CARDIOVASCULAR MR TO ASSESS MYOCARDIAL VIABILITY IN CHRONIC ISCHAEMIC LV DYSFUNCTION

1359

T A M Kaandorp, H J Lamb, E E van der Wall, A de Roos, J J Bax

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Heat failure has become a major problem in clinical cardiology, with recent estimations showing that 4.9 million patients in the USA have chronic heart failure, with 550 000 new patients diagnosed annually, resulting in 970 000 hospitalisations.¹ It appears that coronary artery disease is the underlying cause of heart failure in > 70% of patients.¹ The available therapeutic options include optimised medical treatment, heart transplantation, revascularisation (with optional left ventricular (LV) restoration and/or mitral valve repair) and cardiac resynchronisation therapy. Currently, substantial effort is invested in the development of gene and cell therapy for treatment of heart failure. In daily clinical practice, the choice is frequently between medical treatment and revascularisation. From this perspective, assessment of viability is important to guide management of patients with ischaemic LV dysfunction; patients with viable myocardium may improve in LV function after revascularisation, whereas patients with only scar tissue will not improve. In view of the increased risk for (peri-) operative complications, a pre-operative evaluation for myocardial viability is thus warranted, to select the patients who may benefit from surgery. Currently, many techniques are available for identification of dysfunctional but viable myocardium.^{w1} The most frequently used techniques in the clinical setting include nuclear imaging with positron emission tomography (PET) and single photon emission computed tomography (SPECT) to assess myocardial metabolism, perfusion, cell membrane and mitochondrial intactness; and echocardiographic imaging using dobutamine stress to assess contractile reserve/ischaemia or contrast agents to assess myocardial perfusion. More recently cardiac magnetic resonance (CMR) has become popular for the assessment of myocardial viability. This technique has an excellent spatial resolution and is currently the only imaging modality that allows distinction between transmural and subendocardial processes. Various techniques with CMR provide information on myocardial viability; these will be discussed extensively in this article. Besides assessment of viability, CMR provides for the surgeon additional information needed to select the optimal surgical strategy, including information on LV function, LV volumes, the presence of LV aneurysms (which need LV aneurysmectomy), and ischaemic mitral regurgitation (which require mitral valve repair in terms of restrictive annuloplasty). This article discusses the value of CMR (in particular the different CMR techniques to assess viability) for the evaluation of patients with ischaemic cardiomyopathy. Before entering this discussion, some definitions of viability and the clinical relevance of viability assessment are addressed.

VIABILITY: DEFINITIONS

The observational work by Rahimtoola^{w2} resulted in the awareness that LV dysfunction is not necessarily an irreversible process, but that improvement of LV function is possible after revascularisation. This improvement has been related to the presence of dysfunctional but viable myocardium, which has the potential to recover in function after adequate restoration of blood flow. Over the years, many studies have focused on the identification of viable myocardium and prediction of improvement of function post-revascularisation. Considerable confusion has been raised about the appropriate definition of viable myocardium. Viable myocardium theoretically includes an entire spectrum, ranging from normal myocardium to epicardial regions of viable myocardium in non-transmural infarction. Viable, normal myocardium is not associated with chronic dysfunction. In the clinical setting, viability is only important in regions with chronic contractile dysfunction, to assess whether revascularisation will result in improvement of function. Rahimtoola popularised the concept of hibernation, which refers to a condition of chronically reduced/absent contraction secondary to chronic hypoperfusion in patients with coronary artery disease, in whom revascularisation will result in recovery of function.² Studies with PET, however, showed that chronically dysfunctional myocardium frequently had (near-) normal resting blood flow instead of reduced blood flow. Further studies subsequently revealed that not resting blood flow, but rather flow reserve was reduced in patients with chronically

See end of article for authors' affiliations

Correspondence to:
T A M Kaandorp, MD,
Department of Radiology
C2-S, Leiden University
Medical Center, Albinusdreef
2, 2300 RC Leiden, The
Netherlands; t.a.m.
kaandorp@lumc.nl

