

Incremental value of advanced cardiac imaging modalities for diagnosis and patient management: focus on real-time three-dimensional echocardiography and magnetic resonance imaging

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CHAPTER 17

Agreement and disagreement between contrast-enhanced magnetic resonance imaging and nuclear imaging for assessment of myocardial viability

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ABSTRACT

Objectives: The purpose of this study was to compare contrastenhanced MRI and nuclear imaging with 99mTc-tetrofosmin and 18F-fluorodeoxyglucose (18F-FDG) single photon emission computed tomography (SPECT) for assessment of myocardial viability.

Methods: Included in the study were 60 patients with severe ischaemic left ventricular (LV) dysfunction, who underwent contrast-enhanced MRI, 99mTc-tetrofosmin and 18F-FDG SPECT. Myocardial segments were assigned a wall motion score from 0 (normokinesia) to 4 (dyskinesia) and a scar score from 0 (no scar) to 4 (76–100% transmural extent). Furthermore, 99mTc-tetrofosmin and 18F-FDG segmental tracer uptake was categorized from 0 (tracer activity >75%) to 3 (tracer activity <25%). Dysfunctional segments were classified into viability patterns on SPECT: normal perfusion/18F-FDG uptake, perfusion/18F-FDG mismatch, and mild or severe perfusion/18F-FDG match.

Results: Minimal scar tissue was observed on contrast-enhanced MRI (scar score 0.4 ± 0.8) in segments with normal perfusion/18F-FDG uptake, whereas extensive scar tissue (scar score 3.1 ± 1.0) was noted in segments with severe perfusion/18F-FDG match (p <0.001). High agreement (91%) for viability assessment between contrast-enhanced MRI and nuclear imaging was observed in segments without scar tissue on contrast-enhanced MRI as well as in segments with transmural scar tissue (83%). Of interest, disagreement was observed in segments with subendocardial scar tissue on contrast-enhanced MRI.

Conclusions: Agreement between contrast-enhanced MRI and nuclear imaging for assessment of viability was high in segments without scar tissue and in segments with transmural scar tissue on contrast-enhanced MRI. However, evident disagreement was observed in segments with subendocardial scar tissue on contrast-enhanced MRI, illustrating that the non-enhanced epicardial rim can contain either normal or ischaemically jeopardized myocardium.

INTRODUCTION

Assessment of viability is essential for optimization of treatment in patients with ischaemic left ventricular (LV) dysfunction, since dysfunctional but viable myocardium is likely to improve after revascularization, whereas dysfunctional but nonviable myocardium will not benefit 1. Furthermore, patients with viable myocardium have better survival after revascularization than after medical treatment ². At the present time, several noninvasive imaging modalities are available for the assessment of viability, including dobutamine echocardiography, single photon emission computed tomography (SPECT) and positron emission tomography (PET) ³⁻⁵. Nuclear imaging using tracers such as 99mTc-tetrofosmin and 18F- fluorodeoxyglucose (18F-FDG) allows evaluation of viability by assessment of myocardial perfusion and glucose utilization ⁴. Contrast-enhanced magnetic resonance imaging (MRI) has been more recently introduced for assessment of viability 6-8. This technique offers visualization of scar tissue with high spatial resolution, enabling distinction between subendocardial and transmural scar 9. Kim et al. reported that in segments without contrast-enhancement on MRI, recovery of function is highly likely to occur after revascularization, whereas improvement of function is unlikely in segments with extensive, transmural contrast-enhancement ⁶. However, difficulties arise in dysfunctional segments with subendocardial scar tissue, which show an intermediate extent of recovery, since contrast-enhanced MRI provides only information on scar tissue, whereas the non-enhanced (viable) tissue can contain either normal or ischaemically jeopardized myocardium 10. Hence, the two imaging modalities discussed above provide different information on viability.

To our knowledge, only a few, relatively small studies have evaluated patients using both contrast-enhanced MRI and nuclear imaging to determine viability ^{11–14}. Consequently, the exact relationship between viability assessed with contrast-enhanced MRI and nuclear imaging is still largely unknown. Therefore, the purpose of the present study was to compare contrast-enhanced MRI and nuclear imaging with 99mTc-tetrofosmin and 18F-FDG SPECT for the assessment of viability in patients with severe ischaemic LV dysfunction.

