Review Article

Myocardial Ischemia and Viability by Cardiac Magnetic Resonance: The International Experience and the Greek Reality

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Cardiovascular magnetic resonance (CMR), a relatively new imaging technique, has already proven its efficacy in the assessment of myocardial function, inflammation, tissue characterisation, and viability. Currently, the applications of CMR in coronary artery disease are being extended, making it a powerful diagnostic tool in the evaluation of myocardial perfusion and viability. The aim of this review is to offer a condensed summary of CMR applications in the evaluation of perfusion and viability in coronary artery disease (CAD) and to present the Greek reality in the field.

Ischemia evaluation

Perfusion CMR

The application of perfusion CMR is based on the monitoring of the wash-in kinetics of the paramagnetic contrast medium gadolinium (Gd) into the myocardium during a hyperaemic state, after the use of a vasodilatory agent, such as adenosine. In territories supplied by haemodynamically significantly stenosed coronary arteries the wash-in of Gd is delayed, and this phenomenon can be detected as a dark zone of myocardium during Gd first-pass, when T1-weighted pulse sequences are used (Figure 1).[1-6] In comparison with $^{13}NH_3$-

PET, as the reference standard, the sensitivity and specificity for ischaemia detection by CMR were 91% and 94%, respectively, and for detection of ≥50% diameter stenoses, 87% and 85%, respectively.[7-9] The perfusion protocol includes a stress study after the application of adenosine. Adenosine induces maximal hyperaemia at 0.14 mg/min/kg body weight (administered iv over 3 min), is characterised by a short half-life (<10 s), is safe (1 infarction in >9000 examinations, no death), and is currently the most commonly used agent in pharmacological stress testing.[10,11] The largest perfusion-CMR trial published until now is MR-IMPACT.[12] In 18 centres in Europe and the USA, perfusion-CMR detected coronary artery disease (CAD) with a sensitivity and specificity of 86 and 67%, respectively. In comparison with the entire single-photon emission computed tomography (SPECT) population, perfusion-CMR performed better than SPECT. This superiority was also shown for multi-vessel CAD.[12] The CMR data quality was similar for the three different perfusion territories, as indicated by the similar areas under the curve (AUC) for the detection of stenoses in the left anterior descending (10 segments assigned), left circumflex (two segments assigned), and right coronary arteries (four segments assigned): 0.68 ± 0.08, 0.72 ± 0.09, and 0.70
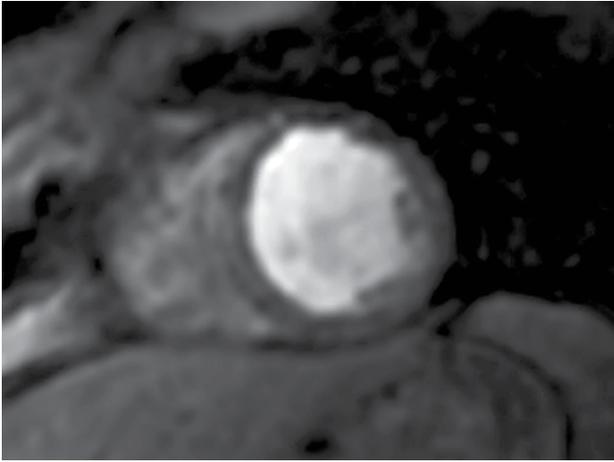
Figure 1. Subendocardial ischaemia (dark area) identified by adenosine stress perfusion study in the anterior and septal wall of the left ventricle.

± 0.08. It is well known that vascular anatomy shows individual differences from patient to patient (e.g. left or right coronary artery dominance), which explains the lower AUC for vessel-based analyses vs. patient-based analyses. Perfusion-CMR performed at 3 T yielded similar results compared to 1.5 T.[13] The best protocol for perfusion CMR is currently being investigated by different studies; however, a high diagnostic performance was reported in several studies from analysis of the hyperaemia data only, and this is in favour of a stress-only protocol.[4,5]

Stress dobutamine CMR

An alternative to perfusion CMR is stress dobutamine CMR, which detects ischaemia by monitoring regional wall motion during infusion of increasing doses of dobutamine, identically to stress echocardiography, but with higher image quality. In a paper comparing the two techniques, dobutamine CMR performed better than stress echocardiography, especially in patients with inferior echo quality.[14] In a study comparing perfusion CMR with stress dobutamine CMR, the predictive value for major adverse cardiac events was similar for both techniques, indicating that both ischaemia tests are similar in performance.[15] However, perfusion CMR is more commonly used in clinical practice, because it is easier, safer and faster compared to dobutamine CMR.