Figure 1 Prediction of functional recovery post-revascularisation in dysfunctional segments with subendocardial scar is difficult. When the epicardial (non-infarcted) region is normal, no recovery will occur (left panel). However when the epicardial regions contain jeopardised (viable) myocardium, the likelihood of recovery is high (right panel).

dysfunctional myocardium. These findings have led to the hypothesis that repeated ischaemic attacks may result in chronic contractile dysfunction, with flow remaining normal or mildly reduced—a situation referred to as “repetitive stunning”.³ From a clinical viewpoint, the differentiation between repetitive stunning and hibernation may not be that important, since revascularisation is required in both conditions in order to improve contractile function; from a practical viewpoint, both conditions can be grouped as “jeopardised myocardium”.

Many studies (using all different imaging techniques) aiming at the prediction of functional improvement post-revascularisation reported a lower specificity, indicating that many dysfunctional segments that were classified as viable did not improve in function post-revascularisation. This is (partially) caused by regions that contain subendocardial scar tissue. In these regions, the epicardial layers still contain viable tissue. However, the question in these regions is whether these epicardial layers contain viable, but normal, myocardium or jeopardised myocardium (fig 1). Only in the latter condition can improvement of function be anticipated. Differentiation between these two conditions is currently one of the most difficult and challenging issues in assessing myocardial viability. All available imaging techniques do not have the spatial resolution to differentiate epicardial and endocardial processes. With CMR however, this differentiation is possible.

VIABILITY: CLINICAL RELEVANCE

Viability assessment is clinically relevant for patient management. Improvement of function after revascularisation is still

considered the “gold standard” for viability. Pooled data from 105 viability studies (using nuclear imaging or stress echocardiography) showed a mean sensitivity and specificity of 84% and 69% to predict recovery of regional function after revascularisation.⁴ Improvement in LV ejection fraction (LVEF) was evaluated in 28 studies; patients with viable myocardium exhibited an improvement in LVEF from on average 37% to 45%, whereas patients without viability did not improve in LVEF (36% before revascularisation versus 36% post-revascularisation).⁴ Finally, viability is related to prognosis. The available 17 prognostic studies (seven with FDG PET, four with thallium-201 imaging, and six with dobutamine echocardiography) showed that patients with viable myocardium who are treated medically had a high event rate (20%), as compared to a low event rate in viable patients who underwent revascularisation (7%).⁴ Thus, the available evidence suggests that patients with viable myocardium should undergo revascularisation, although it is important to realise that prospective, randomised trials on the prognostic value of viability are still lacking.

CMR TECHNIQUES TO ASSESS VIABILITY

Several CMR techniques have been proposed for the assessment of myocardial viability. These techniques include resting CMR (which provides information on end diastolic wall thickness (EDWT)), dobutamine CMR (which provides information on contractile reserve), and contrast enhanced CMR (which provides information on scar tissue). The available studies using these various techniques to predict recovery of function post-revascularisation are summarised below and in tables 1–4.

RESTING CMR TO ASSESS LV END DIASTOLIC WALL THICKNESS

Following acute myocardial infarction, structural changes occur within the infarct zone. In particular, in the presence of extensive, transmural infarction, wall thinning occurs in the centre of the infarct zone. Various studies have demonstrated that wall thinning is frequently associated with transmural scar tissue. Perrone-Filardi *et al*⁵ performed a direct comparison between CMR and PET using metabolic imaging with F18-fluorodeoxyglucose (FDG) in patients with ischaemic LV dysfunction. The authors demonstrated that an EDWT < 8 mm yielded a sensitivity and specificity of 74% and 79% for prediction of absence of metabolic activity. Similarly, Baer *et al*⁶ performed a head to head comparison between resting CMR and FDG PET in 35 patients with chronic ischaemic LV dysfunction. It was shown that regions with an EDWT < 5.5 mm had significantly reduced FDG uptake, whereas regions with an EDWT ≥ 5.5 mm had preserved FDG uptake. This cutoff value for EDWT is in good agreement with data derived from necropsy studies^{7,8}; in these studies it was shown that regions with a chronic