METHODS

Patient population

The study population consisted of 60 patients with severe ischaemic LV dysfunction who underwent MRI, 99mTctetrofosmin SPECT and 18F-FDG SPECT. Patients with myocardial infarction (MI) <3 months before MRI or SPECT were excluded. Other exclusion criteria were (supra-)ventricular arrhythmias, pacemakers, intracranial clips and claustrophobia. Patient

characteristics are presented in Table 1. The local ethics committee approved the study and all patients gave informed consent.

MRI: data acquisition

A 1.5-T Gyroscan ACS-NT/Intera MRI scanner (Philips Medical Systems, Best, The Netherlands) equipped with a five-element cardiac synergy coil was used. Images were acquired during breath-holds of approximately 15 s using vector electrocardiographic gating. The heart was imaged from apex to base 15 with 10-12 imaging levels (dependent on the heart size) in the short-axis view using a balanced turbofield echo sequence with parallel imaging (SENSE, acceleration factor 2). Typical parameters were a field of view of 400×320 mm2, matrix of 256×206 pixels, slice thickness of 10.00 mm, no slice gap, flip angle of 35°, time to echo of 1.67 ms, and time to repeat of 3.3 ms. Temporal resolution was 25 to 39 ms. The geometric settings of the baseline scans were stored and repeated for the contrast-enhanced images to ensure matching of the same slices (and hence, myocardial segments). Contrast-enhanced images were acquired approximately 15 min after bolus injection of gadolinium diethylenetriamine pentaacetic acid (Magnevist, Schering, Berlin, Germany; 0.15 mmol/kg) with an inversion-recovery 3-D turbofield echo sequence; the inversion time was determined with a real-time plan scan. Typical parameters were a field of view of 400×300 mm2, matrix of 256×192 pixels, slice thickness of 5.00 mm, flip angle of 15°, time to echo of 1.1 ms, and time to repeat of 3.00 ms.

MRI: data analysis

To determine global function, endocardial borders were outlined manually on short-axis cine images with previously validated software (MASS; Medis, Leiden, The Netherlands) ¹⁶. Papillary muscles were regarded as part of the ventricular cavity, and epicardial fat was excluded. LV end-systolic volume (ESV) and LV end-diastolic volume (EDV) were calculated. Subsequently, ESV was subtracted from EDV and LV ejection fraction (LVEF) was calculated. To determine regional wall motion, cine MR images were visually interpreted by two experienced observers using a 17-segment model ¹⁷. Each segment was assigned a wall motion/thickening score using the following five-point scale: 0 normal wall motion, 1 mild hypokinesia, 2 severe hypokinesia, 3 akinesia, and 4 dyskinesia. Wall thickening was taken into account for this classification, preempting the problem of postoperative paradoxical septal motion in patients with previous coronary artery bypass grafting. Contrast-enhanced images were scored visually by two experienced observers using the 17-segment model described above

¹⁷. Segmental scarring was graded on each segment using the following five-point scale: 0 absence of hyperenhancement, 1 hyperenhancement of 1% to 25% of

LV wall thickness, 2 hyperenhancement extending from 26% to 50%, 3 hyperenhancement extending from 51% to 75%, and 4 hyperenhancement extending from 76% to 100% ¹⁸.

99mTc-tetrofosmin SPECT: data acquisition

Imaging was performed at rest, with 99mTc-tetrofosmin (500 MBq) using a triple-head SPECT camera (GCA 9300/HG, Toshiba Corporation) equipped with low-energy, general-purpose collimators. A 20% window was used around the 140-keV energy peak of 99mTc-tetrofosmin. A total of 90 projections (step-and-shoot mode of 35 s/projection, total imaging time 23 min) were obtained over a 360° circular orbit. Data were stored in a 64×64, 16-bit matrix. The raw scintigraphic data were reconstructed with filtered back projection using a Butterworth filter (cut-off frequency 0.26 cycles per pixel, order 9). No attenuation correction was used.

99mTc-tetrofosmin SPECT: data analysis

Additional reconstruction yielded standard long- and shortaxis projections perpendicular to the heart axis. Reconstructed slices were 6 mm in all directions. The short-axis slices were displayed in polar map format, adjusted for peak myocardial activity (100%). The myocardium was divided into 17 segments ¹⁷. Segmental tracer activity was categorized visually by two experienced observers on a four-point scale (0 normal tracer activity >75%, 1 mildly reduced tracer activity 50–75%, 2 moderately reduced tracer activity 25–50%, and 3 severely reduced tracer activity <25%).

