (negative) predictor of changes in left ventricular volumes and ejection fraction. In conclusion, we found that functional outcome after revascularization was influenced by both transmural extent of hyperenhancement and procedure related necrosis. However, the presence of a significant residual, viable rim was of no additional diagnostic value.

INTRODUCTION

Late gadolinium enhancement CMR (LGE-CMR) allows the accurate visualization and quantification of both acute and chronic myocardial necrosis (1). There are several ways in which LGE-CMR may contribute to the assessment of myocardial viability.

First, by quantifying the transmural extent of hyperenhancement, LGE-CMR can predict the likelihood of functional improvement after revascularization of chronically ischemic dysfunctional myocardium. Several studies have shown that the likelihood of functional improvement after revascularization of chronically ischemic dysfunctional myocardium is inversely related to the baseline transmural extent of hyperenhancement (2–4). Second, by relating the transmural extent of necrosis to

total wall thickness, LGE-CMR can determine the amount of residual viable tissue within a predefined myocardial region. Dysfunctional regions with preserved wall thickness and a significant rim of viable myocytes within the myocardial wall have higher likelihood of functional recovery (5). Finally, serial LGE-CMR can be used to demonstrate and quantify new regions of hyperenhancement related to procedural myocardial necrosis, which has been shown to negatively influence functional outcome (6, 7).

In this study, our goal was to combine all information from LGE-CMR to evaluate viability in a group of patients with chronic ischemic myocardial dysfunction. We hypothesized that the predictive accuracy of LGE-CMR could be optimized by not only taking into account the transmural extent of hyperenhancement but also the amount of residual, non-enhanced viable myocardium, and the extent of procedure related necrosis. Most CMR viability studies have used visual assessment of segmental wall thickening and extent of delayed hyperenhancement. In this study, all data were analyzed quantitatively, using standardized methods and objective thresholds.

METHODS

Patients

All patients with known coronary artery disease and regional wall motion abnormalities on echocardiography or left ventricular angiography, without CMR contraindications, who were scheduled to undergo surgical or percutaneous revascularization, were study candidates. The Committee on Research Involving Human Subjects of the VU University Medical Center, Amsterdam, approved the study protocol. All patients gave written informed consent.

CMR

Imaging was scheduled on a 1.5T scanner (Sonata, Siemens, Erlangen, Germany) 1 month before and 3 months after revascularization. Segmented steady-state free precession (TE/TR 1.2/3.2 ms; typical voxel size $1.3 \times 1.8 \times 5$ mm) cine images were acquired at 8 to 10 short-axis views obtained every 10 mm, starting at the mitral valve insertion and covering the entire left ventricle. Ten to 15 minutes after injection of a gadolinium-based contrast agent (Magnevist, Schering AG, Berlin, Germany; 0.2 mmol/kg), contrast-enhanced images were acquired in the same orientation as the cine images using a 2D segmented inversion recovery gradient-echo pulse sequence (typical voxel size $1.6 \times 1.3 \times 5.0$ mm).

Definition of segments

Images were evaluated using a 16-segment model (8), dividing the left ventricle into 6 basal, 6 midventricular, and 4 distal segments. By convention, the most basal short-axis slice used for analysis was located just below and exclusive of the left ventricular outflow tract. The 2 most apical slices were excluded because short-axis images at this level preclude a reliable segmental evaluation due to small diameter. To compose the basal, midventricular, and distal segments, data of a maximum of 3 short-axis slices were averaged.

Complete revascularization was defined as revascularization of all vessels with >50% diameter stenosis. For patients in whom revascularization was incomplete, only segments in revascularized coronary artery territories were considered (8).

Functional analysis

All data were analyzed on a separate workstation (Sun Microsystems, Inc., Santa Clara, California, USA) using a dedicated software package (Mass, Medis, Leiden, The Netherlands). Segmental wall thickness was measured at end-systole and end-diastole by the modified center line method (9) after manual tracing of endocardial and epicardial borders in stop-frame images, excluding trabeculae and papillary muscles. Segmental wall thickening (SWT) in millimeters was calculated as: end systolic wall thickness–end diastolic wall thickness. The normal range of SWT was defined in a group of 10 healthy volunteers (age 50–75 years): 4.4 ± 0.7 mm. Segments with SWT <3 mm (mean–2SD) were considered dysfunctional. Registration of follow-up cine images was achieved using standard imaging procedure and various anatomical landmarks, such as right ventricle septal insertion sites, papillary muscle location, and trabecularization patterns in the right and left ventricles. Functional improvement was defined as increase in SWT of ≥ 1.5 mm, based on the in-plane spatial resolution of the cine sequence. Inter- and intraobserver variabilities of SWT analysis (defined in 10 randomly chosen patients) were 0.1 ± 0.7 mm and 0.0 ± 0.4 mm, respectively (mean difference $\pm$ SD).

