Review Article

Cardiac Magnetic Resonance Imaging to Detect and Evaluate Ischemic Heart Disease

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Ischemic heart disease is nowadays the leading cause of morbidity and mortality in the western world. Accurate detection and evaluation of this disease are of major importance. Cardiac magnetic resonance imaging (CMR) has an increasing role in the detection and evaluation of ischemic heart disease—as is illustrated by the increase in the number of publications on CMR in this area—and interest from hospitals in using cardiac CMR is growing.[1] CMR can be used to measure global and regional myocardial function, the presence of ischemia and myocardial scar tissue. It is a noninvasive technique in which all these parameters can be acquired in one imaging session and has the advantage of using relatively safe contrast material without the use of radiation.[2] CMR has demonstrated a low intraobserver, interobserver and interstudy variability with respect to left ventricular volumes, ejection fraction, and mass.[3,4] These characteristics make it possible to use this technique for serial assessment in an individual patient to evaluate the effect of treatment. The different possibilities for CMR in the detection and evaluation of ischemic heart disease will be outlined and an overview of the literature will be discussed in this review.

CMR for the assessment of left ventricular function

Left ventricular function and mass are used in clinical practice as parameters of cardiac function and are frequently used as an endpoint in clinical trials.[5,6] CMR is currently considered as the gold standard for measurement of left ventricular function, volumes and mass. The reproducibility of this technique is high[3,7] as compared to other techniques, such as left ventricular angiography and echocardiography.[4,8,9] To acquire images for functional assessment we use electrocardiography gating and breath holding for approximately 5-10 heart beats. Functional images are acquired using a steady state in free precession (SSFP) sequence with a high contrast between blood pool and myocardium. CMR has a spatial resolution of approximately 1.5 × 1.8 mm and a temporal resolution of 50 ms. Figure 1 is an example of a functional image in both the end-diastolic and the end-systolic phase. Functional images are acquired over several heartbeats during end expiration. The final image is an average of the information acquired over several heartbeats. Most scanners use retrospective gating for functional imaging. The disadvantage of retrospective gating is its sensitivity to rhythm disturbances.

Left ventricular functional parameters are mostly measured on a stack of short-axis cine images covering the entire left ventricle from base to apex. The 2-chamber and 4-chamber end-diastolic images at end-expiration provide the reference images to obtain a series of short-axis views (Figure 2). Depending on the size of the

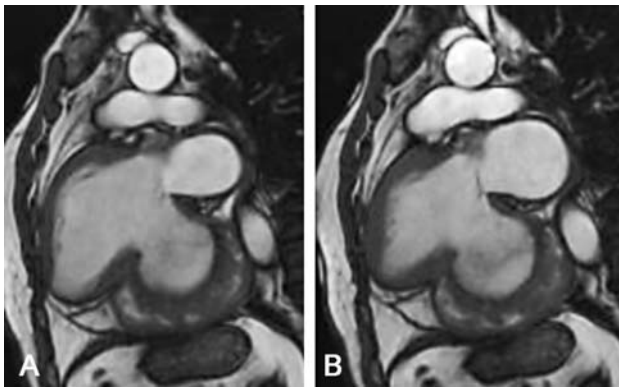

Figure 1. Two-chamber view of the end-diastolic phase (A) and the end-systolic phase (B) of a 64-year-old patient with a giant aneurysm of the left ventricle and a large mural thrombus.

cardiac chamber, 10-12 short-axis slices (mean slice thickness 8 mm with a gap of 2 mm) are required to encompass the whole left ventricle. To calculate left ventricular volume Simpson's rule is used, which avoids assumptions about left ventricular morphology as in echocardiography. Although this has been the standard for many years, variability in left ventricular measurements within CMR is still present. Variability can occur during acquisition when the short-axis (SA) cine images are plotted by an operator on the long-axis localization images. Furthermore, variability is introduced during post-procedure analysis, when the observer has to decide on the upper and lower boundaries of the left ventricle at the base and the apex of the heart. Variability can be reduced using guidelines for acquisition and post-procedure analysis. However, this is a sub optimal solution because it is based only on information from 2D SA images, where the mitral valve annulus and apex have to be identified in the direction with the least (8-10 mm) spatial resolution. Including 3D information from the long-axis images in SA contours for left ventricular functional analysis

