Revascularization in patients with chronic ischaemic myocardial dysfunction: insights from cardiovascular magnetic resonance imaging

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In patients with chronic ischaemic left ventricular dysfunction, revascularization may lead to symptomatic and prognostic improvement.1 Myocardial viability and hibernation (i.e. myocardial dysfunction due to chronic hypoperfusion or repetitive ischaemia)2,3 provide the rationale for revascularization: the contractile function will improve with restoration of adequate blood flow. This reversible state should be clearly distinguished from irreversibly injured or infarcted myocardium, in which case the restoration of coronary blood flow would not be justified. Cardiovascular magnetic resonance (CMR) imaging with its high spatial resolution provides the qualitative and quantitative, global and regional information on myocardial anatomy and function. In combination with a gadolinium-based contrast agent, CMR allows an accurate quantification of the myocardial scar and predicts the likelihood of functional recovery after revascularization.5 – 9 The aim of this review is to summarize our current understanding of the detection of myocardial viability using CMR, and why it may be the preferred technique in the assessment of patients with ischaemic cardiomyopathy.

Keywords
Myocardial viability • Cardiovascular magnetic resonance imaging

CMR techniques in the assessment of myocardial viability

Several CMR techniques can be used in the evaluation of myocardial viability (Table 1). Currently, late gadolinium enhancement (LGE) imaging is by far the most frequently used technique. Alternative techniques are the assessment of end-diastolic wall thickness using cine imaging and the evaluation of contractile reserve using cine imaging in conjunction with low-dose dobutamine stress.

End-diastolic wall thickness

Both echocardiographic and CMR studies have demonstrated that in patients with the chronic ischaemic myocardial dysfunction, segments with the thinned myocardium (end-diastolic wall thickness of ≤5.5–6.0 mm) represent the scar and therefore have a low likelihood of the improved contractile function after revascularization.10,11 However, as reported on several previous occasions,12,13 even segments with significant wall thinning (<5 mm) may regain wall thickness and thickening, as long as there is no or minimal regional scarring at LGE imaging (Figure 1).

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Dobutamine stress cine CMR

Low-dose dobutamine (5–10 μg kg⁻¹ min⁻¹) stress cine CMR is used to evaluate the presence of recruitable contractile reserve (Figure 2) and is performed following imaging protocols comparable to those of dobutamine stress echocardiography.¹⁰,¹⁴ In a head-to-head comparison of dobutamine stress transoesophageal echocardiography and dobutamine stress CMR for the prediction of functional recovery after revascularization in patients with chronic ischaemic heart disease, both tests were highly accurate with the sensitivity and specificity values of, respectively, 82 and 83% for echocardiography and 86 and 92% for CMR.¹⁵ At higher dobutamine doses (up to 40 μg kg⁻¹ min⁻¹), wall motion in dysfunctional but viable segments may further improve or diminish, reflecting inducible ischaemia. This biphasic response appeared to be highly predictive of recovery of function after revascularization in dobutamine stress echocardiography studies.¹⁶ To date there are no reports on viability assessment with high-dose dobutamine cine CMR. Dobutamine stress CMR without gadolinium contrast can be used safely in patients with severe kidney disease. Side effects, such as atrial or ventricular arrhythmia, are unlikely during low-dose dobutamine stress testing.

Late gadolinium enhancement

LGE accurately visualizes a regional myocardial necrosis in ischaemic heart disease.¹ LGE images are typically acquired using an inversion recovery pulse sequence of 8–30 min after an intravenous injection of a gadolinium-based extracellular contrast agent (usually 0.2 mmol kg⁻¹). After the injection, gadolinium rapidly diffuses into the interstitial space. In chronically infarcted regions, the interstitial space is increased as a result of replacement fibrosis. Scan parameters (in particular inversion recovery time) are adjusted by a technician to null the normal non-infarcted myocardium, which would therefore appear uniformly dark. The infarcted areas are easily identified as regions of high signal intensity within or surrounded by non-enhancing normal myocardium.