Left ventricular volumes were normalized to body surface area (m^2). Both intra- and interobserver variability of left ventricular volume measurements were $1 \pm 3\%$. A change of >7% (=intraobserver variability + 2 SD) in left ventricular volumes at follow-up was considered significant.

Hyperenhancement analysis

Areas of hyperenhancement were quantified by computer-assisted planimetry on each of the short axis images, and segmental extent of hyperenhancement (SEH, expressed as percentage of segmental area) was calculated. Hyperenhancement was defined as signal intensity ≥ 5 SD above the signal intensity of remote myocardium in the same slice (10). Segments were assigned to one of the following SEH groups: 1–0%, 2–1 to 25%, 3–26 to 50%, 4–51 to 75%, and 5–76 to 100% hyperenhancement. Using an assumed density of 1.05 g/mL (11), total myocardial scar in grams per patient was calculated by summation of hyperenhanced regions in all slices. Inter- and intraobserver variability of total myocardial scar calculation were 1.2 ± 4.1 g and 0.8 ± 1.6 g, respectively,(mean difference $\pm$ SD). A significant increase in total myocardial scar was defined as ≥ 4 g (intraobserver variability + 2 SD). Mean segmental thickness of the non-enhanced, viable rim was calculated as: total segmental wall thickness*(100%–SEH). A viable rim of ≥ 4.5 mm was considered thick (5).

To assess the relation between changes in global function and viability, we defined a viability index for each patient as: (the

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number of dysfunctional segments with SEH ≤ 25% divided by the total number of dysfunctional segments) * 100%.

Statistical analysis

All values are expressed as mean ± SD. The paired sample t test and the independent samples t test were used to compare means within the study group or between subgroups. We used multilevel logistic regression to adjust for the non-independence of the data (MlwiN, version 1.02.0007, Centre for Multilevel Modelling, London, United Kingdom) (12, 13) to evaluate the relations between hyperenhancement and wall thickening. Results are given as odds ratios, relating the functional outcome of segments with hyperenhancement to that of segments without hyperenhancement. Correlation between total segmental wall thickness and viable rim thickness and SEH and viable rim thickness was assessed using regression analysis for mixed models (SPSS, version 12.0, Chicago, IL). Univariable and multivariable logistic regression analysis was performed to find predictors of global functional improvement, using categorical variables (gender, history of previous myocardial infarction, cardiac risk factors [diabetes, hypertension, hypercholesterolemia, smoking], medical therapy [ACE inhibitors, β-blockers], mode and completeness of revascularization, occurrence of post-procedural new hyperenhancement, and biochemical evidence of peri-operative myocardial infarction [CK-MB >3 × upper limit of normal], and continuous variables [age, baseline LV volumes, ejection fraction, and viability index]). p < 0.05 was considered statistically significant.

RESULTS

Fifty patients were initially included in the study protocol. Four patients declined to return for follow-up, and 1 patient was excluded because coronary artery bypass surgery was accompanied by left ventricular aneurysmectomy. Coronary artery bypass surgery was performed in 32 patients, and percutaneous transluminal coronary angioplasty in 13. CMR was performed 4 ± 2 weeks before and 14 ± 2 weeks after revascularization. There were no ischemic events in the period between the CMR examinations and revascularization. Baseline characteristics of the patient population are listed in Table 1. Complete revascularization was achieved in 27 of the 32 surgically treated patients. Eight of the 9 patients with multivessel disease in the PTCA group revascularization was ischemia-driven and, therefore, limited to the most significant lesion.

