

Cardiac magnetic resonance in ischemic cardiomyopathy: present role and future directions

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Ischemic cardiomyopathy is a significant cause of mortality and morbidity, with peculiar needs for accurate diagnostic and prognostic characterization. Cardiac magnetic resonance (CMR) can help to satisfy these requirements by allowing a comprehensive evaluation of myocardial function, perfusion and tissue composition, with a demonstrated utility in guiding clinical management of patients with known or suspected ischemic cardiomyopathy. When compared with alternative non-invasive imaging modalities, such as stress echocardiography and nuclear techniques, CMR is able to provide accurate (function and perfusion) or peculiar (tissue characterization) information on cardiac pathophysiology, while avoiding exposition to ionizing radiations and overcoming limitations related to the quality of the imaging window. In particular, stress perfusion CMR showed to be accurate, safe, cost-effective, and clinically valuable as a non-invasive test for detecting severity and distribution of myocardial ischemia. In many circumstances, however, local availability of the technique, together with procedural costs, and scanning and post-processing time duration still limit the use of CMR in clinical routine. In the current review, we focused on clinical applications of CMR in ischemic cardiomyopathy. The consolidated role of the technique is described by illustrating both standard and advanced sequences that constitute the current body of a dedicated CMR examination. Ongoing developments and potential future diagnostic and prognostic applications of CMR when assessing ischemic cardiomyopathy are also discussed, with a focus on artificial intelligence-based implementations proposed for refining the efficiency of CMR analysis and reporting.

Introduction

As the most common condition associated with left ventricular (LV) dysfunction, ischemic cardiomyopathy is a significant cause of mortality and morbidity worldwide.¹ Also, an important socioeconomic burden may derive from heart failure symptoms and complications occurring in such patients. Early invasive strategies implemented in acute coronary syndromes led to a substantial lowering in mortality rates during the last decades, although the incidence of adverse cardiac remodelling and the resulting

heart failure syndrome may be still an issue in many cases.¹ Thus, ischemic cardiomyopathy can be related to an adverse LV remodelling after myocardial scar (in some cases from silent infarction) or to recurring/persisting ischemia in chronic coronary artery disease (CAD).

In CAD, clinical management is mostly centred on controlling risk factors, symptoms relief, and demonstration of inducible ischemia.¹ When considering the latter aspect, an initial invasive diagnostic approach, based on coronary angiography followed, when required, by the estimation of fractional flow reserve is usually reserved to patients with very high pre-test probability of significant CAD. Conversely, non-invasive imaging is preferred as a first-line test to demonstrate ischemia for patients in the intermediate-high pre-test probability group,

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followed by coronary angiography only in case when significant ischemia is demonstrated. Multiple imaging techniques are currently available for assessment of ischemia, including stress echocardiography, nuclear imaging methods, and cardiac magnetic resonance (CMR).² Stress echocardiography has proven very useful and versatile for demonstrating inducible ischemia, although the application of this modality may be hindered in many cases by acoustic-window dependency and reliance upon operator's experience. Myocardial single photon emission computed tomography (SPECT) or the less available positron emission tomography are able to provide combined information on myocardial perfusion, viability, and function. Owing to high negative predictive value in assessing CAD, coronary computed tomography (CT) is currently the preferred test in patients with a low-to-intermediate range of clinical likelihood of obstructive coronary disease by using an anatomic-based approach, in some cases combined with functional information provided by non-invasive FFR estimation.² However, the radiation exposure associated with CT and/or nuclear imaging should be considered when choosing the most appropriate approach to study CAD in the single patient.

Over the last two decades, CMR emerged as a powerful tool for the non-invasive assessment of patients with known or suspected CAD. CMR-based techniques can accurately describe functional and structural consequences of recent or previous ischemic insults on the cardiac muscle, both in terms of scar and viability extension, being able to provide at the same time qualitative and quantitative information on rest/stress myocardial perfusion.¹ This review explore the current status and potential future role of CMR in the evaluation of ischemic cardiomyopathy.