18F-FDG SPECT: data acquisition

18F-FDG imaging, to evaluate myocardial glucose utilization, was performed on a separate day, after administration of acipimox (a nicotinic acid derivative, 500 mg, oral dose; Byk, Zwanenberg, The Netherlands) ¹⁹. Acipimox enhances myocardial 18F-FDG uptake by reducing the plasma level of free fatty acids ²⁰. After acipimox administration, the patients received a low-fat, carbohydrate-rich meal. This small meal further enhances myocardial 18F-FDG uptake by stimulating endogenous insulin release ²¹. A blood sample was taken 60 min after acipimox administration to assess plasma glucose levels, and insulin was administered if needed. Then, 185 MBq 18F-FDG was injected at rest. Data were acquired 45 min later at rest using the same SPECT system as described for perfusion imaging, with commercially

available 511-KeV collimators. Data were acquired over 360° and stored in a 64×64, 16-bit matrix. From the raw scintigraphic data, transaxial slices were reconstructed by filtered back projection using a Butterworth filter (cut-off frequency 0.17 cycles per pixel, order 8). Attenuation correction was not applied.

18F-FDG SPECT: data analysis

Further reconstruction yielded standard short- and long-axis projections perpendicular to the heart axis. 18F-FDG shortaxis slides were displayed in polar map format, normalized to the maximum activity (set at 100%); the polar maps were divided into 17 segments ¹⁷. Segmental tracer activity was categorized visually by two experienced observers on a four-point scale (0 normal tracer activity >75%, 1 mildly reduced tracer activity 50–75%, 2 moderately reduced tracer activity 25–50%, and 3 severely reduced tracer activity <25%).

Definition of viability on nuclear imaging

The dysfunctional segments on cine MRI (wall motion score ≥1) were divided into four groups with different patterns of viability. Group I (normal perfusion/18F-FDG uptake) consisted of segments with normal 99mTc-tetrofosmin activity (score 0) and normal 18F-FDG activity (score 0). Group II (perfusion/18F-FDG mismatch) consisted of segments with reduced 99mTc-tetrofosmin activity (score 1, 2 or 3) and preserved/relatively increased 18F-FDG activity (18FFDG score <99mTc-tetrofosmin score). Group III (mild perfusion/18F-FDG match) consisted of segments with a mild reduction in 99mTc-tetrofosmin activity (score 1) and a concordant mild reduction in 18F-FDG activity (score 1). Finally, group IV (severe perfusion/18F-FDG match) consisted of segments with a moderate or severe reduction in 99mTc-tetrofosmin activity (score 2 or 3) and a concordant reduction in 18F-FDG activity.

Statistical analysis

Continuous data are expressed as means \pm standard deviation (SD). One-way ANOVA was used to compare scar score between the groups with different viability patterns. Proportions were compared using chi-squared (χ 2) analysis. P-values <0.05 were considered statistically significant.

RESULTS

Patient population

Clinical data are presented in Table 1. The mean age of the study population was 65±11 years and 50 patients (83%) were men. All patients had evidence of coronary artery disease (CAD) on coronary angiography. No clinical events or interventions were reported between MRI and SPECT examinations.

Table 1. Clinical characteristics of the study population

		No. (%)
Clinical variable	Mean±SD	of patients
		(n = 60)
Age (years)	65±11	
Men		50 (83)
Diabetes mellitus		16 (27)
Hypertension		14 (23)
Hypercholesterolaemia		23 (38)
Smoking		25 (42)
Previous MI		60 (100)
Prior revascularization		34 (57)
Percutaneous coronary intervention		20 (33)
Coronary artery bypass grafting		14 (23)
Extent of CAD (on coronary angiography)		
One-vessel disease		11 (18)
Two-vessel disease		18 (30)
Three-vessel disease		31 (52)
Medications:		
β-Blockers		48 (82)
Calcium channel blockers		10 (17)
ACE inhibitors		55 (92)
Oral anticoagulants		59 (98)
Statins		48 (80)
Nitrates		28 (47)
Diuretics		56 (93)

Magnetic resonance imaging

Mean LVEF in the total study population was $27\pm9\%$. The mean LVESV and mean LVEDV were 250 ± 110 ml and 335 ± 114 ml, respectively. A total of 1020 segments were analysed, of which 692 (68%) showed abnormal wall motion. Of these dysfunctional segments, 91 (13%) showed mild hypokinesia, 248 (36%) showed severe hypokinesia, and 298 (43%) segments were

akinetic and 55 (8%) were dyskinetic. Of the 692 dysfunctional segments, 484 (70%) revealed hyperenhancement, 105 (15%) showed minor hyperenhancement (scar score 1), 107 (15%) had a scar score of 2, 130 (19%) a scar score of 3, and 142 (21%) a scar score of 4.