Regional ventricular function

Of 720 available segments, 644 (89%) were successfully revascularized. Of 356 dysfunctional segments at baseline (mean SWT 1.3 ± 1.1 mm), 322 (90%) were revascularized. Three months after revascularization, 85 (26%) showed functional improvement: 43 of 72 (60%) segments without hyperenhancement; 21 of 76 (28%) segments with 1–25% SEH; 15 of 76 (20%) segments with 26–50% SEH; 6 of 74 (8%) segments with 51-75% SEH; and in none of 24 segments with 76–100% SEH. The likelihood of functional improvement at follow-up de-

Table 1. Patients characteristics

Males/females, n	38/7
Age (yrs)	62 ± 9
Risk factors, n (%)	
Systemic hypertension	10 (22)
Diabetes mellitus	11 (24)
Hypercholesterolaemia	33 (74)
Smoking	14 (30)
Positive family history	7 (15)
Coronary angiography, n (%)	
Single-vessel disease	4 (9)
Two-vessel disease	13 (28)
Three-vessel disease	28 (63)
History of myocardial infarction, n (%)	28 (63)
Previous revascularization, n (%)	
CABG	2 (4)
PTCA	6 (13)
Ejection fraction at baseline (%)	39 ± 11
Months between infarction and baseline CMR (range)	53 (2–177)
Cardiac medication, n (%)	
B-blockers	33 (74)
ACE inhibitors	20 (44)
Aldosterone antagonists	6 (13)
Diuretics	22 (48)
Nitrates	4 (9)
Ca-channel blockers	6 (13)
Aspirin	28 (63)
Acenocoumarol	22 (48)
Antilipid agents	33 (74)

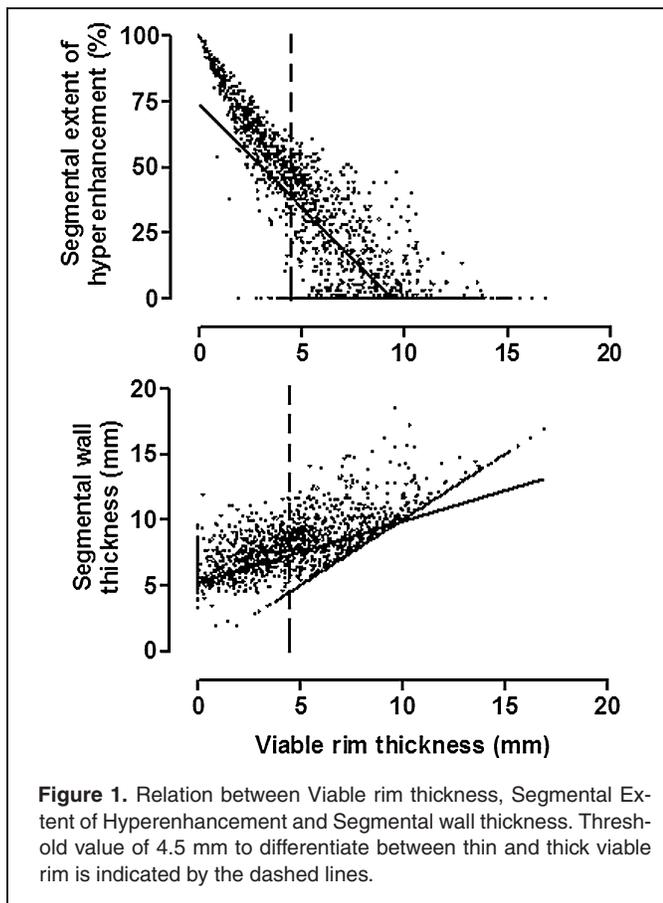CABG = coronary artery bypass grafting, PTCA = percutaneous transluminal coronary angioplasty.

creased with increasing SEH: segments with 1–25%, 26–50%, and 51–75% SEH were 4, 8, and 20 times less likely to have functional improvement than segments without hyperenhancement (multilevel analysis, p < 0.001).

Viable rim

Of the 322 preoperative dysfunctional segments, 209 (65%) had a viable rim of ≥4.5 mm. In our study group, total segmental wall thickness and thickness of the viable rim were strongly correlated (regression analysis for mixed models, p < 0.001). Consequently, viable rim thickness was inversely related to the transmural extent of hyperenhancement (Fig. 1) and had no diagnostic value beyond SEH alone. Almost all (147 of 148, 99%) segments with ≤25% SEH had a thick viable rim, whereas the large majority of segments with >50% SEH (92 of 98, 94%) only had a thin rim of non-enhanced, viable myocardium (Fig. 2). Of 76 segments with 26-50% SEH, 54 (71%) had a preserved viable rim. Functional improvement after revascularization was seen in 20% of these segments versus 18% for segments without a thick viable rim (p = NS).