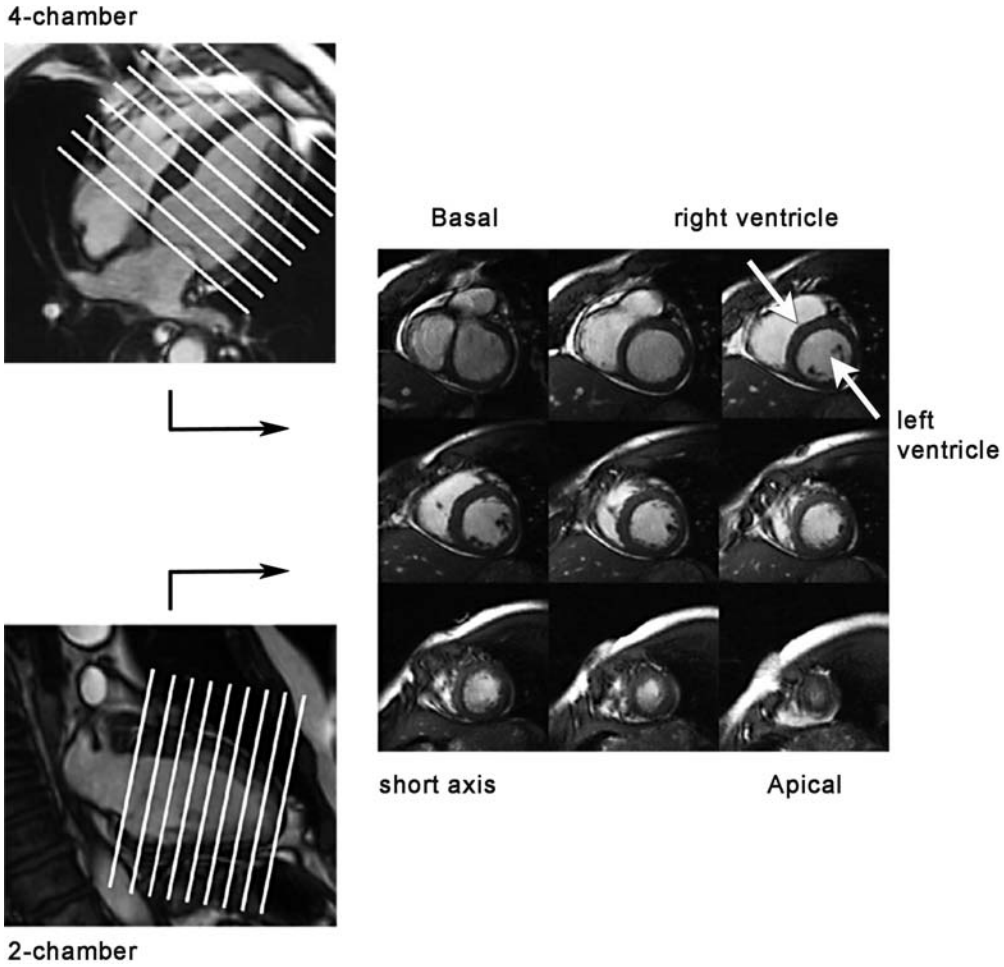

Figure 2. The stack of short-axis images from basal to apical is plotted on the 2-chamber and the 4-chamber long-axis images in the end-diastolic phase.

significantly reduces interstudy variability and may therefore be the preferred method of analysis (Figure 3). Interstudy variability decreased for end-systolic volume (9.6% to 4.7%, $p<0.001$), end-diastolic volume (4.9% to 2.5%, $p<0.005$) and ejection fraction (12.2 to 5.6%, $p<0.05$).[3] Regional functional parameters can be assessed qualitatively (described as normal, hypokinetic, akinetic, or dyskinetic) or quantitatively (relative or absolute wall thickening or wall motion) to evaluate the impact of ischemic heart disease on left ventricular function. Because of the excellent contrast between myocardium and blood pool, and epicardium and fat, contour detection can be performed automatically with good confidence.