Table 1 End diastolic wall thickness

Study	No. of patients	Male (%)	Mean age (years)	Mean LVEF (%)	Patients with MVD (%)	Patients with previous MI (%)	Segments with recovery (%)	Sensitivity (%) (no. of segments)	Specificity (%) (no. of segments)
Baer <i>et al</i> ⁶	43	93	58	41	59	100	46	94 (176/188)	52 (113/219)
Klow <i>et al</i> ¹⁴	17	88	63	40	NA	100	35	98 (63/64)	19 (23/120)
Schmidt <i>et al</i> ⁴	40	93	57	42	72	100	63	100 (25/25)	53 (8/15)
Average	33	91	59	41	66	100	48		
Weighted mean								95 (264/277)	41 (144/354)

LVEF, left ventricular ejection fraction; MI, myocardial infarction; MVD, multivessel disease; NA, not available.

Table 2 Dobutamine stress

Study	No. of patients	Male (%)	Mean age (years)	Mean LVEF (%)	Patients with MVD (%)	Patients with previous MI (%)	Segments with recovery (%)	Sensitivity (%) (no. of segments)	Specificity (%) (no. of segments)
Baer <i>et al</i> ⁵	52	92	58	41	75	?	50	86 (24/28)	92 (22/24)
Baer <i>et al</i> ⁶	35	100	59	42	46	100	52	81 (NA)	95 (NA)
Gunning <i>et al</i> ⁶	23	90	61	24	100	NA	57	50 (NA)	81 (NA)
Sayad ¹⁷	10	70	NA	NA	NA	NA	60	89 (25/28)	93 (14/15)
Baer <i>et al</i> ⁶	43	93	58	41	59	100	46	89 (24/27)	94 (15/16)
Sandstede <i>et al</i> ¹⁸	25	88	58	NA	NA	84	51	61 (65/106)	90 (91/101)
Trent <i>et al</i> ¹⁹	25	100	64	53	NA	100	40	71 (81/114)	70 (163/232)
Lauerma <i>et al</i> ⁹	10	80	69	44	100	70	66	79 (NA)	93 (NA)
Wellnhofer <i>et al</i> ¹¹	29	93	68	32	NA	93	NA	75 (93/124)	93 (152/164)
Average	29	90	62	40	76	91	53		
Weighted mean								73 (312/427)	83 (457/552)

LVEF, left ventricular ejection fraction; MI, myocardial infarction; MVD, multivessel disease. NA, not available.

infarction had a wall thickness < 6 mm. An example of a patient with a previous transmural infarction and severe wall thinning is shown in fig 2.

In a subsequent study, Baer *et al*⁶ tested the value of EDWT for prediction of functional recovery post-revascularisation. The authors showed that segments with an EDWT < 5.5 mm virtually never showed recovery of function post-revascularisation. The alternative was not true: segments with an EDWT ≥ 5.5 mm did not always improve in function post-revascularisation; this is related to the aforementioned issue of non-transmural infarction. Segments with an EDWT ≥ 5.5 mm frequently contain subendocardial scar tissue, with residual viability in the epicardial layers. In the absence of jeopardised myocardium though, recovery of function will not occur after revascularisation. Three studies (with a total of 100 patients) have used EDWT to predict functional recovery; pooling of the data (table 1) confirmed an excellent sensitivity (95%, range 94–100%) to predict recovery, with a lower specificity (41%, range 19–53%). Thus, severe wall thinning appears to indicate scar tissue and has a high accuracy to predict no recovery after revascularisation. However, it was recently demonstrated that even in the presence of severe wall thinning, recovery of function may occur, but only when contrast enhanced CMR excludes scar tissue.⁷

DOBUTAMINE STRESS CMR TO ASSESS CONTRACTILE RESERVE

In addition to assessment of EDWT to identify viable myocardium, the presence of contractile reserve is frequently used to detect viable myocardium. The hallmark of viability is the improvement of contraction in dysfunctional myocardium that is elicited by the infusion of low dosages of dobutamine (5–15 µg/kg/min). Baer *et al*^{5, 6, 15} extensively explored this approach and demonstrated that dobutamine stress CMR can adequately predict improvement of regional

LV function after revascularisation. The authors showed that an increased systolic wall thickening > 2 mm during dobutamine infusion was a reliable marker of predictor of functional recovery.⁶ A total of nine studies with 252 patients using dobutamine stress CMR to predict recovery of function have been published with a mean sensitivity of 73% (range 50–89%) and a mean specificity of 83% (range 70–95%). Thus, dobutamine stress CMR has a high specificity with a slightly lower sensitivity.

