

REVIEW

Cardiovascular magnetic resonance for detection of coronary artery disease – a practical approach

Sebastian Onciul¹, Sven Plein²

Abstract: Coronary artery disease (CAD) is the leading cause of cardiovascular mortality worldwide. Non-invasive diagnosis of CAD is essential for lowering the number of unnecessary invasive coronary angiograms (ICA). Due to the low diagnostic accuracy of electrocardiographic exercise testing (EET), the current practice has shifted to the use of non-invasive imaging testing where available. Cardiovascular magnetic resonance (CMR) is unique among the current non-invasive imaging tests because it offers equally accurate information about cardiac morphology, function, myocardial ischaemia and viability in one single examination, without exposing patients to ionizing radiation. This is particularly important in complex clinical scenarios such as patients with multi-vessel CAD, total chronic occlusions or prior revascularization, in which precise knowledge of ischaemic territories, viability and left ventricular (LV) function are necessary to determine the appropriate treatment. This review is focused on myocardial perfusion CMR imaging while briefly discussing the other CMR methods relevant to the assessment of CAD. We also provide practical information on how to perform stress myocardial perfusion CMR as well as the current guideline indications of CMR in CAD detection.

Keywords: CMR, cardiovascular magnetic resonance, first pass perfusion, coronary artery disease, non-invasive imaging

Rezumat: Boala coronariană ischemică (BCI) reprezintă cea mai frecventă cauză de mortalitate cardiovasculară în întreaga lume. Diagnosticul non-invaziv al BCI este esențial pentru reducerea numărului de angiografii coronariene invazive (ACI) redundante. Dat fiind că testul de efort EKG (TEE) are o acuratețe diagnostică scăzută, acesta a fost înlocuit în practica curentă de teste imagistice non-invazive acolo unde acestea sunt disponibile. Rezonanța magnetică cardiovasculară (CMR) este unică între actualele teste imagistice non-invazive pentru că oferă informații precise privind morfologia și funcția cardiacă, ischemia miocardică, și viabilitatea în cadrul aceleiași examinări, fără a expune pacientul la radiații ionizante. Toate aceste informații sunt deosebit de importante în cazul scenariilor clinice complexe cum ar fi pacienții cu boală coronariană pluri-vasculară, ocluzii coronariene cronice, înainte de revascularizare, situații în care cunoașterea precisă a teritoriilor ischemice, dar și a celor viabile, precum și funcția cardiacă sunt necesare pentru a stabili cea mai oportună variantă de tratament. Acest articol se axează pe imagistica CMR de perfuzie miocardică, amintind pe scurt și alte metode CMR relevante pentru diagnosticul BCI. De asemenea, prezentăm informații practice despre cum se efectuează CMR de perfuzie miocardică percutan și indicațiile CMR în diagnosticul BCI, conform ghidurilor actuale.

Cuvinte cheie: CMR, rezonanța magnetică cardiovasculară, prim pasaj, boală coronariană ischemică, imagistica non-invazivă

THE CURRENT ROLE OF NON-INVASIVE IMAGING FOR CAD DETECTION

Invasive coronary angiography (ICA) remains the definitive test for anatomic definition of coronary stenosis and with the addition of fractional flow reserve (FFR) to determine the functional significance of coronary lesions. However ICA is not a risk-free procedure and recent data show that a large number of ICAs per-

formed in routine practice are unnecessary. A study including almost 400 000 patients showed that almost 60% of patients without known CAD who underwent elective ICA were found to have no obstructive CAD¹.

Performing non-invasive testing can avoid unnecessary ICA in patients with suspected CAD. Therefore, the current European guidelines recommend non-invasive testing for patients at intermediate risk of CAD.

✦ Contact address:

Sebastian Onciul, Multidisciplinary Cardiovascular Research Centre & Division of Biomedical Imaging, Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds LS2 9JT, United Kingdom.
E-mail: s.c.onciul@leeds.ac.uk

¹ Cardiovascular Magnetic Resonance Imaging Fellow, Leeds University, United Kingdom

² PhD, MD Germany, MRCP, Professor of Cardiology, British Heart Foundation Senior Clinical Research Fellow & Honorary Consultant Cardiologist, Head of the Division of Biomedical Imaging, University of Leeds, United Kingdom

Anatomical techniques are excellent for ruling out CAD but do not provide information regarding the functional significance of detected coronary obstructions. For example, CTA is able to precisely localize coronary stenosis but does not provide information regarding their functional significance, unless combined with expensive computational modeling methods such as computed tomography-derived fractional flow reserve (CT-FFR)^{2,3}. However, revascularization is generally recommended only if ischaemia or LV dysfunction are demonstrated, so that functional testing is required to guide the management of patients with CAD.