In ischaemic heart disease, hyperenhancement typically has a subendocardial or transmural distribution. Excellent spatial resolution (1.5 × 1.5 mm in plane resolution) and high contrast between the scarred and viable myocardium allow the quantification of the transmural extent of myocardial necrosis. Viability assessment for clinical purposes is usually performed by visual evaluation of the scar transmurality on a 5-grade scale, ascending from 0 to 1–25, 26–50, 51–75, and >75% scar. Regions with <50% of transmural extent of hyperenhancement are (arbitrarily) considered viable. However, visual analysis of hyperenhanced regions is influenced by image window settings. Several methods have been proposed to differentiate hyperenhanced, non-viable scar from non-enhanced, viable myocardium in an objective, standardized manner, varying from simple thresholding to more complex computer algorithms.¹⁷–¹⁹ A scar may be defined as the myocardial tissue with signal intensity higher than the in-slice mean plus 2–6 SD. The scar may also be defined by using the signal of the infarcted region, the full width at half-maximum (FWHM) method, which uses 50% of the maximal signal within the scar as the threshold. In patients with chronic ischaemic heart disease, the closest agreement between visual and standardized analysis was found at window setting thresholded at 5 SD above the signal of remote, non-infarcted myocardium.¹⁷ However, no significant differences

Table 1 Prediction of regional functional improvement by CMR

<table>
<thead>
<tr>
<th>CMR technique</th>
<th>Viability criteria</th>
<th>No. of patients</th>
<th>Follow-up after revascularization (months)</th>
<th>PPV/NPV (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cine imaging</td>
<td>EDWT &gt;5.5 mm</td>
<td>43</td>
<td>4–6</td>
<td>78/82</td>
<td>Baer et al.¹⁰</td>
</tr>
<tr>
<td></td>
<td>EDWT &gt;6 mm</td>
<td>20, 26</td>
<td>6</td>
<td>90/57</td>
<td>Gutberlet et al.²⁹</td>
</tr>
<tr>
<td>LDD stress CMR</td>
<td>Improved contractility</td>
<td>43</td>
<td>4–6</td>
<td>96/83</td>
<td>Baer et al.¹⁰</td>
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<tr>
<td></td>
<td></td>
<td>23</td>
<td>3–6</td>
<td>77/54</td>
<td>Gunning et al. ⁴⁰</td>
</tr>
<tr>
<td></td>
<td></td>
<td>52</td>
<td>4.9 ± 0.7</td>
<td>92/85</td>
<td>Baer et al.¹⁰</td>
</tr>
<tr>
<td></td>
<td></td>
<td>29</td>
<td>3</td>
<td>85% correct predictions</td>
<td>98/56</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20</td>
<td>6</td>
<td>89/85</td>
<td>Kirschbaum et al.²⁶</td>
</tr>
<tr>
<td>LGE</td>
<td>&lt;25% scar transmurality</td>
<td>41</td>
<td>3</td>
<td>71/79</td>
<td>Kim et al.⁷</td>
</tr>
<tr>
<td></td>
<td></td>
<td>52</td>
<td>6</td>
<td>73/69</td>
<td>Selvanayagam et al.⁸</td>
</tr>
<tr>
<td></td>
<td></td>
<td>29</td>
<td>3</td>
<td>73% correct predictions</td>
<td>74/69</td>
</tr>
<tr>
<td></td>
<td></td>
<td>27</td>
<td>5 ± 1</td>
<td>74/69</td>
<td>Baks et al.⁴¹</td>
</tr>
<tr>
<td></td>
<td>&lt;50% scar transmurality</td>
<td>20</td>
<td>6</td>
<td>99/94</td>
<td>Gutberlet et al.²⁹</td>
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<td></td>
<td></td>
<td>29</td>
<td>6</td>
<td>73/93</td>
<td>Kuhl et al.⁴²</td>
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<td></td>
<td>29</td>
<td>0.5</td>
<td>72/79</td>
<td>Wu et al.⁴³</td>
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<td></td>
<td></td>
<td>35</td>
<td>24 ± 12</td>
<td>77/73</td>
<td>Bondarenko et al.⁵</td>
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<td></td>
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<td>33</td>
<td>6</td>
<td>63/95</td>
<td>Pegg et al.¹³</td>
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<td></td>
<td></td>
<td>43</td>
<td>6</td>
<td>79/67</td>
<td>Kirschbaum et al.²⁶</td>
</tr>
<tr>
<td></td>
<td>Viable rim &gt;4.5 mm</td>
<td>10</td>
<td>11 ± 2</td>
<td>78/78</td>
<td>Knuesel et al.²⁵</td>
</tr>
<tr>
<td></td>
<td>Viable rim &gt;3 mm</td>
<td>43</td>
<td>6</td>
<td>79/81</td>
<td>Kirschbaum et al.²⁶</td>
</tr>
</tbody>
</table>