Viability evaluation

CMR is an excellent tool for tissue characterisation

and it can therefore be used as the ideal diagnostic tool for necrosis detection. It can be visualised with superb resolution, allowing the detection of micro-infarcts below 1 g of mass.[16,17] The late gadolinium enhancement (LGE) technique can clearly identify the scar area, because gadolinium chelates distribute rapidly within the intravascular and interstitial space but are excluded from the intracellular space, creating the typical image of "bright is dead". LGE is currently accepted as the best way to assess viability in both acute and chronic myocardial infarction (MI; Figure 2).[18] LGE imaging not only pinpoints the exact location, but also quantifies the extent and severity of myocardial infarction.[19] In large infarcts, the area of non-reperfused microvascular obstruction (MVO) can be visualised by the LGE approach, as a dark core within a bright infarct zone (Figure 3).[20-22] Several studies have validated LGE vs. biomarkers such as CK, CKMB, and troponin in acute or subacute MI.[19,23] Additionally, the transmural extent of infarction, as expressed by LGE, predicts the likelihood of recovery of regional wall motion. Comparative studies with SPECT[5] and PET have proved the significant advantages of CMR that are due to its higher spatial resolution compared with nuclear methods.[24-29]

Assessment of myocardium at risk

CMR is the ideal technique for evaluating viability. However, it can also give useful information about myocardium at risk. T2-weighted CMR demonstrated a close correlation between the amount of myo-
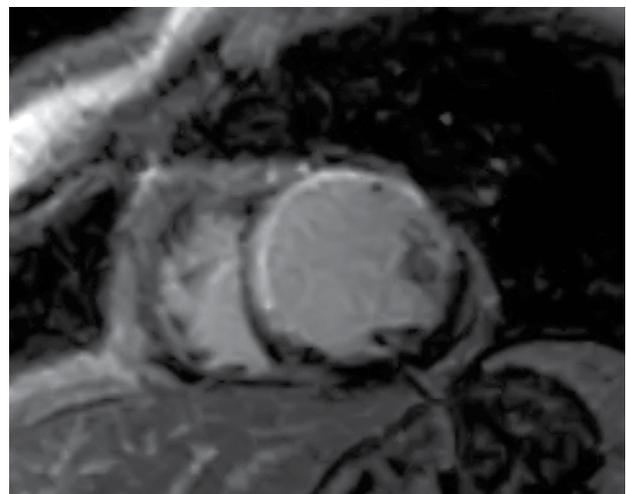