Historically, electrocardiogram exercise testing (EET) has been used as a first line functional test to screen patients presenting with chest pain for the presence of significant CAD. However, as the sensitivity of EET has been reported to be as low as 45-50% when referral bias is considered^{4,5,6} it can no longer be considered as an appropriate first line test for CAD detection. The European guidelines recommend that EET should not be employed in patients with a pre-test probability >65%⁴. In clinical practice, EET is increasingly replaced by stress imaging tests including stress echocardiography, CMR, myocardial perfusion scintigraphy (MPS), computed tomography angiography (CTA) or positron emission tomography (PET).

THE CURRENT APPLICATIONS OF CMR IN CAD

Among the non-invasive imaging modalities, CMR stands out because it provides both structural and quantitative functional information without patient exposure to ionizing radiation and without limitations relating to the patient's body habitus. Historic contraindications such as implantable cardiac devices are being overcome through the development and increasing use of MR safe and conditional devices⁷.

Ischaemia detection is only one of the many applications of CMR in CAD. Using cine imaging in reproducible orientations and with whole heart coverage, CMR is currently considered the reference method for quantification of left ventricle (LV) and right ventricle (RV) dimensions and function.

Furthermore, CMR has the unique capacity of tissue characterization. Among the available CMR methods, T2 weighted CMR is sensitive to myocardial oedema and late gadolinium enhanced (LGE) CMR detects myocardial necrosis or scar with very high contrast and spatial detail. Using these methods, in the setting

of acute myocardial infarction, CMR can delineate irreversible damage from the area at risk providing an accurate estimation of the final infarct size; it can also detect microvascular obstruction and intramyocardial hemorrhage, all of which have proved important prognostic value in this population⁸.

In the context of acute myocardial infarction with non-obstructed coronary arteries, CMR can provide the final diagnosis in up to 70% of cases, differentiating between myocarditis, myocardial infarction, Tako-Tsubo or other cardiomyopathies, with a significant clinical impact on patient management⁹.

In chronic CAD, CMR can establish the location and extent of myocardial scar and can identify lipomatous metaplasia, a finding associated with high arrhythmic risk. The transmural extent of myocardial scar is a measure of myocardial viability and predicts functional recovery after revascularization¹⁰.

Finally, ischaemia by CMR can be detected with either vasodilator stress myocardial perfusion CMR or inotropic stress wall motion imaging.

In short, CMR is an anatomical and functional test able to offer a multitude of complex information within a single examination.

DIAGNOSTIC ACCURACY OF STRESS PERFUSION CMR FOR THE DETECTION OF CAD

Stress perfusion CMR has demonstrated high accuracy for the detection of CAD in several studies. When using invasive FFR as the reference standard, stress CMR demonstrated a sensitivity and specificity of 82% and 94% respectively, with an area under the receiver-operator characteristic curve of 0.92 to detect coronary stenosis at a threshold of FFR <0.75 in one of several recent single-centre studies¹¹. Similarly, a meta-analysis of 14 studies showed that with FFR as the reference standard, the diagnostic ability of stress CMR to detect CAD is high with pooled sensitivity and specificity of 90% and 87% respectively¹².

The largest prospective, real world randomized study that assessed the diagnostic accuracy of CMR in detecting CAD was the CE-MARC study, which recruited 752 patients who underwent CMR and MPS with ICA as the reference standard for CAD detection. The study clearly showed superiority of CMR over MPS for detection of CAD. For CMR the sensitivity was 86.5%, specificity 83.4%, positive predictive value 77.2%, and negative predictive value 90.5%¹³. The sensitivity of MPS was 66.5%, specificity 82.6%, positive

predictive value 71.4%, and negative predictive value 79.1%¹³. CE-MARC was a single centre study, but similar results were obtained in the multi-centre, multi-vendor MR-IMPACT 2 study. In this study, the sensitivity of CMR to detect CAD was superior to MPS, while its specificity was inferior to MPS¹⁴.