Some patients find it difficult to hold their breath or have an irregular heart rhythm. This can result in a lower image quality due to breath hold artifacts or mistriggering due to rhythm problems. Real-time cine imaging can be performed in these cases. This technique allows continuous real-time dynamic acquisition without breath holding or cardiac gating. Each image is acquired in a heartbeat, as compared to conventional cine CMR using segmented data acquisition over multiple heart beats. A disadvantage of the real-time technique is its lower spatial and temporal resolution and it should therefore not be used in routine clinical practice.[10]

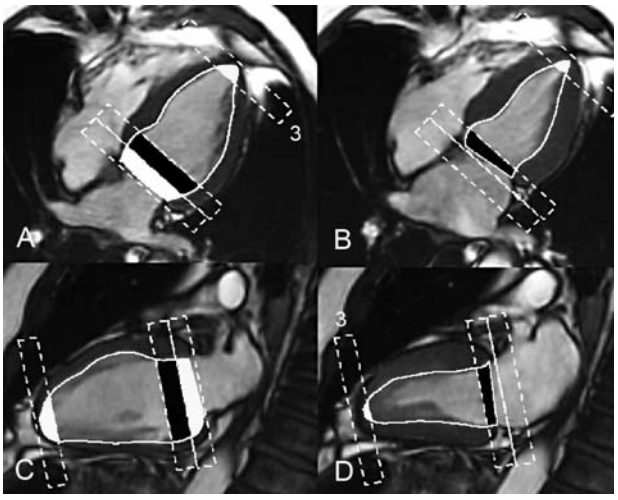

Figure 3. Illustration of the method using the information from the long axis to achieve ventricular volumes, mass and function. During the end-diastolic phase (A, C), slice 1 is partially included in the left ventricular volume, slice 2 is totally included based on the long-axis areas, while during systole (B, D) 0% is included of slice 1 and slice 2 is only partially included. At the apex, slice 3 is partially included for both phases (A, B, C and D) in left ventricular functional assessment. Reproduced from: Kirschbaum SW, Baks T, Gronenschild EH, Aben JP, Weustink AC, Wielopolski PA, Krestin GP, de Feyter PJ, van Geuns RJ; Addition of the long-axis information to short-axis contours reduces interstudy variability of left-ventricular analysis in cardiac magnetic resonance studies, Investigative Radiology, 43, 1, 1-6. Copyright Lippincott Williams & Wilkins. Used with permission.

CMR for the detection of ischemia

Multiple modalities are available nowadays for detecting the presence of hemodynamically important coronary artery stenosis: for example, treadmill testing, stress echocardiography and nuclear imaging. These stress studies are often sub optimal, as treadmill testing does not detect the location of ischemia, while using echocardiography the image quality and reproducibility are moderate. The reproducibility of nuclear stress testing is good, but it exposes the patient to radiation, image resolution is limited, and the technique may suffer from attenuation artifacts. Most stress testing with CMR is performed using a pharmacological stressor: for example, dobutamine, adenosine or dipyridamole.

Functional cine imaging can be used to visualize the induction of regional contractile dysfunction due to ischemia by addition of dobutamine. Most protocols use an increasing dose of 10, 20, 30 and 40 μg/kg/min with 3 minutes at each stress level. Imaging is repeated at every level in long- and short-axis orientations. The patient should be closely monitored during stress CMR by measuring blood pressure and hearth rhythm during infusion of these pharmacological stressors. A disadvantage of CMR is that the ST-segment is not reliable in the static magnetic field so it is not possible to detect the presence of ischemia by looking at the ECG, which should only be used to monitor the cardiac frequency. Therefore, it is important to closely monitor the development of wall-thickening abnormalities. If wall-thickening abnormalities develop, then the test is positive for a hemodynamically significant coronary stenosis and the infusion of dobutamine is ended.

