Cardiac magnetic resonance imaging to guide complex revascularization in stable coronary artery disease

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Coronary revascularization has been a cornerstone of the management of patients with coronary artery disease (CAD) for many years. Both coronary artery bypass grafting and percutaneous coronary intervention have evolved and improved over time such that increasingly complex and challenging cases can now be tackled with a high degree of procedural success. In parallel with this, there have been major advances in medical therapy for CAD. Consequently, one of the main decisions in the contemporary management of stable CAD concerns which patients and lesions should be revascularized. This is particularly true for patients with complex disease such as multivessel disease or those with left ventricular impairment. Such patients will potentially benefit the most but are also at highest risk of complications and it is therefore important that they are carefully selected. Recent major trials have challenged the conventional view that consideration of coronary anatomy alone is sufficient in this decision-making. An accumulating body of evidence underscores the importance of functional investigations when assessing the potential benefits of revascularization in these complex patients. In parallel with these developments, cardiac magnetic resonance (CMR) has matured into a robust technology that is able to measure many of the parameters required to accurately characterize these patients. This article will review the importance of myocardial viability and ischaemia when selecting patients with stable CAD for revascularization, the use of CMR imaging for assessing this pathophysiology, and planning complex revascularization, and finally give an outlook on how CMR may help address some important outstanding clinical questions.

**Keywords**
- Cardiac magnetic resonance imaging
- \textsuperscript{†} Revascularization
- \textsuperscript{†} Percutaneous coronary intervention
- \textsuperscript{†} Coronary artery bypass grafting
- \textsuperscript{†} Ischaemia
- \textsuperscript{†} Viability

**Background**

Despite many advances in the prevention, detection, and treatment of coronary artery disease (CAD), it remains a leading cause of morbidity and mortality. Coronary revascularization has a central role in the management of patients with stable CAD; however, despite extensive published literature, appropriate selection of patients and lesions for revascularization in stable CAD continues to be an area of controversy. Patients with complex CAD including multivessel disease, complex anatomy, and with associated left ventricular (LV) impairment are at higher risk of procedural complications but also potentially benefit the most from revascularization. Information regarding risks and benefits is therefore of critical importance for appropriate patient selection.

Literature on coronary revascularization is dominated by anatomical classification of CAD with decisions regarding revascularization made solely on the basis of coronary angiographic appearances. Such an anatomy-driven approach fails to assess coronary blood flow, myocardial perfusion, and viability, which are central to the pathophysiology of CAD. Coronary artery blood flow is reduced when the luminal diameter of a coronary artery narrows below a threshold, and as a result, a reduction in coronary artery diameter of $>50–70\%$ is considered to be flow limiting. However, this relationship between flow and luminal narrowing was determined in animal models using...
discrete, non-atherosclerotic narrowing of the coronary arteries and does not translate well into human clinical practice. Anatomic assessment of the severity of a coronary artery stenosis has been repeatedly shown to correlate poorly with the haemodynamic effects. A number of factors contribute to the discrepancy between anatomic and physiological assessment such as the diffuse nature of CAD, the presence of collateral vessels and calcification, dynamic changes in vasomotor tone, and difficulties identifying a truly normal vessel segment as a reference diameter. In addition, the anatomy-only approach fails to take into account the viability of the myocardium subtended by the diseased artery.

These considerations are widely accepted and the importance of functional assessment prior to revascularization is reflected in guidelines for percutaneous coronary intervention (PCI) in stable CAD. Despite this, many major contemporary trials continue to treat CAD as a purely anatomical disease. An example is the recent SYNTAX trial which compared PCI and coronary artery bypass grafting (CABG) for the treatment of left main stem and/or three-vessel CAD. Patients randomized to both PCI and CABG underwent protocol-mandated complete anatomic revascularization, i.e. all lesions of ≥50% in vessels of ≥1.5 mm were treated without prior physiological assessment.