CONTRAST ENHANCED CMR TO ASSESS SCAR TISSUE

Contrast hyperenhancement on delayed resting CMR was first described more than 20 years ago^{15, 17} and is defined as regions of increased image intensity on T1 weighted images, acquired more than five minutes after the intravenous administration of a contrast agent. In a study in 2001, Kim *et al*¹⁸ investigated an improved pulse sequence and measured image intensities in “delayed hyperenhanced regions” to be 485% higher than in normal regions. The mechanism underlying the hyperenhancement appears related to the interstitial space between collagen fibres, which is larger in scar tissue as compared to the densely packed myocytes in normal myocardium, and the contrast agent will be trapped in these areas in infarcted tissue.

Kim *et al*¹⁸ elegantly validated the value of contrast enhanced CMR to detect scar tissue in animal experiments. In chronically instrumented dogs with previous infarction, the authors showed a perfect agreement between the extent of scar tissue on contrast enhanced CMR and the histological extent of necrosis using TTC staining of the explanted hearts. The major advantage of contrast enhanced CMR over other imaging techniques is that because of the superior spatial resolution, differentiation between transmural and subendocardial infarction is possible. Examples of contrast enhanced CMR are shown in fig 3.

Table 3 Delayed contrast enhancement

Study	No. of patients	Male (%)	Mean age (years)	Mean LVEF (%)	Patients with MVD (%)	Patients with previous MI (%)	Segments with recovery (%)	Sensitivity (%) (no. of segments)	Specificity (%) (no. of segments)
Kim <i>et al</i> ¹⁰	41	88	63	43	NA	42	53	97 (411/425)	44 (211/379)
Lauerma <i>et al</i> ⁹	10	80	69	44	100	70	66	62 (NA)	98 (NA)
Selvanayagan <i>et al</i> ²⁰	52	87	61	62	NA	50	59	95 (326/343)	26 (71/269)
Wellnhofer <i>et al</i> ¹¹	29	93	68	32	NA	93	NA	90 (111/124)	52 (85/164)
Average	33	87	65	45	NA	64	59		
Weighted mean								95 (848/892)	45 (367/812)

LVEF, left ventricular ejection fraction; MI, myocardial infarction; MVD, multivessel disease. NA, not available.

Table 4 Sensitivity and specificity for the different imaging techniques (based on weighted mean values from available studies)

	No. of patients	Sensitivity (%)	95% CI	99% CI	Specificity (%)	95% CI	99% CI
End diastolic wall thickness	100	95	91 to 99	90 to 100	41	31 to 50	28 to 53
Dobutamine stress	259	73	68 to 78	66 to 80	83	78 to 87	77 to 89
Delayed contrast enhancement	132	95	91 to 99	90 to 100	45	37 to 54	34 to 56

Critical values 99%, 95% were 2.58 and 1.96, respectively, CI, confidence interval.

Klein and colleagues⁹ evaluated 31 patients with depressed LVEF (mean (SD) 28 (9)%) with FDG PET and contrast enhanced CMR. The agreement between both techniques for assessing scar tissue was 91%. Importantly, 11% of segments defined as viable on FDG PET had some extent of scar tissue on contrast enhanced CMR. This reflects the superior resolution of CMR allowing discrimination of small sub-endocardial infarcts.