Figure 2. Myocardial scar (white area) identified by late gadolinium enhancement in the anterior and septal wall of the left ventricle.
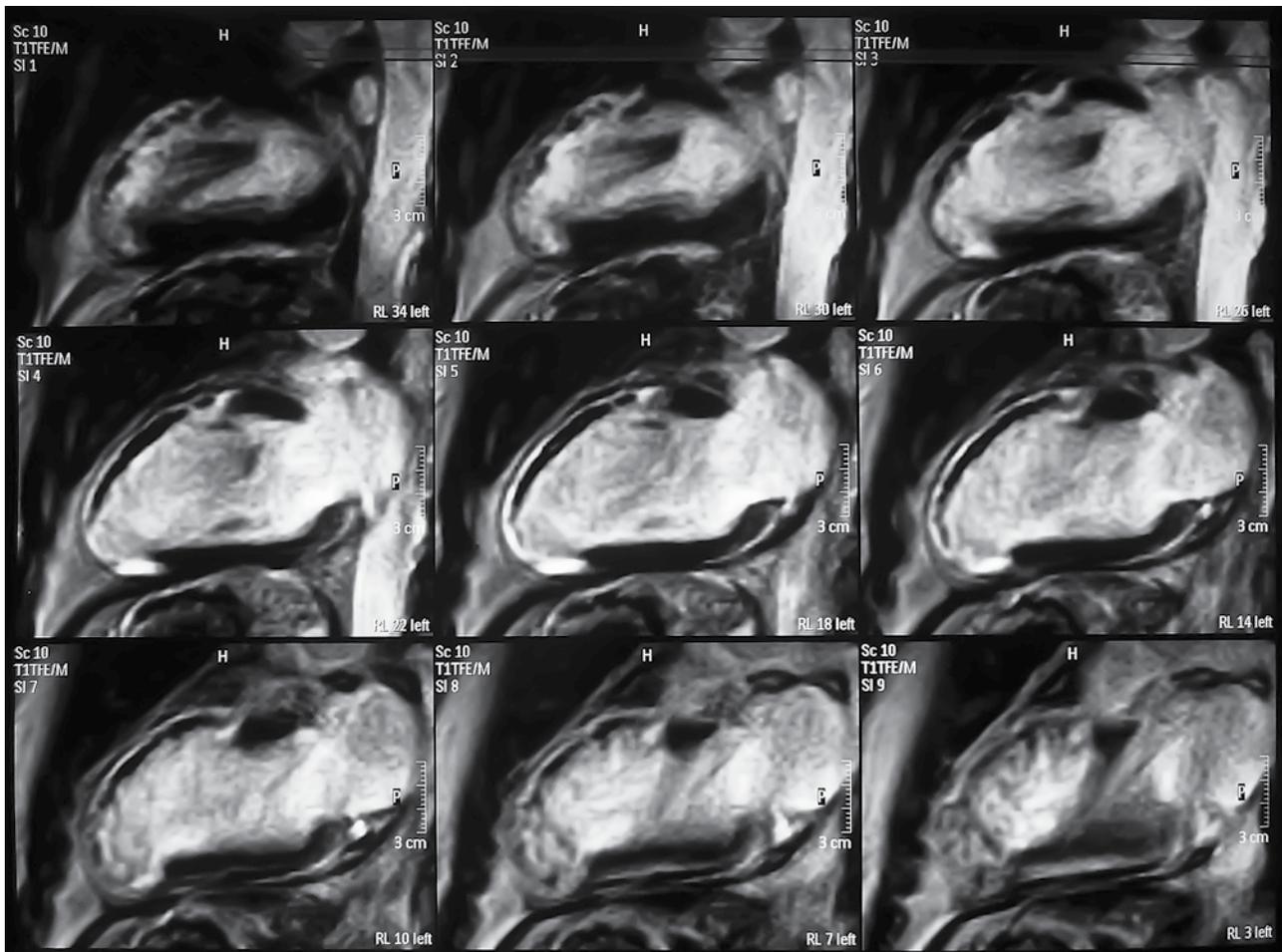
Figure 3. Microvascular obstruction presented as dark area within the myocardial scar (white area) in the anterior wall of the left ventricle.

cardial oedema and the area at risk as assessed by microspheres.[30] From the subtraction of necrotic myocardium from the myocardium at risk a myocardial salvage index can be calculated, which has been used to identify the amount of salvaged myocardium in patients with acute MI.[31] This index has also been shown to predict major adverse cardiovascular events (MACE).[32] Another type of myocardial injury that can be visualised by CMR is intramyocardial haemorrhage. Haemorrhage influences the T2 properties of myocardium and gives low signal areas on T2-weighted images corresponding to the haemorrhagic area on histology.[33,34] The presence of haemorrhage in the core of the infarcted area may influence the healing processes and contribute to adverse remodelling of the left ventricle.[35] However, a lot of work is still needed to improve the technique of T2 weighted imaging in order to achieve sufficient quality for assessment of area at risk.