PROGNOSTIC INFORMATION FROM STRESS PERFUSION CMR

In several single-centre studies, stress perfusion CMR has demonstrated a high negative predictive value for major adverse cardiac events (MACE). A meta-analysis of 14 of these studies, recruiting 12 178 patients identified a negative predictive value for MACE of a normal CMR of 98.12% during a mean follow-up of 25.3 months¹⁵. This translates into an event rate after a negative stress CMR scan of 1.03% per annum which is similar to that of a normal population. On the other hand, a positive stress CMR was associated with a 3-fold increased risk of MACE¹⁵.

Five-year follow-up of the CE-MARC study indicates that compared with MPS, stress perfusion CMR is a stronger predictor of risk for MACE, independent of cardiovascular risk factors, angiography result, or initial patient treatment¹⁶.

TECHNICAL ASPECTS OF STRESS CMR

The most widely used CMR method for CAD detection is first-pass perfusion imaging during vasodilator stress, and this review refers only to this technique. Dobutamine stress CMR is another stress CMR method, but it is less performed worldwide.

FIRST-PASS PERFUSION CMR - HOW DOES IT WORK?

As the name implies, the first-pass perfusion technique is based on visualization of myocardial perfusion

on defects immediately after the intravenously injected Gadolinium based contrast agents (GBCA) reaches the LV cavity and enters the myocardium. The contrast can be visualized as entering the right heart chambers and then entering the left heart chambers, and finally entering the myocardium which becomes brighter in proportion to the amount of contrast uptake in the myocardium (Figure 1). Areas with reduced myocardial perfusion will receive less GBCA and will therefore appear darker than normally perfused regions which will appear brighter as they receive relatively more GBCA.

Usually, basal, mid and apical short axis LV slices are acquired in each cardiac cycle, allowing assessment of 16 of the 17 segments in the *American Heart Association* (AHA) classification. The addition of a long axis view is feasible, although rarely used in clinical practice, to also cover the apical segment. Conventionally, data are acquired over 40-60 consecutive cardiac cycles to accurately assess the persistence of any perfusion defect after contrast administration.

In order to detect ischaemia, the image acquisition is performed during maximal hyperemia induced by infusion of a vasodilator agent. A rest study is usually performed 15 minutes before or after the stress imaging, using the same CMR sequence, slice positions and contrast dose, but in the absence of vasodilatation (Figure 3).

STRESS AGENTS IN CLINICAL USE

Adenosine, regadenoson and dipyridamole are the vasodilators used in first-pass perfusion CMR. Adenosine acts on 4 receptors A1, A2A, A2B and A3, while regadenoson is a selective A2A receptor agonist. Dipyridamole acts by inhibiting adenosine reuptake and thus increasing the availability of endogenous adenosine¹⁷. Adenosine and regadenoson have similar

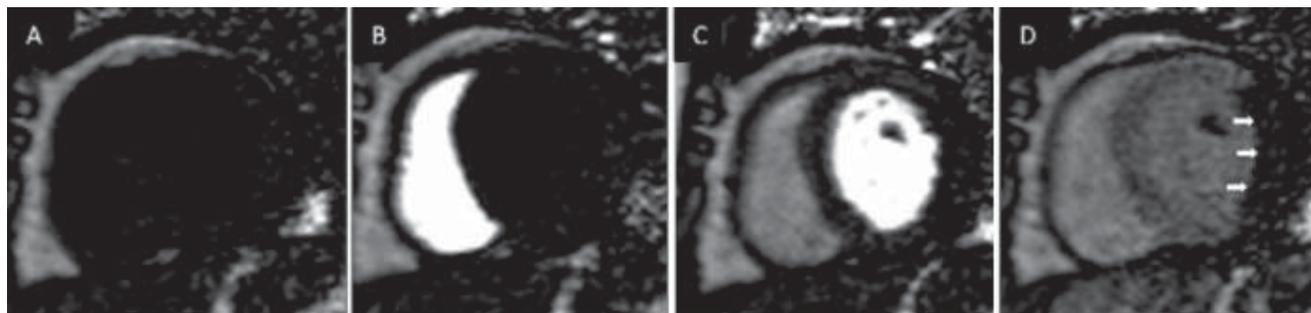


Figure 1. Example of a first pass perfusion CMR study (only the mid slice is shown). The acquisition begins before contrast is present in the heart chambers (A). Contrast can be first visualized entering the right ventricle (B) then the left ventricle (C) and finally it enhances the myocardium (D). In this case a myocardial perfusion defect is observed in the lateral and infer-lateral walls (white arrows).

coronary vasodilator potency and both are superior to dipyridamole¹⁷.