Present role of cardiac magnetic resonance

Cardiac magnetic resonance allows a three-layered approach to characterize ischemic cardiomyopathy (*Figure 1*): (1) functional assessment; (2) tissue characterization; and (3) myocardial perfusion.

The high spatial, temporal, and contrast resolutions of CMR allow for a clear identification of the blood-myocardium interface, which makes assessment of ventricular volumes and function very accurate. Based on volumetric (three-dimensional) approaches, CMR provides measurements that are free from geometric assumptions and are characterized by unbeatable levels of intra- and inter-operator reproducibility.^{3,4}

Cardiac magnetic resonance distinguishes fat, fluid, and soft tissue using different sequences that exploit the specific magnetic properties of such tissues. T2-weighted (T2W) imaging, typically utilizing dark-blood short-tau inversion recovery (STIR) sequences, detects myocardial edema and inflammation. The increased water content of edematous tissues, which usually appears early after an ischemic insult, translates into longer T2 relaxation times, leading to a brighter signal on T2W images. The presence of necrosis and replacement fibrosis can be easily identified by late-gadolinium enhancement (LGE) imaging as areas of myocardial hypoenhancement (bright signal). LGE imaging is based on the T1 shortening, which is the result of the accumulation of the gadolinium-based contrast agents. Typically, these are extracellular and

extravascular agents and, therefore, accumulate in case of either ruptured cell-membrane or expanded extracellular volume. In the setting of ischemic myocardial damage, the accumulation of contrast within the ventricular wall mirrors the ischemic wave, starting from the sub-endocardium and extending, with different degrees of transmural, to involve one or more territories of coronary distribution. Converging evidence has been produced about the diagnostic and prognostic role of LGE in ischemic cardiomyopathy.¹ In particular, LGE imaging has been shown to be useful in differentiating between ischemic and non-ischemic causes of LV dysfunction and to recognize stunning/hibernating myocardium from necrotic tissue. Furthermore, the transmural extent of myocardial LGE predicts chances of post-revascularization functional recovery, as LV segments with enhancement extending for more than 50% across the wall are not expected to recover after the blood flow is restored.⁵ Late-gadolinium enhancement has also been demonstrated to carry significant prognostic information. In fact, tissue heterogeneity induced by the simultaneous presence of healthy and infarcted myocardium at the regional level constitutes a potential substrate for arrhythmias. Moreover, the extent of necrosis may help to predict the response to the cardiac resynchronization therapy. In acute settings, the combination of STIR and LGE images can identify additional valuable features of ischemic myocardial damage like the area-at-risk, which represents the area of edematous (but not necrotic) myocardium that can be salvaged by reperfusion therapies. The presence of myocardial no-reflow (due to either microvascular obstruction and intramyocardial haemorrhage), can easily be detected on CMR. Both microvascular obstruction and intramyocardial haemorrhage tend to appear as hypointense signal (dark) on LGE images, since the contrast agent cannot reach them, while intramyocardial haemorrhage areas only show a reduced signal intensity in the STIR T2W sequences.

When aiming to myocardial tissue characterization, traditional CMR sequences may have some limitations: low-quality images are not uncommon with some of those techniques, including STIR T2W sequences, especially in patients with irregular/high-frequency heart rates or with limited ability to co-operate during image acquisition; furthermore, LGE imaging requires contrast injection, and may fail to identify diffuse myocardial damage. Parametric mapping sequences (T1, T2, T2* mapping) may help to overcome some of such limitations and, thus, are becoming an integral component of the scanning protocols in ischemic cardiomyopathy. Cardiac magnetic resonance mapping techniques are based on reconstructed mapping images, in which every pixel intensity relates to the value of the corresponding myocardial voxel for that specific magnetic parameter. Every tissue has definite T1, T2 or T2* magnetic properties; as such, those techniques helps obtaining a fine-grained myocardial tissue characterization. In acute myocardial infarction, native T1 and T2 mapping images demonstrate increased T1 values, as acute ischemic damage leads to inflammation and edema. They can be used to differentiate between acute and chronic ischemic insults, as well as to recognize the myocardial areas at risk. T2* relaxation times are shortened by both iron deposition and the accumulation of the products of the haemoglobin breakdown. Therefore, T2* mapping is currently regarded as the gold