Periprocedural hyperenhancement

LGE-CMR demonstrated hyperenhancement in 41 of the 45 patients at baseline (mean total myocardial scar 21 ± 16, range 3–80 g). After revascularization, scar mass increased in 11 patients (9/2 coronary artery bypass surgery/percutaneous

Figure 1. Relation between Viable rim thickness, Segmental Extent of Hyperenhancement and Segmental wall thickness. Threshold value of 4.5 mm to differentiate between thin and thick viable rim is indicated by the dashed lines.

transluminal coronary angioplasty) and 1 surgically treated patient without myocardial scar at baseline developed new hyperenhancement. Mean total increase in total myocardial scar was quantified at 9.8 ± 5.4 g (range 4.0–19.7 g). Fig. 3 shows an example of new hyperenhancement in a patient after surgical revascularization in a region not related to baseline scar. The majority of the patients with periprocedural enhancement had extensive coronary artery disease: there were 1, 2, and 8 patients with single, two-, and three-vessel disease, respectively. Crea-

Figure 2. Viable rim thickness according to Segmental Extent of Hyperenhancement (SEH).
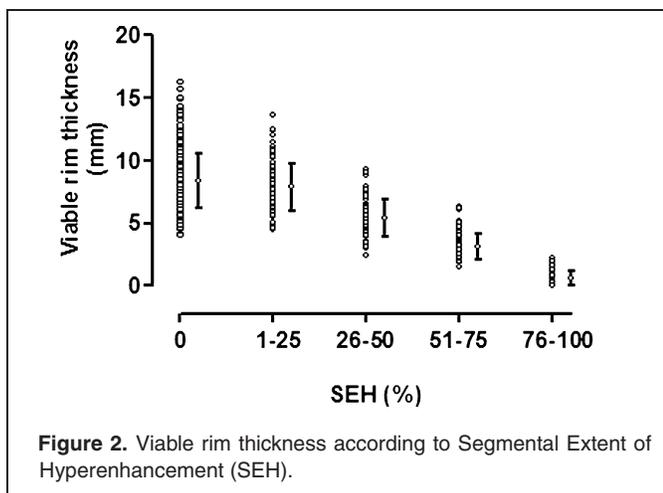
tine kinase-MB isoenzyme measurements were obtained in all 32 surgical patients at 6, 12, 24 and 48 hours after the procedure. Only 4 patients with increased total myocardial scar had electrocardiographic (new Q waves) and/or biochemical evidence (creatine kinase-MB isoenzyme elevation >3 times the upper normal limit) (14) of perioperative myocardial infarction. Thirteen patients had smaller degrees of scar expansion, less than our predefined cutoff value of 4 g (see **Methods**), with mass range of 1.4–3.6 g. None of these patients had elevated cardiac enzymes or new Q waves.

After revascularization, SEH score increased in 60 segments (mean number of segments per patient 5 ± 2, range 2–9 segments). Among those there were 26 pre-operative normal segments, 5 of which became dysfunctional at follow-up. Another 34 segments were already dysfunctional at baseline. Postoperative new enhancement was seen in 16% of segments that failed to improve: 6 of 29 (21%) segments with 0% SEH; 8 of 55 (15%) segments with 1–25% SEH; 9 of 61 (15%) segments with 26–50% SEH; and 11 of 68 (16%) segments with 51–75% SEH at baseline. There was no significant relation between the presence of myocardial scar at baseline and occurrence of postoperative new hyperenhancement (multilevel regression analysis, $p = NS$).

Global ventricular function

After revascularization, ejection fraction improved in 20 patients (mean change $4 \pm 3\%$), while it remained unchanged or worsened in 25 patients (mean change $-4 \pm 4\%$). Univariable predictors of changes in ejection fraction and left ventricular volumes are shown in Table 2. The occurrence of new hyperenhancement after revascularization was the only (negative) multivariable predictor of change in ejection fraction (odds ratio 0.13, 95% confidence interval 0.02 to 0.74, $p = 0.02$) and end-systolic and end-diastolic volumes (odds ratio 0.01, 95% confidence interval 0 to 0.24, $p = 0.01$ and odds ratio 0.07, 95% confidence interval 0.01 to 0.54, $p = 0.01$, respectively).

DISCUSSION

The major findings of our study are as follows. First, we found that the likelihood of segmental functional improvement after revascularization was inversely related to the segmental extent of hyperenhancement on LGE-CMR in patients with chronic ischemic left ventricular dysfunction. Second, thickness of the viable rim largely paralleled total segmental wall thickness and, therefore, did not add to the predictive power of the segmental extent of hyperenhancement alone. Third, periprocedural necrosis was found in a significant part of our study population (27%) and was the only (negative) predictor of changes in global left ventricular function and volumes.