99mTc-tetrofosmin SPECT

Of the 692 dysfunctional segments, 182 (26%) showed normal 99mTc-tetrofosmin activity (score 0), 91 (13%) showed mildly reduced tracer activity (score 1), 147 (21%) showed moderately reduced tracer activity (score 2), and 272 (39%) showed severely reduced tracer activity (score 3).

18F-FDG SPECT

Normal 18F-FDG activity was observed in 220 segments (32%) of the 692 dysfunctional segments. Mildly reduced tracer activity (score 1) was seen in 157 segments (23%), moderately reduced tracer activity (score 2) in 108 segments (16%), and severely reduced tracer activity (score 3) in 207 segments (30%).

Viability patterns assessed with nuclear imaging

Of the 692 dysfunctional segments, 183 (26%) showed normal perfusion/18F-FDG uptake, 145 (21%) showed perfusion/18F-FDG mismatch, 73 (11%) showed mild perfusion/18F-FDG match, and 291 (42%) showed severe perfusion/ 18F-FDG match. Of the 353 akinetic and dyskinetic segments, 40 (11%) showed normal perfusion/18F-FDG uptake, 78 (22%) showed perfusion/18F-FDG mismatch, 35 (10%) showed mild perfusion/18F-FDG match, and 200 (57%) showed severe perfusion/18F-FDG match.

Viability: nuclear imaging versus contrast-enhanced MRI

The mean scar scores measured in the segments grouped according to viability pattern on nuclear imaging are presented in Figure 1. Minimal scar tissue was observed on contrast-enhanced MRI in segments with normal perfusion/18F-FDG uptake on nuclear imaging (scar score 0.4 ± 0.8), whereas extensive scar tissue (scar score 3.1 ± 1.0) was noted in segments showing severe perfusion/18F-FDG match on nuclear imaging (p <0.001). Next (Figure 2), the dysfunctional segments were grouped according to the transmural extent of the scar

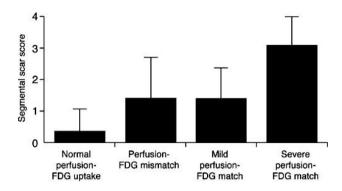


Figure 1. Mean scar scores on contrast-enhanced MRI for segments grouped according to viability pattern on nuclear imaging. (one-way ANOVA: p <0.001). Error bars represent standard deviations.

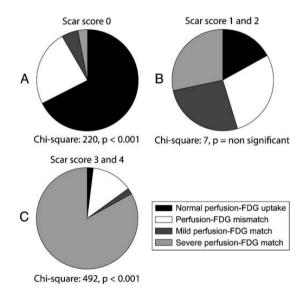


Figure 2. Relationship between contrast-enhanced MRI and nuclear imaging for dysfunctional segments showing the frequency of the four viability patterns assessed with nuclear imaging in segments without scar tissue (a), with subendocardial scar tissue (b) and with transmural scar tissue (c) on contrast-enhanced MRI.

tissue on contrast-enhanced MRI. The majority of segments without scar tissue on contrast-enhanced MRI (scar score 0, Figure 2a) showed normal perfusion/18F-FDG uptake (67%) or perfusion/18F-FDG mismatch (24%). Considering viability, agreement in these segments was high (91%), since segments without scar tissue on contrast-enhanced MRI as well as segments with normal perfusion/18F-FDG uptake or perfusion/18F-FDG mismatch on nuclear imaging are regarded as viable tissue. Conversely, the majority (83%) of segments with transmural scar tissue on contrast-enhanced MRI (scar scores 3 and 4, Figure 2c) showed severe

perfusion/18F-FDG match on nuclear imaging. Accordingly, agreement in these segments was also high (83%), since segments with transmural scar tissue on contrast-enhanced MRI and segments with severe perfusion/18F-FDG match on nuclear imaging represent nonviable tissue. Of note, in segments with subendocardial scar tissue on contrast-enhanced MRI (scar scores 1 and 2, Figure 2b), the various viability patterns assessed with nuclear imaging were evenly distributed, indicating that segments with subendocardial scar tissue on contrast-enhanced MRI, may have normal perfusion/18F-FDG uptake, perfusion/18F-FDG mismatch, mild perfusion/18F-FDG match or severe perfusion/18F-FDG match. Figure 3 shows an example of a patient with subendocardial scar tissue on contrast-enhanced MRI and perfusion/18F-FDG mismatch on nuclear imaging.