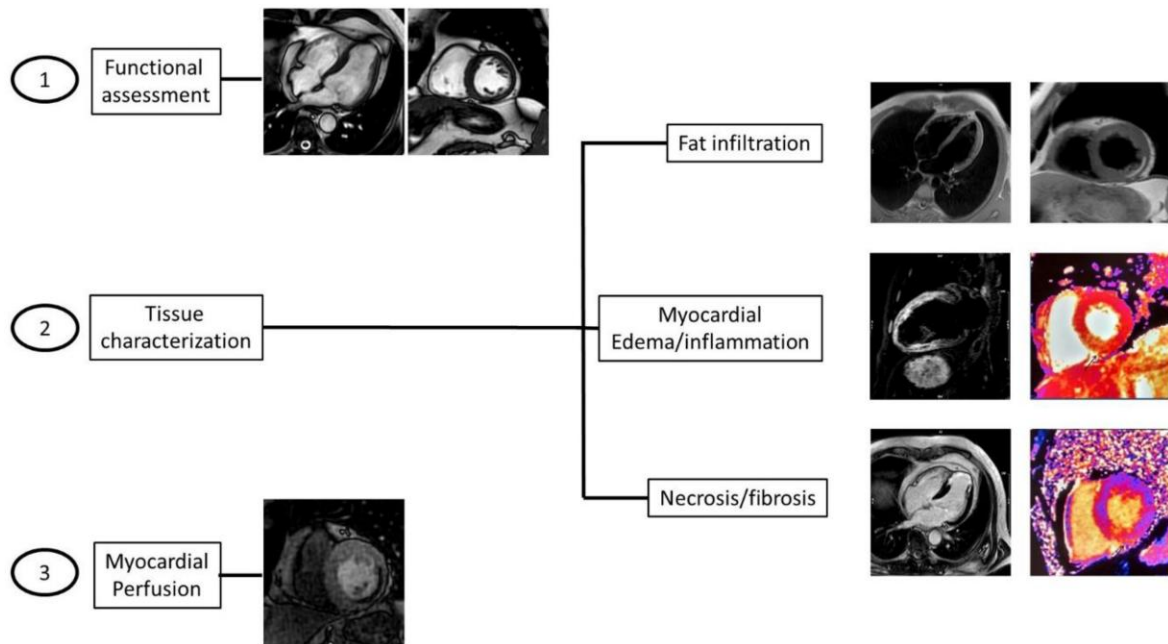


Figure 1 The three-layered cardiac magnetic resonance approach in the characterization of ischemic cardiomyopathy: (1) *Functional assessment*: the images showed are cine steady-state free precession in four chamber and short-axis view. (2) *Tissue characterization*: T1 weighted images in four chamber and short-axis views for fat infiltration; cine steady-state free precession T2 weighted image in two chamber view and short-axis T2 mapping for myocardial edema/inflammation; late-gadolinium enhancement four chamber view and short-axis T1 mapping for necrosis/fibrosis assessment. (3) *Myocardial perfusion*: first-pass post-contrast short-axis image for the evaluation of perfusion defects.

standard to detect the presence of intramyocardial haemorrhage after an acute myocardial infarction.^{6,7}