There may, of course, be some value in classifying patients according to their anatomy. For example, CABG has been shown to confer a prognostic benefit in patients with left main stem disease or reduced LV function and two- or three-vessel disease involving the proximal left anterior descending artery. However, consideration of anatomy alone and ignoring the physiology when selecting patients and lesions for revascularization over simplifies a complex disease and trials adopting this approach risk underestimating the benefits of revascularization. (This particular evidence also pre-dates modern medical and surgical therapy and is therefore of questionable current relevance.)

**Ischaemia**

The presence of myocardial ischaemia in stable CAD is associated with an adverse prognosis whether detected by exercise testing, single photon emission computed tomography (SPECT), stress echocardiography, or cardiac magnetic resonance (CMR). However, the evidence that myocardial revascularization improves prognosis in these patients is limited.

Hachamovitch assessed survival in 10,627 patients who had undergone clinical SPECT studies in a single US centre. Patients with no or mild baseline ischaemia had an improved prognosis with medical therapy compared with revascularization, while conversely those with moderate-to-severe ischaemia had an improved prognosis with revascularization. An ischaemic threshold of 10–12.5% of myocardium differentiated patients who benefited from revascularization from those who did not. Even though these data are from a very large cohort and the conclusions are interesting, there are inherent limitations to the study as it was a non-randomized, retrospective observational study which used a propensity score to adjust for non-randomization.

In the Asymptomatic Cardiac Ischemia Pilot study, patients with asymptomatic ischaemia randomized to revascularization (PCI or CABG) had significantly lower rates of death or myocardial infarction (MI) than those randomized to medical therapy. There were however relatively few events (31 in total) and the medical therapy used reflected practice at the time rather than current routine aggressive therapy. In the SWISSI II trial, patients post-MI with demonstrable silent ischaemia had a significantly reduced rate of major adverse cardiac events with PCI than with medical therapy.

The landmark randomized controlled COURAGE trial on the other hand concluded that there is no prognostic benefit from PCI in addition to optimal medical therapy as an initial treatment for stable CAD. This was despite the fact that the majority of participants had objective evidence of ischaemia at baseline, including 54% of patients with reversible defects on nuclear imaging. These data generated considerable controversy and led many to re-evaluate entirely the role of PCI in stable CAD. It seems paradoxical that there was no incremental benefit from PCI given that the presence of demonstrable ischaemia confers a worse prognosis. Although there are a number of possible explanations for this, the most likely is because the study design favoured inclusion of lower-risk patients with a lower burden of pre-treatment myocardial ischaemia. For example, patients with an exercise test positive in the first stage were excluded and only a third of patients in the PCI arm had a significant reduction of ischaemia following PCI.

In apparent contradiction to the main study, the nuclear sub-study of the same trial suggested that PCI might confer a prognostic benefit especially in patients with moderate-to-severe baseline ischaemia. This suggests that revascularization may confer a prognostic benefit in patients with a significant ischaemic burden and improved patient selection may allow this benefit to be realized.

Recognition of the importance of ischaemia is reflected in patients undergoing PCI with a change of emphasis away from complete anatomic revascularization towards targeted revascularization, i.e. treating only the lesions causing ischaemia. Complete revascularization and incomplete revascularization are purely anatomic terms. By also assessing the physiology, it is possible to achieve complete resolution of ischaemia without performing complete anatomic revascularization. In patients undergoing PCI, there is evidence from subgroup analyses and registry data that complete anatomic revascularization is superior to incomplete anatomic revascularization. The most compelling data, however, supports intervention targeted only at flow-limiting lesions even when this results in incomplete anatomic revascularization. The DEFER study demonstrated that in single-vessel disease, it is safe to defer treatment of angiographically moderate stenoses that do not cause ischaemia as determined by fractional flow reserve (FFR). The recent FAME study demonstrated the utility of extending this approach to a multi-vessel setting. This large multicentre, randomized, controlled trial demonstrated that ischaemia-guided PCI confers a prognostic benefit (reduced rate of death, non-fatal MI, and repeat revascularization) over PCI guided by angiographic appearances alone.