Nagel et al[11] were the first to compare dobutamine stress CMR (DSMR) with dobutamine stress echocardiography (DSE). They reported that DSMR has a higher diagnostic accuracy compared to DSE in patients with suspected coronary artery disease. The sensitivity increased from 74% to 86% and specificity increased from 69.8 to 85.7 (both $p<0.05$) for DSE and DSMR, respectively, in the detection of coronary artery disease, using coronary angiography as the gold standard. Hundley et al[12] performed DSMR in patients with a poor acoustic window. They reported a sensitivi-

ty of 75% to 92%, depending on the extent of the disease, and a specificity of 83% for the detection of coronary artery disease with luminal narrowing >50%, determined using quantitative coronary angiography. A meta-analysis of DSMR using 14 datasets demonstrated a sensitivity of 83% and a specificity of 86% on a per-patient level.[13] More studies are presented in Table 1. These studies included patients who were selected to undergo catheterization and had a relatively high prevalence of disease of 71%.

DSMR can also be used to risk stratify the patients for cardiac events. In a study by Hundley et al,[14] patients who were referred for diagnosis of ischemia with dobutamine echocardiography and did not have adequate endocardial echocardiographic visualization underwent DSMR. Patients with inducible ischemia during CMR were associated with a higher adverse events rate at 20 months' follow up than those without inducible ischemia during CMR.

Another method for the detection of a hemodynamically important coronary stenosis is myocardial stress perfusion CMR using a pharmacological stressor such as adenosine or dipyridamole. With perfusion CMR a bolus of contrast agent is used to visualize the perfusion of the contrast material throughout the myocardium. The first pass of the contrast material is delayed in areas perfused by a hemodynamically important stenosis. Perfusion of the myocardium can be assessed visually (perfusion present or absent) or quantitatively by calculating the myocardial perfusion reserve index (MPRI).[15] To calculate MPRI, the relative upslope of the signal intensity of a given segment during stress is divided by the relative upslope of the same segment at rest. Relative upslope is the maximum upslope of the signal intensity curve divided by the maximum upslope of the left ventricular cavity curve. The MPRI has been validated during coronary angiography and an MPRI of 1.5[16] or 2.0[17] correlated with fractional flow reserve measurements of ≤0.75 or with ≥50% diameter stenosis.

Schwitter et al[18] reported that the sensitivity and specificity of perfusion CMR in the detection of coronary artery disease in patients who were referred for coronary angiography were 87% and 85%, respectively; this was a prospective single center study. The MR-Impact trial[19] was a multicenter, multivendor prospective trial, which compared perfusion CMR with single photon emission tomography (SPECT) for the detection of ischemia, with quantitative coronary angiography as gold standard. They reported that perfusion CMR in the entire study population was superior to SPECT. Using an optimal contrast dose of 0.1 mmol/kg, perfusion CMR was comparable to SPECT. A meta-analysis of Nandalur et al[13] reported that perfusion CMR has a sensitivity and specificity of 91% and 81% in the detection of coronary artery disease in patients with a relatively high prevalence of disease (57.4%). Only limited data are available for patients with a low or intermediate prevalence of disease. Klem et al[20] reported that combined perfusion CMR and delayed enhancement CMR for the detection of coronary artery disease in patients with a prevalence of disease of 40%, had sensitivity and specificity 89% and 87%, respectively. More data are presented in Table 2. The superior sensitivity and specificity of stress perfusion CMR, as compared to SPECT, is most likely due to the superior spatial resolution. The advantage of stress perfusion CMR is the ability to distinguish between subendocardial and transmural perfusion defects, which is important for the severity of ischemia. One has to keep in mind that these results are from centers with long experience of perfusion CMR. Perfusion CMR is a difficult and relatively new technique and therefore it can be difficult to reproduce these results. In contrast, nuclear stress testing has

Table 1. Sensitivity and specificity of dobutamine stress MRI.