EDWT, end-diastolic wall thickness; LDD, low-dose dobutamine; LGE, late gadolinium enhancement; NPV, negative predictive value; PPV, positive predictive value.
between thresholding by 2–8 SD and the FWHM method were found, when the quantification of LGE was evaluated in relation to the functional outcome after revascularization.\textsuperscript{20}

Figure 1 Cine and late gadolinium enhanced (LGE) images of two patients (A and B) at the baseline and cine images after coronary revascularization. Both patients have wall thinning accompanied by severe regional dysfunction of the anterior wall at the baseline. Patient A shows no contrast enhancement in the dysfunctional area. Patient B has a transmural myocardial infarction. After revascularization patient A exhibits the recovery of contractile function and normalization of wall thickness, while no improvement is observed in Patient B.

Revascularization in patients with chronic ischaemic myocardial dysfunction

The high resolution of LGE permits the assessment of viability in segments with advanced wall thinning, which makes it superior to the simple assessment of wall thickness. The risk of nephrogenic
systemic fibrosis in patients with renal failure is extremely low with the use of cyclical agents and lower doses, although careful consideration of the indication in patients on haemodialysis is still needed.21,22 A general limitation to the use of CMR is that pacemakers, defibrillators, and other implantable electronic devices are still contraindicated, although newer, MRI compatible devices are being developed.23

Predicting functional improvement after revascularization

Kim et al.7 were the first to show that in patients with chronic ischaemic myocardial dysfunction the likelihood of regional functional improvement is inversely related to the transmural extent of hyperenhancement on LGE images. They found that 78% of dysfunctional segments without hyperenhancement improved, compared with 1 of 58 segments with >75% hyperenhancement. Using a cut-off value of ≤25% of the scar transmurality to define viability, sensitivity and specificity were, respectively, 71 and 79%, when the regions with any degree of dysfunction were evaluated. Expressing diagnostic utility as sensitivity and specificity (or positive- and negative-predictive values) using a single cut-off is appealing to the clinician and facilitates clinical decision-making. However, the gradual relation between functional improvement and the scar transmurality emphasizes that the concept of viability as a binary process is an artificial one. As a necessary consequence, this makes it more difficult to predict whether segments with intermediate degrees of scar (25–75%) will improve after revascularization.

Several strategies have been proposed to improve the diagnostic accuracy of LGE CMR in segments with intermediate degree of myocardial scar. Wellhofer et al.9 found low-dose dobutamine stress CMR to be superior to LGE predicting functional recovery after revascularization in dysfunctional segments with 1–74% transmural extent of chronic infarction. Bove et al.24 reported similar improvement of percentage of wall thickening in dysfunctional segments with 1–25 and 26–50% scar after surgical revascularization. However, within the same segments, those who responded to low-dose dobutamine by improvement in wall thickening to normal range before revascularization demonstrated greater improvement of percentage of wall thickening after revascularization than those who did not. Therefore, performing low-dose dobutamine stress CMR in addition to LGE should therefore be considered in cases with intermediate likelihood of functional recovery. Knuesel et al.25 focused on a viable rim, i.e. non-enhanced myocardium. These authors compared LGE CMR and FDG-PET in 19 patients and assessed functional improvement in 10 patients after revascularization. They found that a residual non-enhanced viable rim of 4.5 mm corresponded with ≥50% FDG uptake. In their study metabolically active segments with preserved viable rim had a high improvement rate after revascularization (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). Kirschbaum et al.26 found evidence that combining data on unenhanced viable rim (≥3 mm) with contractile reserve assessment by low-dose dobutamine is helpful predicting functional improvement after revascularization in segments with intermediate degree of chronic myocardial scar. However, the evidence is still limited and more studies are needed. Moreover, dysfunctional regions with the intermediate scar extent (e.g. 50% of transmural extent of hyperenhancement) contain viable myocardial tissue and might appear viable when examined with nuclear techniques and show (pseudo-) improvement in response to dobutamine stress. Nevertheless, they may not be hibernating, i.e. since their full potential of function is already used, these segments will not demonstrate further improvement in resting contractility after revascularization. LGE CMR is the only technique that allows the side-by-side visualization and quantification of scarred and viable myocardial tissue. Thus, it may be used to further refine the assessment of viability and potential of functional recovery in patients with ischaemic cardiomyopathy. As an example, LGE imaging provides more insight into why the contractile function does not always recover after revascularization.