Due to its ultra-short half-life (<10 seconds), adenosine effects are neutralized immediately after its infusion is stopped making the administration of the antidote almost redundant¹⁷.

Early studies from the nineties showed a low incidence of adverse reaction with adenosine infusion even when 6 minutes protocols were employed¹⁸. More recently, very large registry data showed even lower incidence of adverse events when the stress agent was administered according to currently recommended protocols. European cardiovascular magnetic resonance (EuroCMR) registry gathered data from more than 27000 patients from 57 centers in 15 countries. Mild complications occurred in 3.6%, and severe complications in only 0.026% of patients¹⁹. Although traditionally adenosine was contraindicated in patients with asthma or chronic obstructive pulmonary disease, evidence from clinical trials have shown that adenosine is safe in patients with history of mild, well-controlled lung obstructive disease²⁰.

In terms of symptoms patients may experience chest pain, shortness of breath, facial flushing, lightheadedness, diaphoresis, or a metallic taste during adenosine infusion. These symptoms are transitory, usually lasting less than one minute.

GADOLINIUM BASED CONTRAST AGENTS

Perfusion CMR uses T1 weighted pulse sequences, meaning that the contrast between different tissues is based on their different T1 relaxation times. Due to its paramagnetic properties, Gadolinium shortens T1 relaxation time thus it enhances contrast between tissues with different relaxation properties. In the context of first-pass perfusion imaging, the normally perfused myocardial segments will appear brighter than the abnormal segments, due to T1 prolonging effects of GBCA.

There are 2 structurally distinct categories of GBCA: linear or macrocyclic. The latter are considered safer because the Gadolinium ion is more tightly attached to a chelating molecule and thus it is less likely to dissociate. Lower dissociation rates are translated into lower risk of gadolinium deposition in various organs of the body. GBCA are not nephrotoxic, however exposure to linear GBCA has been associated with nephrogenic systemic fibrosis (NSF), an extremely rare but serious disease of fibrosis of the

skin and internal organs. No cases of NSF have been reported in patients with normal renal function and macrocyclic contrast agents appear to be much less likely to cause NSF. Because of concerns over tissue retention, the *European Medicines Agency* has recently recommended the suspension of the marketing authorizations for linear GBCA.

ABOUT THE PHYSICS

First-pass perfusion imaging can be performed on both 1.5 and 3.0 Tesla MRI scanners. A higher magnetic field strength is associated with increased signal to noise and contrast to noise ratio which can be used to boost spatial and/or temporal resolution. However, 3.0 Tesla imaging is also more challenging due to its inherent susceptibility to artifacts due to greater magnetic field inhomogeneity.

The pulse sequence used for first-pass perfusion is made up of a saturation recovery preparation pulse followed by a fast imaging technique for read out such as steady state free precession (SSFP), spoiled gradient echo (GRE) or echo planar imaging (EPI). The saturation recovery preparation pulse has the role of enhancing contrast between the low GBCA uptake areas and the normally perfused myocardium. Methods such as non-cartesian sampling, parallel imaging, partial-Fourier and spatio-temporal undersampling with methods such as *k-t* Broad Linear Speed up Technique (*k-t* BLAST) have been introduced to accelerate data acquisition and allow acquisition of higher spatial resolution data.

In a small pilot study, high-resolution perfusion-CMR using *k-t* BLAST (1.6×1.6 mm in-plane) had higher overall diagnostic accuracy than standard-resolution acquisition (2.5×2.5 mm in-plane) for the detection of CAD in both single- and multivessel disease²¹. Furthermore a reduction in endocardial dark-rim artifact was reported with high-resolution perfusion images. These methods require further validation in larger cohorts.

A TYPICAL CMR PROTOCOL FOR SUSPECTED OR KNOWN CAD

An example of a CMR protocol indicated in patients with suspected or known CAD is depicted in Figure 2. This protocol aims to identify stress induced myocardial ischaemia and myocardial viability during a 45-50 minutes scan as well as providing an assessment of LV contractile function and general cardiac morphology.