Author (ref#)	n	Sensitivity (%)	Specificity (%)
Baer[30]	23	78	
Hundley[12]	41	83	83
Jahnke[31]	40	89	75
Nagel[11]	172	86	86
Paetsch[21]	79	89	81
Paetsch[32]	150	78	88
Rerkpattanapipat[33]	27	79	85
Schalla[34]	22	81	83
Syed[35]	19	89	100
Wahl[36]	160	89	84

Table 2. Sensitivity and specificity of perfusion MRI.

Author (ref#)	n	Sensitivity (%)	Specificity (%)
Doyle[37]	184	57	78
Ishida[38]	104	90	85
Klem[20]	92	89	87
Nagel[39]	84	88	90
Nandalur[13]	1183	91	81
Pilz[40]	171	96	83
Plein[41]	82	88	74
Plein[42]	68	96	83
Sakuma[43]	40	81	68
Schwitter[18]	47	86	70

already been used for over 20 years for the detection of ischemia and many studies have been performed until now, with very good long-term follow-up results.

Paetsch et al[21] compared both new CMR techniques, adenosine perfusion CMR and DSMR, in 79 patients. They reported a higher sensitivity and a lower specificity for adenosine perfusion CMR compared to DSMR using >50% luminal narrowing with quantitative coronary angiography as the gold standard. They reported that DSMR is the method of choice for treatment regimes to detect ischemia in patients with a high prevalence of disease (67%) but no history of prior myocardial infarction.

CMR for the detection of viability

Global cardiac function is an important prognostic indicator and is the result of the contractility of all individual (17 in AHA guidelines) segments.[22] However, this parameter does not report the degree of myocardial infarction. It should be recognized that areas with no or little contraction do not automatically correspond to areas of necrosis. The amount of necrosis is a stronger predictor of future cardiac events than left ventricular functional parameters in the setting shortly after acute myocardial infarction, where significant areas of stunning may be present.[23] Myocardial function can also be chronically impaired in regions with reduced coronary blood flow due to atherosclerotic coronary artery disease. Hibernation refers to regions with repetitive transient ischemia or persistent reduced myocardial blood flow that must be distinguished from infarcted myocardium. In hibernating myocardium, function will recover in weeks, months or years after revascularization, whereas myocardial function will not improve in infarcted myocardium after revascularization. Patients with ischemic cardiomyopathy will benefit from revascularization if viable tissue is present. With CMR it is possible to differentiate viable from non-viable myocardium.

Several parameters are used to detect the presence of viable tissue in dysfunctional segments. From echocardiography studies end-diastolic wall thickness (EDWT) has emerged as a possible parameter. With the improved endocardial and epicardial border definition from cine MRI, Baer et al[24] investigated the use of this technique for viability detection. They reported that the presence of significantly reduced EDWT has a high sensitivity in the prediction of functional recovery but a low specificity when a cutoff value of 5.5 mm was used.

Improvement in contractility during low dose dobutamine (at doses of 5 and/or 10 μg/kg/min) infusion is another way to identify viability (Figure 4). In this study, Baer et al[24] also used low-dose dobutamine to predict which segments would recover after revascularization. Low-dose dobutamine was reported to be of additional value in segments with a preserved EDWT. Overall DSMR had a higher diagnostic accuracy than EDWT for the prediction of recovery after revascularization (91% compared to 79% for preserved EDWT).