Cardiac magnetic resonance can also provide information on myocardial perfusion as assessed under resting conditions and during stress. Typical stressors used for stress perfusion CMR are vasodilator drugs (adenosine, dipyridamole, regadenoson). When present, an inducible myocardial perfusion defect is visually identified on images acquired at peak stress as a subendocardial/transmural area of low-signal intensity detected during the first-pass of a small bolus of contrast agent.⁸ The qualitative/visual assessment of inducible myocardial ischemia is the most used reporting approach to stress CMR. Nonetheless, semi-quantitative and quantitative methods aiming to estimate myocardial blood flow (MBF) and myocardial perfusion reserve (MPR) may also be deployed, although infrequently used. The diagnostic accuracy, cost-effectiveness, and prognostic value of stress CMR have been largely confirmed as non-inferior or superior to other non-invasive stress tests, such as nuclear imaging or stress echocardiography.^{9,10} The 2019 ESC guidelines on the management of chronic coronary syndromes recommend the use of stress CMR in symptomatic patients with intermediate-to-high clinical likelihood of CAD, when the suspected disease cannot be excluded by basal clinical assessment (class I, level of evidence B). The choice of CMR vs. alternative non-invasive functional tests (including SPECT and stress echocardiography) should be based on local availability and expertise.¹¹ The MR-INFORM trial has demonstrated the non-inferiority of CMR, as compared to invasive angiography supported by FFR, in guiding clinical management of patients with stable angina and intermediate-to-high risk of CAD as well as its ability to

reduce the number of coronary revascularizations.¹² The recent multi-centre Stress CMR Perfusion Imaging in the United States (SPINS) study exploited stress CMR for predicting the occurrence of death and/or myocardial infarction in patients presenting with chronic chest pain syndrome.¹³ Confirming previous observations, authors found patients with no CMR evidence of ischemia or LGE experiencing lower annualized rates of the primary outcome, defined as cardiovascular death or non-fatal myocardial infarction. Furthermore, the presence but also the extent of ischemia has been reported as a strong predictor of worse prognosis, even when corrected for occurrence of reduced LV ejection fraction and for scar burden as defined on LGE images.¹⁴

Recently, the ISCHEMIA trial (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) supported medical therapy over revascularization as first-line management for most of the patients with stable CAD, with the scale needle going towards revascularization only for specific subgroups of patients (i.e. those with substantial ischemia-related symptoms).¹⁵ However, this trial was not intended to assess the differential role of non-invasive imaging modalities in the management of chest pain and stress CMR was employed only in ~5% of the recruited patients.

Finally, in patients with a tentative diagnosis of MINOCA (myocardial infarction with non-obstructive CAD), CMR can identify specific features of myocardial injury that can allow a final diagnosis of acute ischemic damage, acute myocarditis, takotsubo syndrome, and other forms of non-ischemic cardiomyopathy, with the related differential management strategies and prognostic implications.¹⁶

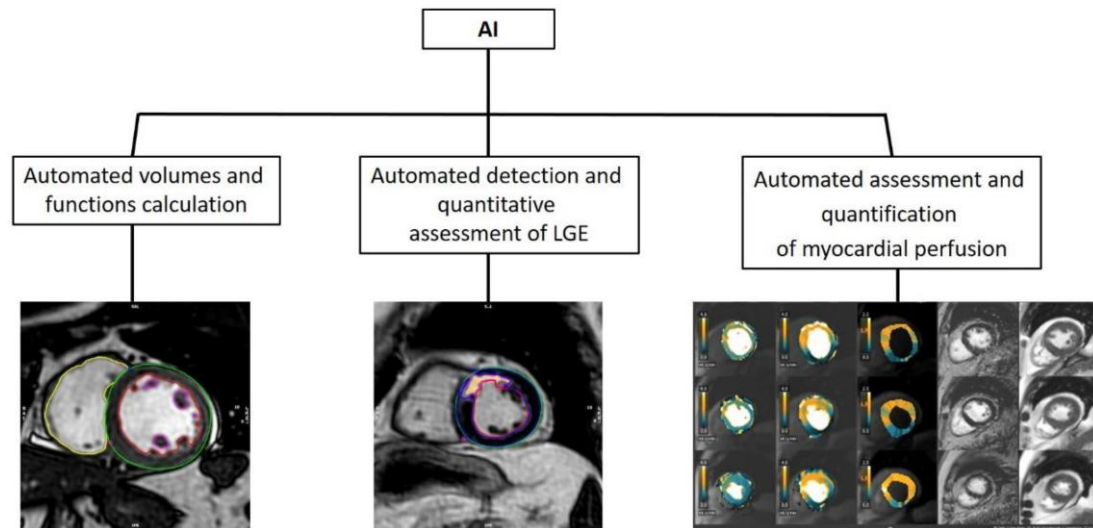


Figure 2 Clinical applications of artificial intelligence in cardiac magnetic resonance post-processing.