To evaluate further the value of contrast enhanced CMR for predicting functional recovery, Kim and co-workers studied 50 patients with chronic infarction and LV dysfunction undergoing revascularisation.¹⁰ Contrast enhanced CMR and resting LV function were assessed before revascularisation, and recovery of function was assessed 11 weeks post-revascularisation. The likelihood of segmental recovery of function post-revascularisation paralleled the transmural extent of infarction of the segments: improvement of function decreased progressively as the transmural extent of scar tissue increased. In particular, 78% of dysfunctional segments without contrast enhancement improved in function, as compared to 2% of segments with scar tissue extending > 75% of the LV wall (fig 4). Using a cutoff value of 25% transmural extent of scar tissue, the sensitivity and specificity were 86% and 61% to predict improvement of function. Changing the cutoff value to 75% transmural extent, sensitivity and specificity would be 100% and 15%, respectively. With nuclear imaging, 50% tracer uptake is frequently used to assess viability; when a cutoff value of 50% transmural extent was applied, the sensitivity and specificity were 97% and 44%, respectively. Pooling of the four available studies in patients undergoing revascularisation (total 132 patients) confirmed these findings and revealed a sensitivity of 95% with a specificity of 45% (table 3).

The suboptimal specificity is related to the presence of segments with subendocardial necrosis (and epicardial viability) that do not improve in function. The low specificity indicates that information on the constitution of the epicardial regions is needed: do they contain normal, viable tissue or jeopardised myocardium?

COMPARISON OF CMR TECHNIQUES TO PREDICT FUNCTIONAL RECOVERY

There are currently not many direct comparisons in large groups of patients undergoing revascularisation. Baer *et al*⁶ performed a head to head comparison between EDWT and dobutamine stress CMR in 43 patients undergoing revascularisation. The sensitivities of both techniques were comparable (92% *v* 89%), whereas the specificity was higher for dobutamine CMR as compared to EDWT (94% *v* 56%).

Two studies directly compared dobutamine stress CMR with contrast enhanced CMR. Lauerma *et al*⁹ reported a superior sensitivity and specificity for dobutamine stress CMR in 10 patients undergoing revascularisation. Wellnhofer and colleagues¹¹ demonstrated in 29 patients undergoing revascularisation a higher sensitivity for contrast enhanced CMR, with a higher specificity for dobutamine stress CMR to predict functional recovery.

When pooled data are compared, the differences in accuracy of the various CMR techniques to predict functional recovery post-revascularisation become more clear (table 4). The sensitivity of EDWT and contrast enhanced CMR are significantly higher than that of dobutamine stress CMR, as evidenced by the absence in overlap of 95% confidence intervals. Conversely, the specificity of dobutamine stress CMR is significantly higher than that of EDWT and contrast enhanced CMR.

Integrated use of CMR techniques can be considered for optimal prediction of functional recovery. A very sensitive technique, such as contrast enhanced CMR, may serve as a first step. In the presence of minimal scar tissue (transmural extent < 25%), recovery of function is likely to occur, whereas segments with extensive scar tissue (transmural extent > 50–75%) will not recover (as shown in the study by Kim *et al*¹⁰). Segments with an intermediate extent of scar tissue (transmural extent 25–50%) have an intermediate likelihood of recovery, and in these segments additional testing may be needed. Dobutamine stress CMR may serve as a second step in these segments in order to further differentiate between segments with low (without contractile reserve) and high

Figure 2 Corresponding short axis slices (left panel, end diastole; right panel, end systole) of a patient with a previous anterior and inferior infarction. The anterior region (white arrow) shows preserved wall thickness (≥ 5.5 mm) suggesting viable tissue, whereas the end diastolic wall thickness (EDWT) in the inferior region (black arrow) is ≤ 5.5 mm, indicating scar tissue.

Figure 3 Examples of contrast enhanced CMR studies. Panel A: transmural antero-septal infarction (hyperenhancement, white tissue). Panel B: non-transmural infarction with scar tissue extending from the septum to the lateral wall. Panel C: transmural inferior infarction. Panel D: non-transmural infarction in the inferior region.

likelihood (with contractile reserve) to improve in function post-revascularisation. Kaandorp *et al*¹² recently demonstrated the feasibility of integrated assessment of contrast enhanced CMR and dobutamine stress CMR. The accuracy of this approach, however, needs further evaluation in patients undergoing revascularisation.