Prediction of functional improvement: a quantitative approach

We specifically chose to use quantitative analysis for this study. Although valid for most clinical purposes, qualitative assessment of wall motion and extent of hyperenhancement may

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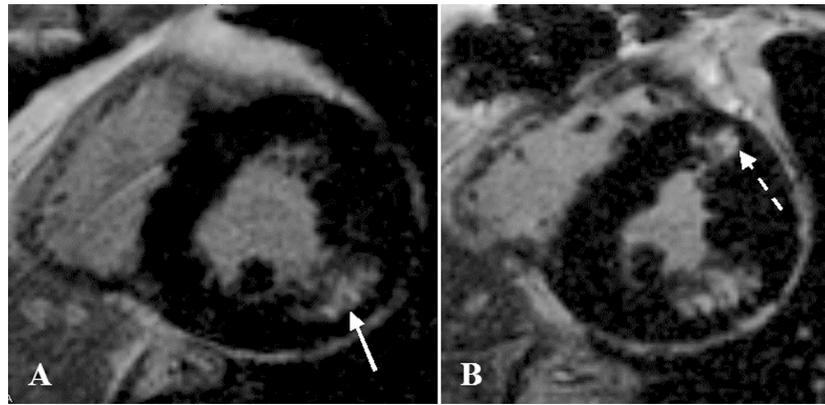
Figure 3. Midventricular short axis LGE-CMR image demonstrating hyperenhancement before surgery (A, white arrow) and new hyperenhancement after surgery (B, dotted arrow) in a patient without enzymatic or electrocardiographic perioperative infarction.

lead to inaccuracy related to intra- and interobserver variability. All methods were standardized (ie, data acquisition, contour delineation, DE-image window settings, etc.), and objective thresholds derived from reproducibility studies were used to calculate segmental and global function and scar extent. In addition, we used multilevel logistic regression for the evaluation of the segmental changes, which takes into account the nonindependence of segmental data. Our results clearly demonstrate the inverse relation between extent of hyperenhancement and functional outcome: segments with 1–25%, 26–50%, and 51–75% SEH were 4, 8, and 20 times less likely to have functional improvement than segments without hyperenhancement. The negative predictive value was high: no segments with >75% SEH and only 5% with >50% SEH improved.

The overall rate of improvement (26%; 85 of 322 segments) and the positive predictive value (60% of segments without hy-

perenhancement and 43% with ≤25% SEH) were lower than in recent studies using LGE-CMR (2–4, 6). Schinkel et al recently studied 258 patients with ischemic cardiomyopathy using echocardiography and found an almost identical improvement rate of 27% 3–6 months after coronary artery bypass surgery (15). The higher improvement rates from other LGE-CMR studies may be partly explained by the variable time course of improvement of viable myocardium. This may be considerably prolonged, and a longer follow-up time interval may be required to view the full extent of improvement (16, 17).

Viable rim

Baer et al (18) showed that preserved end-diastolic wall thickness >5.5 mm (defined with cine CMR) has high sensitivity for the prediction of functional recovery after revascularization.

Table 2. Predictors of global functional improvement: univariable analysis

	EF ↑ (n = 20)	EF ↓ or = (n = 25)	p	LVEDVI ↓ (n = 20)	LV EDVI ↑ or = (n = 25)	p	LVESVI ↓ (n = 18)	LVESVI ↑ or = (n = 27)	p
Age, y	62 ± 12	61 ± 8	0.74	58 ± 11	65 ± 7	0.02	60 ± 11	63 ± 8	0.25
Men, n	15	23	0.14	17	21	0.93	14	24	0.32
LV EDVI, mL/m^2	117 ± 31	120 ± 32	0.69	125 ± 24	113 ± 35	0.18	128 ± 21	112 ± 35	0.09
LV ESVI, mL/m^2	75 ± 29	72 ± 29	0.76	78 ± 23	70 ± 32	0.34	80 ± 23	69 ± 31	0.24
LV EF, %	37 ± 11	41 ± 9	0.19	39 ± 10	40 ± 11	0.59	39 ± 11	40 ± 10	0.64
Viability index	22 ± 14	20 ± 11	0.49	22 ± 14	20 ± 12	0.72	23 ± 14	20 ± 12	0.44
Previous infarction, n	14	15	0.49	15	14	0.19	13	16	0.37
Periprocedural hyperenhancement, n	2	10	0.04	2	10	0.04	1	11	0.03
CABG, n	14	18	0.88	15	17	0.61	14	18	0.42
Complete revascularization, n	15	16	0.43	15	16	0.43	15	16	0.10
Diabetes, n	5	6	0.94	6	5	0.44	4	7	0.78
Hypertension, n	2	7	0.15	4	5	1.00	3	6	0.65
Smoking, n	6	8	0.89	5	9	0.43	3	11	0.10
Hypercholesterolemia	2	6	0.24	2	6	0.24	2	6	0.35
ACE inhibitors	13	12	0.26	14	11	0.09	14	11	0.02
β-blockers	17	16	0.12	15	18	0.82	13	20	0.89