Conversely, in the case of CABG, there is a large volume of evidence demonstrating a symptomatic and prognostic benefit with complete over incomplete revascularization and thus complete revascularization is widely considered the gold standard. Unlike with PCI, these data are largely non-randomized and retrospective. However, improved prognosis with complete revascularization has been consistently reported and it is plausible that technical differences between the two techniques may explain why complete revascularization is the method of choice in CABG and targeted...
revascularization in PCI. In the case of PCI, the risk of complications is proportional to the number of lesions treated, whereas the number of grafts seems to add little to the overall risk of CABG.

**Viability**

Left ventricular dysfunction is an important determinant of prognosis. When considering revascularization in stable patients with LV impairment, it is important to consider myocardial viability as revascularization of patients with significant viable myocardium is associated with improved LV function and survival.

Demonstration that the contractility of viable myocardium improves after restoration of coronary blood flow comes from pooled data from 105 trials using nuclear techniques or stress echocardiography. This meta-analysis demonstrated a combined mean sensitivity of 84% and specificity of 69% for the prediction of regional functional recovery. An improvement in global LV ejection fraction (LVEF) was detected in 28 studies. In patients with viable myocardium, LVEF improved on average from 37 to 45%, whereas patients without viability showed no improvement in LVEF (36% before and after revascularization).

Improved survival with revascularization in patients with viable myocardium is summarized well in a 2002 meta-analysis that pooled the data of 3088 patients from 24 viability studies. Viability was determined using nuclear perfusion techniques, positron emission tomography (PET), or dobutamine stress echocardiography and patients followed up for ~2 years. Analysis of the combined results demonstrated a strong association between myocardial viability identified by non-invasive testing and improved survival after revascularization. Revascularization in patients with viable myocardium was associated with a 79.6% reduction in mortality from 16% with medical therapy to 3.2%. Conversely, in the absence of viability, there was no significant difference between the risk of death with revascularization (7.7%) or medical therapy (6.2%).

Although this evidence supports revascularization of patients with viable myocardium, prospective randomized trials on the prognostic value of viability are still lacking.

**Non-invasive functional assessment**

On the basis of this evidence, most clinicians accept that combining anatomical information with a functional assessment pre-revascularization in patients with complex CAD is important. A number of non-invasive imaging modalities are available each with its own inherent advantages and disadvantages. Clinicians can decide which method is most appropriate according to the clinical situation and availability. Single photon emission computed tomography and PET are well established and effective. Most evidence today supporting the concept of ischaemia imaging as an essential part of the workup of these patients comes from SPECT imaging. However, both require the use of ionizing radiation and have inferior spatial resolution compared with CMR, and the availability of PET remains very limited. Echocardiography is well validated and widely available. It remains a valuable, non-ionizing technique often used first line, but can be limited by poor acoustic windows and endocardial definition. Computed tomography can potentially assess LV function, perfusion, and viability; however, this is not currently well established and its main strength at present is coronary artery imaging. Non-invasive coronary artery imaging is of limited value in these patients as coronary artery calcification is prevalent, limiting image interpretation and also invasive angiography is usually necessary to plan complex revascularization. The major disadvantage of CT is its significant radiation exposure particularly if coronary angiography, function, perfusion, and viability are all studied. Cardiac magnetic resonance has emerged as a highly accurate and versatile tool for making these assessments and guiding decision-making. The advantages of CMR include freedom from ionizing radiation, generation of high-quality images, and, most importantly, the generation of a complete workup incorporating LV volumes and function, myocardial viability and scar, as well as ischaemia within a single study lasting ~1 h. The main disadvantages are that imaging is contraindicated in patients with certain implants, e.g. pacemakers, limited availability, and rarely reduction of imaging quality due to patient claustrophobia, poor gating, or patient motion.

**Cardiac magnetic resonance assessment of ischaemia**

The two main CMR methods for the assessment of myocardial ischaemia, high-dose dobutamine stress with wall motion assessment and first-pass myocardial perfusion, use pharmacological stress.