Usually the study begins with a low resolution survey scan of the chest and upper abdomen which allows

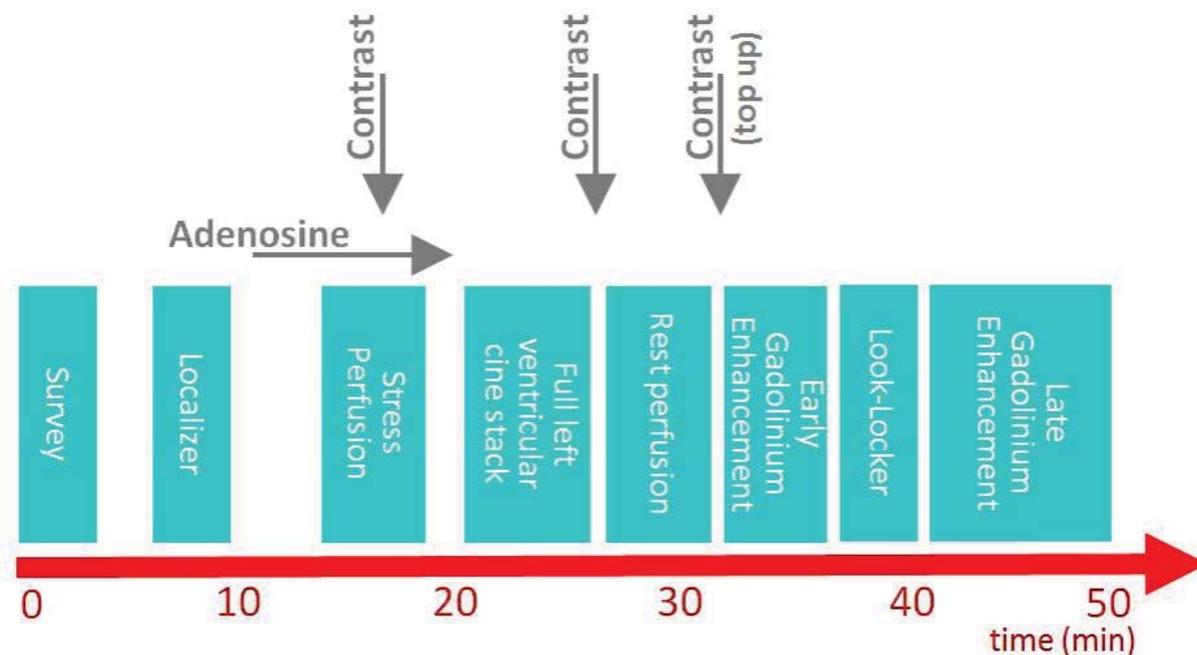


Figure 2. An example of a first pass perfusion CMR protocol. In this particular case, the total dose of contrast is administered divided in 3 equal doses: first during stress perfusion, second during rest perfusion and the last just before the early gadolinium enhancement imaging. This protocol provides information regarding left ventricular dimension and function, myocardial ischaemia and viability.

for localization of the heart within the thorax. Then, orthogonal slices through the heart are obtained similar to those in conventional echocardiography: two-chamber, four-chamber and short-axis views. During this stage, the basal, mid and apical short axis slices are planned for use in subsequent first-pass perfusion imaging.

The next step consists in intravenous infusion of the vasodilator agent. The infusion rates are 140 $\mu\text{g}/\text{kg}/\text{min}$ for Adenosine and 0.56 mg/kg for dipyridamole. Regadenosone is injected as a single 400 μg bolus (fixed dose, no need weight adjustment). When adequate stress is obtained, a bolus of contrast (0.05-0.1 mmol/kg body weight) is injected at a rate of 3-7 ml/s , followed by a saline chasing bolus (30 ml). Immediately the three short axis slices previously prescribed are acquired in every cardiac cycle.

After approximately 10-15 minutes delay to allow wash out of contrast agent from the myocardium, rest perfusion images are acquired in the same slices, using the same sequence and the same dosage of GBCA, the only difference being the absence of vasodilator stress. Between stress and rest acquisitions, a stack of short axis cine images covering the whole left ventricle is acquired for functional analysis. Six-to-eight mm thick slices are acquired with a 2-4 mm slice gap, the number of slices depending on the long axis dimension of

the LV. This acquisition offers an exhaustive coverage of the whole LV providing accurate measurements of LV dimensions and function.