Integration of EDWT with another technique can also be considered, but the problem is as follows. It has been demonstrated that EDWT has a high sensitivity, but low specificity. Thus, as a first step, assessment of EDWT is

possible, and segments with EDWT < 5.5 mm should be considered scar tissue. Then, in the remaining segments (with EDWT ≥ 5.5 mm) a second test is needed. However, with the recent evidence that even in segments with EDWT < 5.5 mm recovery of function is possible,⁷ all segments need to undergo a second test.

Figure 4 The likelihood of recovery of function post-revascularisation is high in the absence of infarcted tissue or in the presence of minimal infarction (< 25% of the left ventricular wall). The likelihood of recovery is minimal in the presence of transmural infarction (> 75% of the left ventricular wall). Intermediate extents of infarction have an intermediate likelihood of recovery. Data based on Klein *et al*.⁹

Figure 5 Severely dilated left ventricle with mitral annulus dilatation, systolic leaflet retraction resulting in central ischaemic mitral regurgitation (arrow).

Figure 6 Large left ventricular aneurysm of the inferior wall; the contrast enhancement reveals extensive scar tissue in this region. The black area within the LV aneurysm (arrow) indicates thrombus formation.

ADDITIONAL INFORMATION PROVIDED BY CMR

With more aggressive surgical approaches, more information is needed preoperatively to determine the optimal surgical procedure. This includes information about the LV function—that is, the LVEF to assess the risk of surgery; patients with lower LVEF are at higher risk for (peri-)operative morbidity/mortality. CMR should currently be considered as the “gold standard” for assessment of LVEF.^{w10}

In addition, LV volumes are important to determine the likelihood of recovery of function post-revascularisation. It was recently demonstrated that patients with severely dilated left ventricles have a low likelihood to improve in LVEF despite the presence of viable tissue.^{w11} In 61 patients with substantial viability (≥ 4 viable segments), the likelihood of improvement in LVEF $> 5\%$ was minimal when the LV end systolic volume exceeded 153 ml.

Another issue of importance is the presence of ischaemic mitral regurgitation. This phenomenon is frequently observed in ischaemic cardiomyopathy, as a consequence of mitral annular dilatation,^{w12} and mitral valve repair should be performed in addition to revascularisation. As illustrated in fig 5, ischaemic mitral regurgitation can be visualised adequately with CMR. Moreover, the feasibility of precise quantification of regurgitant volume with CMR was reported recently.¹³

Finally, with the increasing use of LV aneurysmectomy or surgical LV restoration, information on the presence of LV aneurysms is needed.^{w13} In fig 6, an example of a large LV aneurysm (with thrombus formation) is demonstrated using contrast enhanced CMR.

CONCLUSION

With the increasing number of patients with ischaemic heart failure, information on myocardial viability is needed to guide patient treatment. Accurate viability assessment is possible with CMR using different techniques including EDWT assessment, dobutamine stress CMR, and contrast enhanced CMR. While dobutamine stress CMR has the highest specificity to predict functional recovery post-revascularisation, EDWT and contrast enhanced CMR have a higher sensitivity. Integrated use of particularly dobuta-

CMR viability assessment in chronic ischaemic LV dysfunction: key points

- ▶ Dobutamine stress cardiovascular magnetic resonance (CMR) has the highest specificity to predict functional recovery post-revascularisation
- ▶ End diastolic wall thickness (EDWT) and delayed contrast enhanced CMR have a higher sensitivity to predict functional recovery
- ▶ Integrated use of dobutamine stress CMR and contrast enhanced CMR may be preferred for optimal prediction of functional recovery
- ▶ Additional information can be provided by CMR on left ventricular ejection fraction (LVEF), LV volumes, ischaemic mitral regurgitation, and LV shape

mine stress CMR and contrast enhanced CMR may be preferred for optimal prediction of functional recovery.

Finally, CMR can provide additional information on LVEF, LV volumes, ischaemic mitral regurgitation and LV shape (aneurysms), which can be used to plan the surgical strategy.

Additional references appear on the *Heart* website—<http://www.heartjnl.com/supplemental>

Authors' affiliations

T A M Kaandorp, H J Lamb, A de Roos, Department of Radiology, Leiden University Medical Center, the Netherlands
E E van der Wall, J J Bax, Department of Cardiology, Leiden University Medical Center, the Netherlands

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