CABG = coronary artery bypass grafting, CK-MB = creatine kinase – MB isoenzyme, LV EDVI = Left Ventricular End-Diastolic Volume Indexed, LV EF = Left Ventricular Ejection Fraction, LV ESVI = Left Ventricular End-Systolic Volume Indexed, ULN = Upper Limit of Normal.

Specificity, however, is low, which may be explained by the fact that segments with preserved wall thickness may consist of various degrees of myocardial scar. Theoretically, segments with intermediate ranges of scar extent (25–75%) could still show functional improvement if wall thickness and the residual viable rim were preserved. Knuesel et al (5) recently compared LGE-CMR and ^{18}F-Fluorodeoxyglucose positron emission tomography (FDG-PET) and found that a residual non-enhancing (thus viable) rim of 4.5 mm corresponded to a 50% FDG-uptake. In their study, metabolically active segments with a preserved viable rim had a high improvement rate (85%). Thin, metabolically inactive segments and segments with either reduced FDG-uptake or a thin viable rim all had a low likelihood of improvement (13%, 23%, 36%, respectively). We sought to improve the diagnostic accuracy of LGE-CMR by also taking into account the presence of a significant residual viable rim, which can easily be determined on the contrast images. However, in our study, 98% of the segments with 0–25% SEH had a viable rim of at least 4.5 mm, while 94% segments with 50–100% SEH had a viable rim of <4.5 mm. Therefore, the presence or absence of viable rim had no diagnostic importance in these categories. In segments with 25–50% SEH, the presence of a viable rim resulted in a non-significant, slightly better functional outcome: 20% improvement vs. 18%. However, the number of segments with intermediate hyperenhancement was limited, and further study is required to establish the added value of preserved wall thickness and a significant residual, non-enhancing viable rim.

Procedural myocardial necrosis

Selvanayagam et al recently reported on the incidence and extent of revascularization related myocardial injury (6, 7, 19). Using LGE-CMR, these authors found new regions of hyperenhancement in 38% and 28% of patients after coronary artery bypass grafting and percutaneous coronary intervention, respectively. Using a 56 segment left ventricular model, they observed that, after surgery, 36% of segments with ≤25% SEH that did not improve had evidence of surgery related necrosis. In our mixed coronary artery bypass grafting and percutaneous coronary intervention population, we had comparable results: 12 of 45 patients (27%) demonstrated new regions of hyperenhancement at follow-up, and likely contributed to the non-recovery of 17% of 84 segments with no or minimal hyperenhancement (≤25% SEH). In addition, we found that procedure related necrosis was the only (negative) multivariable predictor of changes in global left ventricular volumes and function. These data confirm the prognostic relevance of myocardial necrosis sustained during revascularization and imply that considerable gain may be achieved by optimizing periprocedural myocardial protection and aggressive medical treatment to prevent early graft failure.

Limitations

Data of several short axis slices were averaged for the 16 segment left ventricular model that we used because this is commonly used in daily practice. Although averaging of information obligatory causes some loss in detail, it may be less sensitive

to misregistration that is always a potential source of error in follow-up studies. In our hospital, creatine kinase-MB isoenzyme is routinely used to identify revascularization procedure related myocardial necrosis. The use of troponins might have increased the enzymatic detection of periprocedural myocardial damage (20).

CONCLUSIONS

We performed a quantitative evaluation of LGE-CMR-derived parameters of myocardial viability in patients with chronic ischemic left ventricular dysfunction before and after revascularization. In line with previous studies, the transmural extent of hyperenhancement was inversely related to the likelihood of functional improvement. In our study, the presence of a significant viable rim was of no additional diagnostic value. Procedure related myocardial necrosis was a frequent finding and was the only multivariable predictor of changes in global function and volumes.

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