After the rest perfusion imaging, an optional bolus of GBCA may be administered (top-up) immediately after which the early Gadolinium enhancement (EGE) images are acquired; these allow for identification of intracavitary thrombus or evidence of MVO in the context of an acute ischaemic event.

Seven-to-ten minutes after the last dose of GBCA, late gadolinium enhancement (LGE) images are acquired to detect myocardial scar or fibrosis.

ARTIFACTS AND PITFALLS IN REPORTING FIRST-PASS PERFUSION IMAGING

As with all functional imaging techniques, accurate detection of ischaemia requires adequate stress. Insufficient vasodilator stress (ie. caffeine antagonism) can result in false negative results. In clinical practice it is accepted that adequate stress is obtained when the heart rate increases with 10% and/or the blood pressures decreases with 10 mmHg compared to the pre-vasodilator administration values. Symptom occurrence is a confirmation that the stress agent is effective. Furthermore, adequate stress can be objectively assessed by the presence of splenic switch-off,

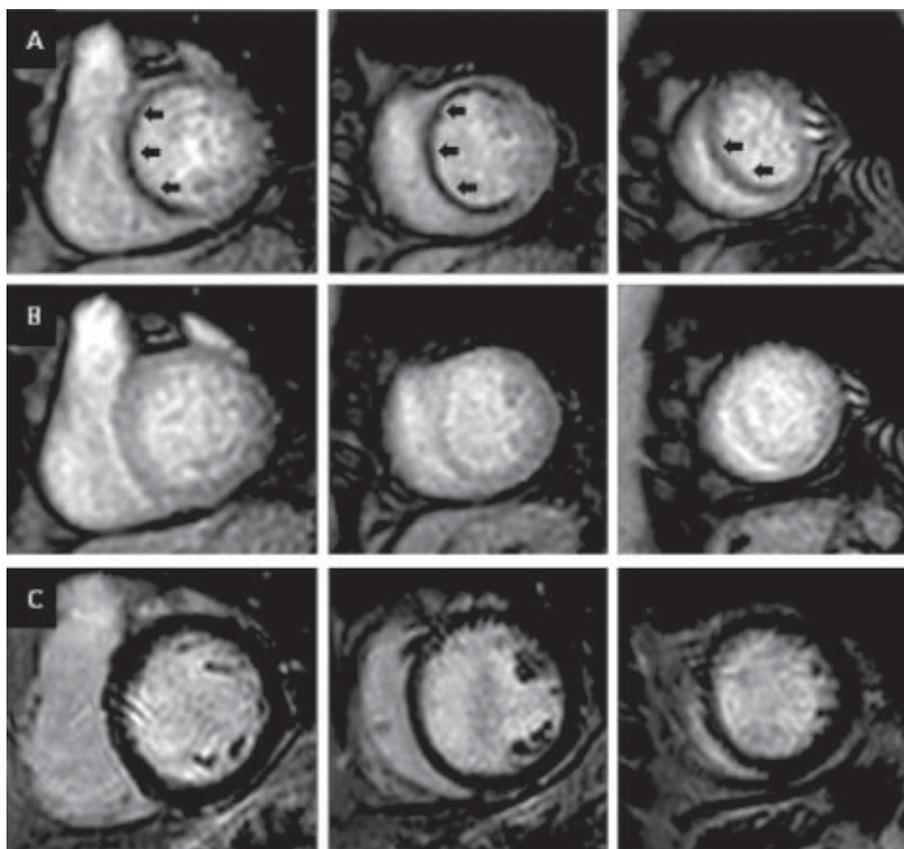


Figure 3. Example of a CMR study in suspected CAD. Basal, mid and apical short axis perfusion slices are acquired during stress (A). An extensive myocardial perfusion defect (black arrows) is noted in the basal anterior, antero-septal and infero-septal segments, mid anterior, antero-septal and infero-septal segments as well as in apical septal segment (in total 7 segments from 17). These perfusion defects are not visualized on rest acquisition (B). Late gadolinium enhancement imaging (C) does not show any evidence of scar/focal fibrosis, indicating that the myocardium is entirely viable with good outcome if revascularized.

which is the attenuation of splenic perfusion in the stress images compared with the corresponding rest images, due to splenic vasoconstriction by adenosine²². As the spleen is usually included in the short axis views acquired during first-pass perfusion imaging, the splenic-switch off is a straightforward method to objectify adequate vasodilator stress. Regadenoson does not produce a splenic switch-off phenomenon, as it acts selectively on A2 receptors in coronary microcirculation with no effects on renal, mesenteric, or peripheral circulation.