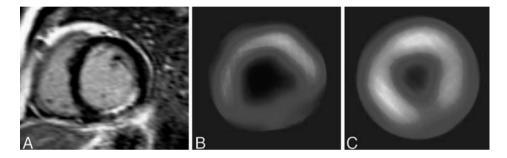


Figure 3. Patient with inferior subendocardial scar tissue on contrast-enhanced MRI (a) and a severe reduction in 99mTc-tetrofosmin activity (b) but preserved 18F-FDG activity (c) on SPECT (perfusion/18F-FDG mismatch), indicating ischaemically jeopardized myocardium, highlighting the discrepancy between information derived from contrast-enhanced MRI and nuclear imaging.

Finally (Figure 4), the akinetic and dyskinetic segments were analysed separately. The majority of these segments without scar tissue on contrast-enhanced MRI (scar score 0, Figure 4a) showed normal perfusion/18F-FDG uptake (47%) or perfusion/18F-FDG mismatch (39%) on nuclear imaging. Consequently, agreement between the two techniques for assessment of viability was high (86%). Conversely, in the majority of segments with transmural scar tissue on contrast-enhanced MRI (scar scores 3 and 4, Figure 4c), severe perfusion/18F-FDG match was observed on nuclear imaging (84%). Accordingly, agreement was also high (84%) in this category. Of interest, in segments with subendocardial scar tissue on contrast-enhanced MRI (scar scores 1 and 2, Figure 4b), the viability pattern on nuclear imaging varied highly between normal perfusion/18F-FDG uptake, perfusion/18FFDG mismatch, mild perfusion/18F-FDG match and severe perfusion/18F-FDG match.

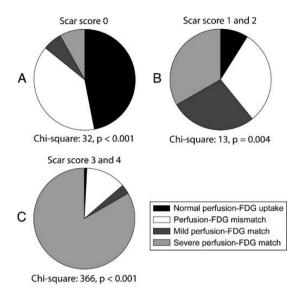


Figure 4. Relationship between contrast-enhanced MRI and nuclear imaging for akinetic and dyskinetic segments showing the frequency of the four viability patterns assessed with nuclear imaging in segments without scar tissue (a), with subendocardial scar tissue (b) and transmural scar tissue (c) on contrast-enhanced MRI.

DISCUSSION

The major finding in this study is that agreement between contrast-enhanced MRI and nuclear imaging for assessment of viability is high in segments without scar tissue as well as in segments with transmural scar tissue on contrast-enhanced MRI. Disagreement between the two imaging modalities regarding viability assessment was observed in segments with subendocardial scar tissue on contrast-enhanced MRI.

Contrast-enhanced MRI has been introduced as a reliable noninvasive technique for visualization of scar tissue in patients with previous MI ^{6,18} and in patients with clinical suspicion of CAD but without a history of MI ²². Kim et al. evaluated the accuracy of contrast-enhanced MRI for the assessment of scar tissue in dogs with previous MI and reported excellent agreement between the extent of scar tissue on contrast-enhanced MRI and the histological extent of necrosis ²³.

Subsequently, Kim et al. studied the value of scar tissue assessed with contrast-enhanced MRI for prediction of functional recovery after revascularization in 41 patients with chronic CAD ⁶. They reported that the majority of segments (78%) without scar tissue improved in function after revascularization, whereas improvement was virtually absent in segments with transmural scar tissue ⁶. Importantly, difficulties arise in segments with subendocardial scar tissue (transmural extent 1–50%), with only 53% of segments showing functional recovery ⁶.

Pooling of four studies in patients (n = 132) undergoing revascularization revealed a high sensitivity (95%), but a relatively low specificity (45%) of contrast-enhanced MRI for predicting improvement in function ¹⁰. The suboptimal specificity is related to segments with subendocardial scar tissue (transmural extent 1–50%), that do not improve in function. These findings highlight the fact that contrast-enhanced MRI is an excellent technique to delineate scar tissue (anatomical imaging), but the technique does not provide information on the pathophysiological substrate of the non-scarred tissue, which results in suboptimal prediction of functional recovery after revascularization.