Another parameter for evaluating the presence or absence of viable tissue is the transmural extent of infarction (TEI). The TEI is calculated by dividing the hyper-enhanced infarcted area on delayed-enhancement MRI by the total area of a given segment. De-

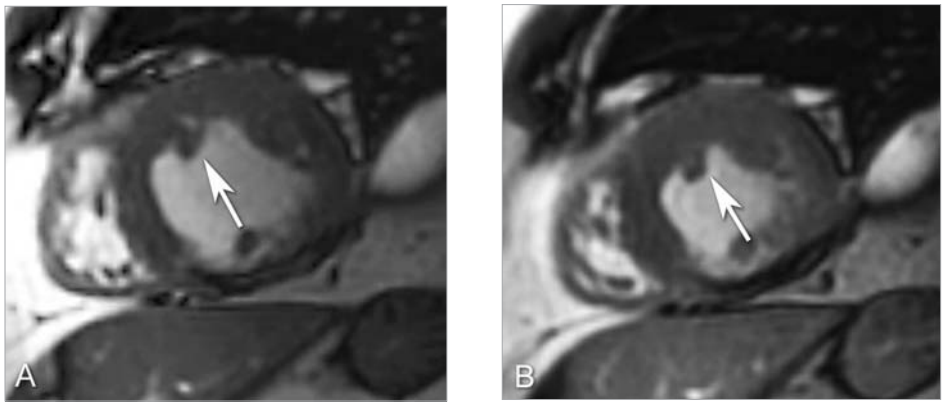

Figure 4. A short-axis image in the end-systolic phase at rest (A) of a patient with an old inferior wall infarction and a chronic total coronary occlusion of the left anterior descending artery; and a short-axis view of the same patient after administration of low dose dobutamine (B), where an improvement in contractility was detected in the anterior wall.

layed-enhancement MRI is a technique with a high spatial resolution that uses an extracellular gadolinium-based contrast agent. In acute myocardial infarctions the cellular membrane is ruptured and an extracellular gadolinium-based contrast agent diffuses passively into the intracellular space. This causes increased signal intensity on delayed-enhancement MRI. In chronic myocardial infarctions, on the other hand, the infarcted tissue mainly contains collagenous material; thus, there is an absence of the living myocytes with increased extracellular space that result in increased contrast concentration and enhancement on delayed-enhancement MRI.

Gadolinium itself is toxic but is chelated to other molecules and can therefore be safely administered to patients. Gadolinium is not nephrotoxic and adverse reactions to gadolinium are rarely seen. Delayed-enhancement images are acquired 10-20 minutes after the administration of contrast material. There is a delayed washout of the contrast material in infarcted tissue, leading to a high local concentration, while the contrast material is washed out of healthy myocardium, resulting in a lower tissue concentration. With a T1-sensitive inversion recovery gradient echo sequence the difference in concentration of the T1 shortening contrast agent can be visualized with high contrast. The magnetization of the heart is prepared by a 180-degree inversion pulse to increase T1 weighting. The inversion time, which is the time between the pulse and data collection, is manually selected to null the signal of the remote non-infarcted myocardium to obtain contrast with the infarcted myocardium, which then appears bright in the image. The optimal inversion time varies per patient and is dependent on the dose of contrast injection and the time after contrast injection. An example of a subendocardial and transmural infarct using this technique is shown in Figure 5.

Kim et al[25] compared infarct size using delayed enhancement with infarct size using TTC staining in dogs. They demonstrated that both acute and chronic myocardial infarction enhance and that the extent of hyperenhancement on CMR matches the spatial extent on *ex vivo* TTC staining (Figure 6).

Subsequently, Kim et al[26] were the first to report that the likelihood of recovery of function after revascularization in a human study was inversely related to the amount of infarcted myocardium. The larger the TEI, the less was the likelihood of recovery. In segments with a TEI <25%, 80% of the segments recover after revascularization, whereas in segments with a TEI >75% only 2% recovered. In segments with a TEI between 25-75% only 25% of the segments recovered after revascularization. Delayed-enhancement imaging is a good diagnostic tool for the detection of the presence or absence of recovery of segments after revascularization with a TEI of <25% and >75%. In segments with TEI between 25-75% the likelihood of improvement is intermediate. These results were confirmed in a study by Baks et al,[27] investigating revascularization for chronic total coronary occlusion representing hibernating tissue. To improve diagnostic accuracy in segments with an intermediate TEI low-dose dobutamine may be of additional value. Wellnhofer et al[28] reported that low-dose dobutamine is probably superior to delayed-en-