Algorithms for approaching ischaemia and viability

Chronic coronary artery disease

Nowadays, the international community of cardiologists has been moving away from the idea of "early treatment of CAD" towards the concept of "early risk stratification in CAD". According to updated guidelines, we have to assess risk based not only on symptoms, but also on risk factors, and to revascularise patients based on the extent and severity of ischaemia (Table 1).[36]

The prediction of cardiac death and non-fatal MI by non-invasive ischaemia detection, according to seven large studies that included more than 20,000 patients, showed that the prognostic value of SPECT is large, and a few studies are also available for CMR.[37] These large-scale data demonstrate that, in patients who do not have ischaemia, complication rates are very low, justifying a conservative treatment based

Table 1. Algorithm for evaluating patients with coronary artery disease.

High risk	Intermediate risk	No resting ECG changes
↓	↓	↓
Direct coronary angiography	Ischaemia testing, SPECT, stress echo, perfusion CMR	Stress ECG

on risk factor management. Furthermore, these data confirm that ischaemia (extent and severity) is the most powerful predictor for future infarctions.[38-41]

Additionally, since CAD is a chronic disease with stable phases interrupted by episodes of instability (plaque ruptures), the monitoring of its activity requires a non-invasive, non-radiating, easily applicable and reproducible test. CMR fulfils all these criteria and is currently entering the routine work-up of CAD patients, as shown in the European CMR registry, in which data from more than 11,000 patients are included.[42]

Acute chest pain syndromes

In ST-elevation MI (STEMI) syndromes, the diagnosis is usually straightforward in emergency departments. However, the great majority do not have the typical clinical presentation and this may create diagnostic problems. In acute chest pain, the American College of Cardiology/American Heart Association (ACC/AHA) Guidelines on acute coronary syndromes (ACS) recommend a non-invasive approach, both in patients with severe co-morbidities and in those with a low likelihood of ACS.[43] Similarly, the European Society of Cardiology (ESC) guidelines recommend non-invasive imaging in acute chest pain with repetitive negative troponin and normal or undetermined ECGs.[44]

The first major clinical trial to assess the diagnostic performance of CMR in the emergency department, in patients with 30 min of chest pain and no ST elevation, detected MI with a sensitivity and specificity of 100% and 79%, respectively.[45] The incorporation of T2-weighted imaging into the protocol can differentiate acute from chronic wall motion abnormalities, improving the overall results to a sensitivity of 85% and a specificity of 96%.[46] In another study, in patients with acute chest pain in whom MI was excluded by serial ECG and troponin-I, adenosine perfusion-CMR was performed within 72 h of

presentation and yielded the highest sensitivity and specificity (100% and 93%, respectively) of any single CMR protocol component.[47,48] Furthermore, no patients with a negative CMR scan had any cardiovascular event during a 1-year follow up.[49] Recently, CMR was shown to reduce the overall cost of evaluating patients with intermediate-risk chest pain.[50]

Ischaemic cardiomyopathy

Patients with ischaemic cardiomyopathy also need assessment of ischaemia and viability during their evaluation for possible revascularisation procedures. Kim et al demonstrated the ability of CMR to predict the recovery of segmental contractile function post-revascularization in relation to the transmurality of scar tissue in dysfunctional segments.[50] After revascularisation, about 80% of segments with ≤25% transmurality of scar recovered function. However, when transmurality exceeded 50% of wall thickness, only <10% of segments recovered function.[50] Additionally, a scar thickness of ~4 mm has a very low likelihood for functional recovery, because of tethering, while a viable rim of ~4 mm is required to allow for recovery of function.[51] In addition to tissue characterisation, low-dose dobutamine CMR can be performed in parallel with viability evaluation to assess the likelihood of functional recovery. Thus, patients with ischaemic cardiomyopathy and substantial hibernating or stunning myocardium can be readily detected by CMR and can benefit from revascularisation. Furthermore, scar mass and MVO detection predict the patients' outcome.[52-54] In patients who had no MVO, MACE-free survival was ~90% at 18 months, but decreased to ~50% in patients with MVO. Finally, the amount of scar tissue was shown to predict the responsiveness to cardiac resynchronisation therapy.[55]