Dobutamine stress involves the administration of a standard dobutamine/atropine protocol to achieve a target heart rate. The occurrence of new wall motion abnormalities during increasing doses of dobutamine is considered diagnostic of ischaemia. Nagel et al. were the first to validate dobutamine CMR for the detection of CAD. Dobutamine CMR performed better than stress echocardiography in the identification of CAD using at least 50% stenosis on coronary angiography as the gold standard. Cardiac magnetic resonance sensitivity and specificity in this study of 208 patients were 88.7 and 85.7%, respectively. Many validation studies have been performed and reported similar results since. However, as the studies are relatively small, the confidence intervals are often wide. Nandalur et al. pooled the data from 14 studies and 724 patients and confirmed good sensitivity [83%; 95% confidence interval (CI) 79–88%] and specificity (86%; 95% CI 81–91%) of stress-induced wall motion abnormalities against X-ray coronary angiography for the detection of CAD. It is noteworthy that there was a high prevalence of CAD (70.5%) in the 735 participants included from the combined 13 studies.

High-dose dobutamine-atropine stress CMR is safe in addition to being effective. In a series of 1000 patients, adverse events included 1 case (0.1%) of sustained and 4 cases (0.4%) of non-sustained ventricular tachycardia, 16 cases (1.6%) of atrial fibrillation, and 2 cases (0.2%) of transient second-degree atrioventricular block.

Exercise stress CMR is also technically possible using a specific magnetic resonance imaging-compatible cycle ergometer. Recent work suggests that it may be possible to overcome some of the technical limitations, such as motion and difficulties in breath holding by using real-time exercise stress CMR images. However, at present, exercise stress is not in routine clinical use, despite good preliminary clinical results.
First-pass myocardial perfusion involves achieving maximal coronary vasodilation, usually with intravenous adenosine, and imaging the first passage of a contrast bolus into the myocardium. Perfusion of contrast into the myocardium subtended by vessels with flow-limiting CAD does not increase with stress as much as perfusion of contrast into myocardium supplied by normal vessels. In the clinical setting, this is usually analysed qualitatively as a defect in the contrast perfusion into the myocardial wall visible with stress but not at rest (Figures 1A–C). There are a number of single-centre studies and a few multicentre trials comparing CMR to established methods of detecting myocardial ischaemia. In the above-mentioned meta-analysis, perfusion CMR was also assessed using data from 24 studies and 1516 patients resulting in a sensitivity of 91% (95% CI 88–94%) and a specificity of 81% (95% CI 77–85%) against X-ray coronary angiography. Again there was a relatively high prevalence of CAD (57.4%) in the pooled population.

MR-IMPACT is the largest perfusion CMR multicentre trial published thus far comparing CMR and SPECT for the detection of myocardial ischaemia. Perfusion CMR was determined to be non-inferior to SPECT for the detection of CAD with ≥50% stenosis on quantitative X-ray coronary angiography as the reference standard. This was however a dose-finding study and only 42 patients formed the CMR cohort on which this analysis was based.

One of the difficulties in validating non-invasive methods for the detection of myocardial ischaemia is the absence of a clear gold standard for comparison. The studies discussed above use coronary angiography as the gold standard with the limitations discussed previously in this article. For a more direct comparison of invasive vs. non-invasive physiological measurements, CMR has been validated against FFR. These studies have also revealed overall good correlation between the two methods with CMR perfusion sensitivities ranging from 88 to 92.9% and specificities from 56.7 to 94%.

Cardiac magnetic resonance assessment of viability
Cardiac magnetic resonance is the gold standard for evaluation of LV volumes and function, which are routinely obtained during any CMR examination. Cardiac magnetic resonance viability assessment is achieved using low-dose dobutamine (functional response), late gadolinium enhancement (LGE) scar imaging (morphological assessment of viability), or a combination of both methods. A comparison between PET and low-dose dobutamine CMR demonstrated close agreement between the two techniques for the assessment of viability with CMR sensitivity of 88% and specificity of 87% compared with PET. When contractile improvement post-revascularization, rather than PET, is considered to be the gold standard, dobutamine CMR maintains a high specificity and sensitivity, although the sensitivity may be reduced with more severely impaired baseline LV function.