Figure 2 End-diastolic and end-systolic still-frames in a patient with ischaemic left ventricular dysfunction, old inferior infarction and occluded left anterior descending artery at coronary angiography. The end-systolic frame shows akinesis of a thinned inferior segment, severe hypokinesis of the anterior and lateral wall and hypokinesis of the septum. During low-dose dobutamine stress, contraction improves in all segments except the inferior segment. The corresponding late gadolinium enhanced image shows no enhancement of the improving segments and transmural enhancement in the inferior segment.
First, it may be used to assess both likelihood, as well as time course of functional improvement. In patients with the chronic ischaemic myocardial dysfunction improvements of dysfunctional but viable myocardium may be considerably delayed: it may take >1 year to improve after successful revascularization. Extensive structural changes found by histological analysis of tissue samples obtained from areas of myocardial hibernation, including the loss of myofilaments with the replacement by glycogen and increasing degree of fibrosis, impede the timely functional improvement. In accordance with these data, we recently showed that the time course of improvement is more delayed in segments with more extensive hyperenhancement at the baseline. As a consequence, follow-up examination scheduled at 3 or 6 months after revascularization, may not be long enough to assess the full potential of recovery.

Second, the high reproducibility of LGE imaging allows the identification of new, clinically undetected areas of necrosis between the baseline and follow-up examinations. Procedure-related necrosis may offset the improvement in the regional function in viable segments and has been shown an important negative predictor of the functional outcome.

Third, combining LGE with cine imaging and rest perfusion imaging can help to make distinction between truly hibernating, i.e. hypoperfused, hypocontractile segments from dysfunctional segments due to the presence of scar.

Thus, a considerable amount of viable tissue, a successful revascularization procedure as well as patience are required for global functional improvement. It has been estimated that at least 25% viable myocardial tissue is necessary for significant functional improvement. It has been estimated that at least 25% segments due to the presence of scar. As a consequence, follow-up examination scheduled at 3 or 6 months after revascularization, may not be long enough to assess the full potential of recovery.

Viability assessment in the management of patients with ischaemic cardiomyopathy

According to current guidelines on myocardial revascularization of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery, the detection of myocardial viability should be included in the diagnostic work-up of patients with the systolic LV dysfunction and known coronary artery disease, and surgical revascularization should be considered in the presence of viable myocardium. The level of evidence for this recommendation is limited and based on retrospective studies. The recently published STICH trial was the first randomized trial evaluating the prognostic effect of coronary artery bypass grafting on top of optimal medical therapy in patients with ischaemic cardiomyopathy. Results from the viability substudy showed that, regardless of the presence of significant amounts of viable myocardium, surgery did not contribute to improved overall survival. However, the methodology of the viability substudy has been questioned. After slow initial patient recruitment, the study protocol was modified and referral for viability testing was left to the discretion of the treating physician. This may have resulted in the selection bias which is suggested by the fact that the large majority of the patients in the viability substudy (81%) met the stringent viability criteria. In addition, four different SPECT protocols and dobutamine stress echocardiography were allowed as the viability test. Differences in the viability information provided by these two methods (one related to membrane integrity and the other to contractile reserve) and in analytic approaches pose further limitations on the outcome of the trial. Data on functional (ejection fraction, volumes) outcome might have allowed better interpretation of the results, but, unfortunately, these were not included in the recent publications. Finally, the gradual relation between hyperenhancement and both functional outcome after revascularization as well as its time course strongly favour the present concept of hibernation. More randomized studies are necessary to fully establish the role of viability testing and revascularization in patients with heart failure and ischaemic cardiomyopathy. CMR seems the optimal technique to assess pre-operative viability status, peri-operative injury and long-term functional changes. The quantification of LGE images should be standardized to optimize reproducibility and reliability and to facilitate the comparison between different centres. Novel methods such as T1 mapping, which bypass the influences of windowing and variations in signal enhancement by directly measuring the underlying T1 relaxation times of the different areas of the myocardium, might further expand the use of CMR in patients with ischaemic cardiomyopathy.

Conflict of interest: none declared.

References