The *dark rim* artifact is defined as a transient low signal line localized at the interface between blood pool and myocardium during the early phases of a myocardial perfusion study. The phenomenon is temporary, as it disappears after myocardial enhancement has occurred (after 8-10 cardiac cycles). The accurate differentiation between a true perfusion defect and dark rim artifact requires experience. A true myocardial perfusion defect persists longer, and is usually characterized by a larger width, generally accompanied

by a gradient from darker subendocardial towards a brighter subepicardial area with variable transmural extent. True perfusion defects also correspond to a coronary artery distribution.

Aliasing artifacts due to respiratory motion (parallel imaging artifacts) are associated with parallel imaging techniques, which are usually employed for shorter acquisition time. This technology works by under-sampling in the phase encoding direction and consequently the region outside the field of view wraps around in the middle of the image. If this artifact is not correctly recognized it might be misinterpreted as a myocardial perfusion defect (Figure 4). The artifact can be avoided by reducing the acceleration factor, or by increasing the field of view in order to encompass the entire chest.

EQUIPMENT AND STAFF REQUIREMENTS

An MRI scanner of minimum 1.5 Tesla is necessary for first-pass perfusion imaging. The scanner should

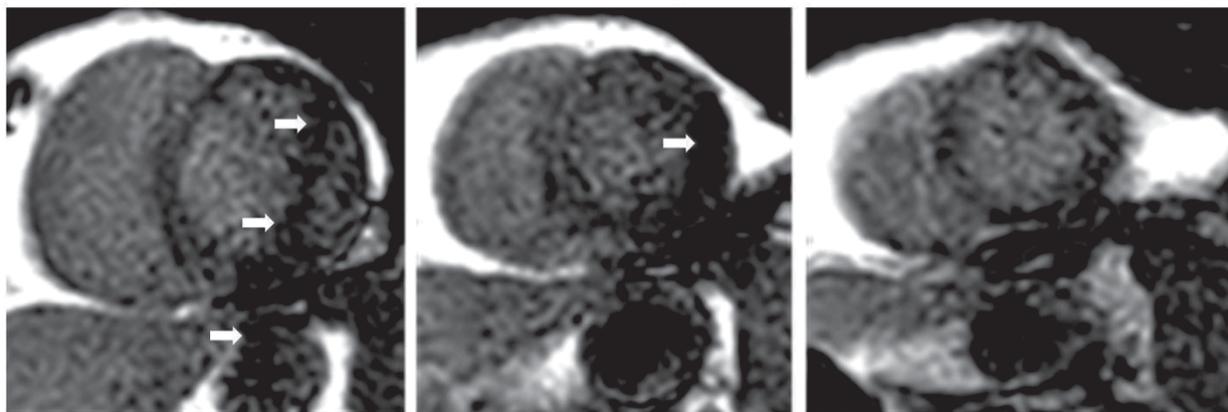


Figure 4. Example of a respiratory aliasing artifact (white arrows) on basal, mid and apical slices of a first pass perfusion CMR study. The dark appearance may be mistakenly interpreted as a perfusion defect.

be equipped with a phased-array surface coil, as well as artifact resistant electrocardiogram ECG hardware/software (e.g. vectorcardiogram) for efficient gating. An MRI-compatible power injector must be employed for contrast infusion. Resuscitation facilities (including defibrillation/oxygen/suction) should be available as well as drugs to deal with potential reactions to GBCA and stressors.

Stress CMR can be performed and reported by either radiologists or cardiologists with appropriate expertise, depending on the national laws and regulations. In some countries cardiologists and radiologists report jointly, maximizing the benefits to patients. The *European Society of Cardiology (ESC)* and the *European Society for Cardiovascular Radiology* offer processes for certification in CMR. ESC Level 3 competency is required for individuals wishing to perform, interpret, and report CMR studies fully independently, to lead a CMR laboratory and to supervise CMR training programmes in an accredited CMR training centre. To obtain level 3 certification an individual must spend at least 12 months under the supervision of a level 3 certified expert.