Future directions

In the clinical routine of patients with ischemic cardiomyopathy, the main limitations to a wider use of CMR are its high associated costs, low availability of both dedicated scanners and expertise, and relatively long duration of the scan together with the time-consuming post-processing. Moreover, CMR has long been contraindicated in patients with implanted devices, such as pacemakers or implantable cardiac defibrillators (ICD). More recently, the development of MR-conditional devices has helped to overcome this issue. Many studies proved the safety, feasibility, and diagnostic accuracy of CMR in patients with MR-conditional pacemakers/ICDs, provided appropriate device programming and patient's monitoring.¹⁷ Using stress CMR in patients with Pace Maker, Pezel *et al.* have shown that the absence of inducible ischemia and LGE was associated with reduced risk of major adverse cardiovascular events over a 7-years follow-up period, confirming the prognostic value of stress CMR in this specific subgroup of patients.¹⁸ Therefore, it is foreseeable that stress CMR will be increasingly used to assess ischemic cardiomyopathy in patients with implantable cardiac devices.

Nowadays, many automated or semi-automated software tools are available to speed up the calculation of volumes and function with CMR, further improving reproducibility and allowing for a quicker reporting process. However, the role of CMR in the evaluation of ischemic cardiomyopathy is also based on the assessment and the quantification of LGE and myocardial perfusion, which are time-consuming, not entirely objective and less standardized as compared with similar applications based on cardiac nuclear imaging. Artificial intelligence (AI) techniques are emerging in order to provide automated recognition and quantification of LGE extent (Figure 2). Moreover, a new respiratory motion-corrected myocardial perfusion method, which yields a pixel-wise perfusion mapping, has been recently developed with encouraging initial clinical validations.¹⁹ The proposed approach provides a rapid and quantitative assessment of MBF and MPR using perfusion maps generated and displayed on-line within

minutes. This could certainly help the objective assessment of presence and severity of CAD, also opening to a more accurate recognition of myocardial ischemia from microvascular dysfunction. By increasing the efficiency of image acquisition and interpretation, AI is likely to play an important role in further promoting the use of CMR in ischemic cardiomyopathy with potential for improving the clinical and prognostic power of this imaging modality. Large-scale specific datasets are needed to effectively train AI algorithms and, as such, clinical databases dedicated to ischemic cardiomyopathy are warranted to promote adequate introduction of AI into the clinical practice.

Conclusions

In patients with known or suspected ischemic cardiomyopathy, multi-parametric CMR allows a comprehensive evaluation of myocardial function, perfusion, and tissue composition (including myocardial scar/viability) with high diagnostic and prognostic performance, and a demonstrated utility in guiding clinical management. In particular, detection and quantification of myocardial ischemia has relevant clinical implications, even in the post-ISCHEMIA trial era. In this regard, stress perfusion CMR confirmed to be accurate, safe, and clinically valuable as a non-invasive test for detecting severity and distribution of myocardial ischemia. A recent analysis of pooled data from the Euro CMR (European Cardiovascular Magnetic Resonance) and the SPINS registries reported CMR-based strategies for management of patients with stable CAD to be consistently more cost-effective when compared with those using invasive coronary angiography alone or implemented with FFR.²⁰

AI techniques are refining the efficiency of CMR analysis and reporting, with strong potential for improving the yield of this imaging modality for the diagnosis and risk stratification of patients with ischemic cardiomyopathy. Aiming to better fulfill the prescription of current clinical guidelines, putting CMR as a first-line modality for CAD

assessment, a wider access to the test and a more conscious and efficient use could provide clinicians the possibility to pursue a modern patient-centered imaging approach to this condition.

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Data availability

No new data were generated or analysed in support of this research.

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