Late gadolinium enhancement scar imaging correlates very closely with post-mortem infarct assessment in animals and also with PET data in humans. When contractile improvement post-revascularization is taken as the gold standard, LGE can predict viability as demonstrated in a seminal paper in 2000. This demonstrated that transmurality of LGE and the likelihood of functional recovery following revascularization are inversely related. The positive and negative predictive values of this technique vary according to the extent of scar that is taken as a cut-off value to define viability. These values also vary depending on whether all segments or only the most dysfunctional are considered. For example, using a cut-off of >25% transmurality of scar and considering all segments, the positive and negative predictive values are 71 and 79%. When only akinetic or dyskinetic segments are considered, this increases to 88 and 89%. On the other hand, if a 50% cut-off value is used and all segments considered, the negative predictive value increases to 92%, but the positive predictive value falls to 66% (Figures 2A–D).

Wellnhofer et al. compared dobutamine and LGE CMR for the prediction of viability in 29 patients and found dobutamine CMR to be slightly superior in predicting recovery after revascularization. Late gadolinium enhancement CMR predicted 73% of hibernating segments correctly compared with 85% correctly predicted by low-dose dobutamine. This difference was particularly relevant for myocardial segments with an intermediate extent (1–74%) of LGE.
Although these techniques for assessing viability are very useful, neither of them is perfect. In addition, as with ischemia testing, there is no clear gold standard for validation purposes.

Additional value from cardiac magnetic resonance imaging

Cardiac magnetic resonance examination of patients being worked-up for coronary revascularization frequently provides the clinician with other valuable data including prognostic information and even alternative diagnoses. High spatial resolution allows for analysis of the distribution of the scar within the myocardial wall and differentiation of ischemic from dilated cardiomyopathy. This additional information obtained from CMR is clinically relevant as demonstrated in a recent registry of 11,040 patients. A CMR examination for suspected CAD or ischaemia assessment resulted in a new, previously unsuspected diagnosis in 19.6% of patients. Furthermore, patient management was influenced in >70% patients. Similarly, 23% of patients with suspected CAD but no history or electrocardiographic evidence of prior MI have an MI detected by LGE. This has prognostic implications as detection of even a very small scar is associated with a greater than seven-fold increase in major adverse cardiovascular events. Finally, there are also data to suggest that scar detected by CMR is a stronger predictor of adverse clinical outcome than LVEF and volumes.

The cardiac magnetic resonance examination

Cardiac magnetic resonance assessment of volumes, function, scar, wall motion, and ischaemia are performed in a standardized way according to internationally recognized guidelines published on behalf of the Society for Cardiovascular Magnetic Resonance. The examination is tailored to the individual patient depending on the clinical scenario (Table 1). However, as a standard examination, we perform left and right ventricular function and volumes, first-pass perfusion imaging with adenosine stress followed at an interval by rest perfusion, and LGE. When the main clinical question concerns viability, we also perform low-dose dobutamine imaging. Illustrated CMR protocols that we use are shown in Figure 3. If clinically indicated, high-dose dobutamine can be used rather than first-pass perfusion imaging.

Cardiac magnetic resonance coronary angiography is also possible and the technique has evolved over the years. However, coronary artery imaging with CMR is still a cumbersome method with a higher failure rate, longer scan times, and lower positive predictive value in comparison to CT and is of limited value in this specific patient group.