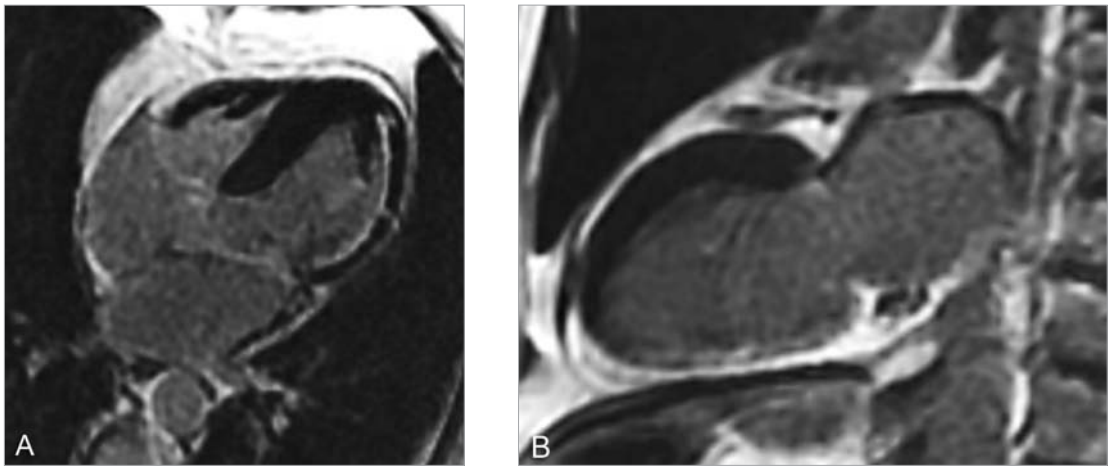

Figure 5. A: 4-chamber delayed-enhancement image with a subendocardial infarct in the lateral wall having a transmural extent of infarction (TEI) <25% of the total wall thickness. B: 2-chamber delayed-enhancement image with a transmural infarction of the inferior wall.

Figure 6. A: short-axis delayed-enhancement image *in vivo* with a transmural infarction in the lateral wall. B: short-axis *ex vivo* delayed-enhancement image with a transmural infarct in the lateral wall. C: Corresponding *post mortem* histochemistry image.

hancement imaging in the prediction of recovery after revascularization. It should be mentioned that in this study, as in many others, a follow-up duration of 3 or 6 months was used, but recovery of hibernating segments may take longer and this effect may not be mimicked with low-dose dobutamine CMR.

In the same patient population as the study by Baks et al, we recently demonstrated an additional improvement of segmental wall thickening in segments with a TEI of <25% but also in segments with a TEI between 25-75% at 3 years' follow up.[27,29]

In summary, different tools are nowadays available for the detection of the presence or absence of viable myocardium in CMR. End-diastolic wall thickness is easy to measure but has a lower accuracy in the prediction of recovery than delayed-enhancement CMR. Low-dose dobutamine is probably a more accurate tool. A disadvantage is that close monitoring of the patient is necessary and, therefore, performing low-dose dobutamine studies takes more time. Delayed-enhancement CMR is an easy technique that uses a contrast material that is relatively safe for the patient, is fast, has a high spatial resolution, and can therefore easily be used in daily clinical practice. However, in segments with a TEI between 25% and 75% the predictive value is less and here low-dose dobutamine may still be necessary.

Conclusion

CMR is an emerging diagnostic tool for the detection and assessment of ischemic heart disease. It is nowadays considered the gold standard for quantitative measurements of left ventricular function and has high accuracy and reproducibility. Using modern CMR techniques, ischemia detection is reliable both for DSMR and vasodilator-induced myocardial perfusion CMR. Myocardial viability is a clinically relevant issue in patients with ischemic heart disease and can easily be detected with contrast-enhanced MRI, while CMR is gradually becoming the technique with the highest diagnostic accuracy.

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