It should also be emphasised that the location and the morphology of scar has important clinical implications for a patient's diagnosis. In this context, a sub-epicardial or intramural scar is characteristic of myocardial inflammation (infective or non-infective), while a sub-endocardial or transmural scar following the distribution of coronary arteries is typical of myocardial infarction. Specific types of cardiomyopathy, such as hypertrophic cardiomyopathy and amyloidosis, may present different patterns of scar. For example, in hypertrophic cardiomyopathy the scar is usually located in the hypertrophied area, whereas in amyloidosis a diffuse subendocardial fibrosis of the left ventricle can be observed.[56]

Regarding the detection of left ventricular thrombus, in a comparative study of 361 patients with surgical or pathological confirmation of intracardiac thrombus, CMR had a better sensitivity for thrombus detection compared to transoesophageal and transthoracic echocardiography, while all three modalities had excellent specificities of 99%, 96%, and 96%, respectively.[57] Contrast echocardiography, though having double the sensitivity of non-contrast echocardiography in detecting left ventricular thrombi, was still inferior in comparison to LGE, which was particularly powerful for mural and small apical thrombi.[58]

The Greek reality

Although the scientific level of Greek cardiology is very high, cardiologists in Greece have never found an officially legal way to actively participate in the performance and interpretation of different imaging techniques, with the exception of echocardiography. Under these circumstances, although all Greek cardiologists have an excellent training in echocardiography, they are completely "immune" or only partially exposed to other imaging techniques.

As a consequence, echocardiography is the only technique that Greek cardiologists are familiar with, and therefore they believe that "they can see everything using only echocardiography". The easy availability, the excellent training and the relatively low cost make echocardiography the first, and most times unique, unbeatable player in the imaging field in Greece.

Furthermore, even if Greek cardiologists have an internationally certified training in other imaging techniques abroad, the outdated Greek legislation does not allow them to perform and interpret other imaging techniques, apart from echocardiography. It is also striking that, if high-level technology is involved in cardiac decision making, the Greek academic world of cardiology considers these examinations as radiological, even though their interpretation demands an excellent knowledge of clinical cardiology. This concept, promoted by radiologists and passively accepted by cardiologists, has contributed to a strange reality in Greece, where CMR examinations are currently interpreted exclusively by untrained radiologists, whereas internationally trained cardiologists are completely excluded from the field. The end result is that a lot of money is spent on useless CMR examinations, which in practice have no clinical impact on decision making. It seems that this attitude is part of the famous "Greek politics" that has led the country to the financial disaster we face today.

Since 1998, when the first Greek paper by Mavrogeni et al concerning thalassaemia evaluation by CMR was published,[59] many CMR studies have been performed in Greece and published in international journals, including different hot cardiac topics (myocardial iron overload, myocardial inflammation, coronary artery disease, cardiomyopathies); some of these have also been included in the international guidelines concerning the applications of CMR.[59-85] Furthermore, the first paper originating from Greece about stress perfusion CMR in a scleroderma population has recently been published.[86] However, official training in CMR has never been included in the core curriculum of Greek cardiologists, although this is currently recommended by the ESC guidelines.[87] Additionally, the application of stress CMR was started only last year by our team. The reason is that CMR is absolutely in the hands of radiologists and its dynamic expression in the form of stress CMR has been completely ignored. In comparison with the EuroCMR registry, where stress CMR is the second most common clinical indication, in Greece CMR has been almost exclusively used for thalassaemia and myocarditis evaluation. Our current experience of stress CMR in Greece includes adenosine perfusion CMR in a number of diabetic patients (early screening for CAD and diabetic cardiomyopathy), in CAD patients with contradictory results from other imaging techniques, and in autoimmune patients. Our results, although very preliminary, are of important value, while the technique has proved safe, fast, reliable and easily accepted by the patients.

Our purpose in this review is not to create troubles in the relationship between cardiology and radiology in Greece. On the contrary, by presenting a rather sad reality, we aim to promote training of both cardiologists and radiologists in order to get the maximum from CMR. We also hope to convince the Greek medical community to support all internationally trained individuals (cardiologists or radiologists) so that they can offer the full benefit of their expertise in the field. Furthermore, the adequate training of clinicians so that they understand "which patient for which technique" is absolutely necessary.

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