EMERGING TECHNOLOGIES FOR ASSESSING MYOCARDIAL PERFUSION - THE QUANTITATIVE ASSESSMENT

In current clinical practice, myocardial perfusion defects are assessed qualitatively by distinguishing darker low-perfused areas from brighter normally perfused myocardium (see above). This approach is subjective and is highly dependent on the presence of differences in signal intensities between healthy and ischaemic myocardium – in addition to substantial observer experience. However in the presence of significant is-

chaemia in all three coronary territories, the accurate visualization of perfusion defects may be challenging as there is no healthy reference myocardium to use as a visual comparator. Quantitative perfusion assessment by CMR can provide absolute myocardial blood flow (MBF) in units of ml/g/min. Myocardial perfusion reserve (MPR) can be calculated as the ratio between MBF during vasodilator stress and MBF at rest. Although historically quantitative perfusion analysis was associated with long post-processing times, recently developed technologies permit rapid, inline quantification of myocardial perfusion without prolonging scanning or reporting times²³.

When compared to PET which is the gold standard imaging modality for non-invasive myocardial blood flow quantification, studies showed good correlation between MPR (CMR) and MPR (PET)²³.

IS CMR THE BEST IMAGING MODALITY FOR DETECTING CORONARY ARTERY DISEASE?

As shown, first-pass perfusion CMR has several advantages over other non-invasive imaging modalities in diagnosing CAD. First of all, it does not expose patients to ionizing radiation and offers good quality images independently of the patient's body habitus. Myocardial perfusion CMR imaging has better spatial resolution than MPS, thus allowing for detection of smaller perfusion defects and has higher diagnostic accuracy than SPECT. CMR allows quantitative estimates of MBF comparable to PET.

Most importantly, CMR is unique among the other cardiac imaging techniques because of its multiparametric nature. A single study provides information regarding ventricular function, myocardial ischaemia, vi-

ability, and coronary artery anatomy. This is especially important in complex cases with multi-vessel disease, previous myocardial infarction and LV dysfunction in which the most suitable therapeutic strategy depends on demonstration of residual ischaemia, viability and correct estimation of LV ejection fraction.

Subclinical anomalies of the intra-myocardial mechanics including torsion, twist, strain and strain rates can also be assessed by CMR¹¹.

The following are some clinical scenarios in which first pass perfusion might be indicated:

- Patients with suspected CAD with a pre-test probability of coronary artery disease of 15-85% according to ESC guidelines⁴.
- Patients with abnormal resting ECG in which the ST changes during exercise are not interpretable or difficult to analyze: left bundle branch block, paced rhythm, pre-excitation, LV hypertrophy, electrolyte imbalance, and use of digitalis. Electrocardiographic exercise testing receives a class III indication in the European guidelines for patients with $\geq 0,1$ mV ST-depression on resting ECG or taking digitalis⁴.
- Patients with complex coronary pathology, multi-vessel disease, chronic total coronary occlusions, prior PCI/CABG, in which information regarding viability is necessary in order to indicate surgical/interventional revascularization.
- Patients with limited exercise capacity due to orthopaedic or other non-cardiac problems.
- Patients with sub-optimal acoustic windows on echocardiography.
- Women with suspected CAD. Exercise ECG testing demonstrated lower sensitivity and specificity in women⁵. The CE-MARC study showed that CMR has greater sensitivity than MPS in both men and women. These findings, plus an absence of ionizing radiation exposure, mean that CMR should be more widely adopted in women with suspected CAD²⁴.
- Patients with known CAD in whom the interruption of anti-ischaemic medication is not safe. As opposed to dobutamine stress imaging, CMR perfusion imaging does not require interruption of beta-blockers.
- Patients in whom the high risk of malignant ventricular arrhythmias contraindicates dobutamine stress imaging.

CONCLUSION

By performing a CMR scan which usually lasts 45 minutes information regarding cardiac morphology and function, myocardial ischaemia and viability can be obtained. Taking into account its high diagnostic accuracy and safety profile, stress perfusion CMR should be employed more often in the non-invasive detection of CAD. Currently the wide use of stress CMR is restricted by the low availability of scanners and adequately trained doctors.

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