Clinical applications

Cardiac magnetic resonance provides the clinician with comprehensive and clinically relevant information about patients with complex

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**Figure 2** These images are of a 66 year-old man who presented with NYHA class IV heart failure. End diastolic (A) and end-systolic (B) frames from the four-chamber cine cardiac magnetic resonance imaging demonstrate severe impairment of systolic function. LGE imaging (C) demonstrated <50% wall-thickness scar affecting the basal to mid-lateral wall and mid-apical interventricular septum with only a small region of transmural scar in the apex (arrowheads). Coronary angiography demonstrated severe three-vessel coronary angiography. Given that the cardiac magnetic resonance demonstrated significant viability he underwent three-vessel CABG. Post-CABG end-diastolic (D) and end-systolic (E) frames show improved thickening of both the lateral wall and septum but no improvement at the apex. Symptomatically the patient also improved to NYHA class II.
CAD who are being considered for revascularization. The first question that can be answered after the CMR examination is whether revascularization should be undertaken at all. From the available evidence, it is safe and probably preferable to defer revascularization in the absence of demonstrable ischaemia or LV dysfunction with significant viability, regardless of the coronary anatomy.

The second question that can be answered is which vessel should be revascularized. Pre-procedural CMR assessment in complex patients allows targeted PCI and avoids treatment of inappropriate lesions and therefore potentially will reduce complications while maximizing benefit.

The CMR information will also be useful to a surgeon by determining the likely benefits from CABG and also in guiding the surgical approach, for example, targeting the best-quality conduits and choosing between minimally invasive and open surgery. Cardiac magnetic resonance data will be useful to retrospectively compare outcome in patients undergoing complete anatomic and complete functional revascularization, although prospective randomized data on this are unlikely to be forthcoming in the near future.

Finally, in addition to guiding, the management strategy information obtained from a CMR examination allows more accurate risk stratification of patients with stable CAD. This is important for all patients with stable CAD, regardless of the treatment strategy, as it provides a platform for meaningful discussions about care with patients and their families.

**Future perspectives**

**Technical advances**

Perfusion CMR is a focus of considerable ongoing research. Hardware and software continue to evolve to improve spatial resolution, although stronger field gradients and new and faster sequences mean that the spatial resolution already exceeds that
of SPECT by a factor of 25.\(^{48,49}\) Absolute quantification of perfusion is possible with CMR\(^{50,51}\) and may lead to improved accuracy and better comparison of treatment efficacy. Absolute quantification should assist us to define thresholds of perfusion associated with myocardial ischaemia and viability for improved patient management and prognostication. In addition, alternative techniques to not only measure blood flow, but oxygenation, are on their way. As an example, blood oxygen level-dependent (BOLD) magnetic resonance allows CMR perfusion imaging to be performed without contrast agent administration as signal intensity changes are detected as the ratio of oxygenated and deoxygenated haemoglobin in the myocardium changes. This method appears to allow visualization of true ischaemia rather than a surrogate.\(^{52}\) However, at present, BOLD techniques are not available for routine clinical use.

**Clinical studies**

Interesting questions currently under investigation include whether reducing myocardial ischaemic burden per se is of prognostic benefit and whether a non-invasive test can guide revascularization in the same way that FFR has been shown to do in the FAME study.\(^{19}\) Further work also continues aiming to clarify the position of perfusion CMR in relation to more established techniques, particularly SPECT.

Much of the CMR viability work published previously has focused on patients with moderate LV systolic dysfunction. The accuracy of CMR for predicting viability in more severe LV dysfunction is less well established. In addition, the mechanism of how prognosis is improved by revascularization in the absence of an improvement in LV function is an unanswered question. It is likely that with its high spatial resolution, other markers of viability, e.g. the thickness of the epicardial myocardial rim in scarred areas, can be used to improve the accuracy of CMR.

**Conclusions**

Despite the advances in the treatment of CAD, it remains an important disease and many patients continue to experience preventable morbidity and mortality. One of the main management decisions concerns which patients and lesions should be revascularized. Complex revascularization carries more of a risk to patients and so it is important that in deciding whether it is appropriate we obtain as much information as possible. From the available evidence, it is clear that information on coronary anatomy alone is often insufficient to make this decision, and it is crucial to know about myocardial ischaemia and viability. Cardiac magnetic resonance provides a safe, non-invasive, and comprehensive assessment, which yields valid, reliable information on pathophysiology in patients with stable CAD. Cardiac magnetic resonance continues to evolve; however, it is already established as an indispensable tool to assist with our decision-making and assist us in providing optimal evidence-based care for our patients.

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