Combined perfusion-18F -FDG imaging, as used in the current study, permits delineation of viability based on integration of perfusion and glucose utilization ²⁴. This approach has been widely validated (both with PET and with SPECT imaging) for detection of viable myocardium and prediction of functional recovery ^{13,25,26}. Different patterns of perfusion/18F-FDG uptake can be observed. Dysfunctional but viable myocardium can be divided into normal perfusion and 18F-FDG uptake representing repetitively stunned myocardium, whereas reduced perfusion with preserved 18F-FDG uptake represents hibernation. Scar tissue can be divided (based on the concordant reduction in perfusion and 18F-FDG uptake) into subendocardial scar tissue and transmural scar tissue. Based on these different patterns, with integration of perfusion and glucose utilization (assessed by 18F-FDG imaging), it is possible to better characterize the substrate of the dysfunctional myocardium. Few studies have compared contrast-enhanced MRI with perfusion-18F-FDG imaging 11-14,27. Kühl et al. performed contrast-enhanced MRI and perfusion-18F-FDG imaging in 29 patients with chronic CAD ¹³. Comparison between the techniques showed that viable segments on perfusion-18F-FDG imaging contained minimal scar tissue, whereas the extent of scar tissue on contrast-enhanced MRI increased in parallel with the abnormalities on perfusion-18F-FDG imaging; segments with severe matches on perfusion-18F-FDG imaging showed transmural scar tissue on contrast-enhanced MRI 13.

Knuesel et al. studied 19 patients with chronic CAD who underwent 13N-ammonia PET to evaluate perfusion and 18F-FDG PET to evaluate glucose utilization; scar tissue was analysed with contrast-enhanced MRI ¹¹. The authors reported a good correlation (ranging from r = 0.62 to r = 0.82) between segmental 18F-FDG uptake and the transmural extent of scar tissue on contrast-enhanced MRI. In particular, segments with 18F-FDG uptake ≥50% corresponded well with small areas of subendocardial scar tissue on contrast-enhanced MRI (and extensive non-scar tissue, 4.5 mm of the myocardial wall, on contrast-enhanced MRI). Ten patients also underwent revascularization, and the segments with preserved 18F-FDG uptake and minimal scar tissue improved in function after revascularization; conversely, the segments with severely reduced 18F-FDG uptake and extensive, transmural scar tissue, did not improve in function.

Of interest, the segments with severely reduced 18F-FDG uptake, but non-transmural scar tissue on contrast-enhanced MRI, did not improve in function after revascularization. This is

precisely the issue highlighted in the current study. The problem is that contrast-enhanced MRI provides excellent information on the extent and transmural extent of scar tissue (better than any other imaging technique), but it does not provide information on the pathophysiology of the non-scarred myocardium. As shown by Knuesel et al., segments with a small amount of scar tissue on contrast-enhanced MRI, but severely reduced 18F-FDG uptake do not improve in function ¹¹. These observations underscore the need to better characterize the non-scarred myocardium, as can be done with 18F-FDG imaging (in combination with perfusion imaging). Indeed, the findings of the current study illustrate that segments with an intermediate transmural extent of scar tissue (score 1 or 2) can exhibit a wide range of patterns on perfusion-18F-FDG imaging (see Figure 2b).

An important limitation of the current study was the lack of outcome data after revascularization, and therefore the study did not provide information on the functional fate of the segments after revascularization (recovery or not). Additional studies in patients undergoing revascularization are needed to further explore the actual outcome of segments with intermediate amounts of scar tissue on contrast-enhanced MRI and different perfusion-18F-FDG uptake patterns.

CONCLUSIONS

Comparison of contrast-enhanced MRI and perfusion-18F-FDG imaging for assessment of viability in patients with severe ischaemic LV dysfunction revealed high agreement in segments without scar tissue on contrast-enhanced MRI as well as in segments with transmural scar tissue. However, evident disagreement was noted in segments with subendocardial scar tissue on contrast-enhanced MRI, illustrating that the non-enhanced epicardial rim can contain either normal or ischaemically jeopardized myocardium. This differentiation is potentially important for prediction of outcome after revascularization. Indeed, Bove et al. have demonstrated in 15 patients that further refinement of the non-scar tissue (in this particular study assessment of contractile reserve by low-dose dobutamine challenge was used) resulted in superior prediction of outcome after revascularization ²⁸. Further studies, comparing various imaging techniques in patients undergoing revascularization including information on segmental functional outcome are needed to better define the contribution of scar tissue and viable tissue to functional recovery after revascularization.

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