Contemporary Non-Invasive Imaging in Chronic Coronary Syndrome: What Stress Cardiovascular Magnetic Resonance has to Offer

Isabella Leo,[1,2] *Laura Torres Araujo,*[1] *Chiara Bucciarelli-Ducci*[1,3]

Royal Brompton and Harefield Hospitals, Guys' and St Thomas' NHS Trust,[1] *London – United Kingdom*

Department of Medical and Surgical Sciences, Magna Graecia University,[2] *Catanzaro – Italy*

School of Biomedical Engineering and Imaging Sciences, Faculty of Life Sciences and Medicine, King's College University,[3] *London – United Kingdom*

Non-invasive cardiac imaging has an established diagnostic and prognostic role in patients with suspected or known ischemic heart disease (IHD) and the imaging technology has significantly evolved over the years. Cardiovascular magnetic resonance (CMR) has emerged as a robust diagnostic and prognostic imaging modality and it currently represents a valid alternative to other existing and well-validated techniques, but also as a possible first-line strategy.

Major clinical practice guidelines have been increasingly incorporating stress CMR as a clinical test indicated in patients with chest pain, receiving a Class I recommendation first in the 2014 European Society of Cardiology (ESC) guidelines for revascularisation, followed by the 2017 ESC guidelines in the diagnosis and management of ST-elevation myocardial infarction which has been recommending CMR as an alternative test for left ventricular (LV) function when echocardiography is suboptimal, but also for the evaluation of myocardial viability and ischemia.[1] The recently published 2021 American Heart Association (AHA)/ American College of Cardiology (ACC) Guidelines also indicate stress CMR with class I recommendation in patients with acute and chronic chest pain and intermediate risk of coronary artery disease (CAD) (Table 1).[2]

Whilst CMR is the gold standard test for the calculation of left and right ventricular volumes, it is unique compared to other imaging modalities due to its ability to non-invasively characterize the myocardial tissue. Using T2-weighted sequences, CMR can visualize myocardial oedema, whilst the use of T1-weighted sequences with gadolinium-based contrast agents allow the delineation of presence and extent of myocardial scarring or fibrosis, thus determining myocardial viability. Finally, its high spatial resolution in stress perfusion (~ 2 mm, compared to ~ 10 mm of single-photon emission computed tomography [SPECT] and ~ 4 mm of positron emission tomography — PET), provides high diagnostic accuracy for the detection of myocardial ischemia (inducible perfusion defects).

Keywords

Cardiovascular Imaging; Cardiovascular Magnetic Resonance; Stress Imaging; Chronic Coronary Syndrome

Correspondência: Chiara Bucciarelli-Ducci •
Royal Brompton and Harefield Hospitals, Guys' and St Thomas' NHS Foundation Trust
Email: c.bucciarelli-ducci@rbht.nhs.uk

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A multi-parametric CMR protocol that includes myocardial edema, viability and ischemia aims at identifying the cause of chest pain both in the acute and in the chronic setting. Clinical scenarios include identifying the ischemic territory, if any, in patients with known or suspected CAD, identify the culprit vessel (edematous territory) in patients with acute coronary syndrome and multivessel disease with unclear culprit lesion, and assess the extent of myocardial viability and hibernation to guide revascularization. In the acute setting, the presence of edema can guide clinical management such as the identification of recent and old infarction or determine the differential diagnosis in patients with suspected myocardial infarction and unobstructed coronary arteries (MINOCA), whether acute myocarditis, takotsubo cardiomyopathy, or small myocardial infarction. All these differentials can be achieved based on the different patterns of myocardial oedema and fibrosis which differ in each condition.

Finally, initial sequences covering the whole mediastinum and the upper portion of the abdomen are helpful in detecting some of the most common extracardiac causes of atypical chest pain, such as pleural effusion and hiatus hernia.

The CMR stress perfusion protocol is straightforward, with some similarities with the SPECT protocol. The stressor used is mainly a vasodilator, either adenosine at an infusion rate of 140 mcg/kg/min for 2 to 4 minutes (titrated to 210 mg/kg/min to maximize response) or regadenoson as a single injection of 0.4 mg.[3] At maximal vasodilation, contrast agent is injected and first pass perfusion images are acquired (typically 3 short-axis images: base, mid, apical), which are later repeated at rest for comparison. Contraindications are limited, and they include advanced second-degree atrioventricular block, systolic blood pressure < 90 mmHg or > 220/120 mmHg, severe sinus bradycardia (< 40 bpm), active bronchospasm or known hypersensitivity. Dobutamine is used in selected cases such as patients with severe asthmas or those with coronary anomalies and myocardial bridges, following a protocol similar to echocardiography with incremental doses up to a maximum of 40 μg/kg/min. Inducible myocardial perfusion defect, a surrogate for inducible myocardial ischemia, can be assessed qualitatively (visually) as hypointense "darker" (hypoperfused) areas (Figure 1). A semi-quantitative evaluation can complement the visual assessment. Recent technical developments include a respiratory motion corrected method with automated in-line perfusion mapping which provides a quantitative assessment of myocardial blood flow (MBF) and myocardial perfusion reserve (MPR) at a segmental or global level. This novel method has been validated against invasive angiography and demonstrated an excellent diagnostic performance and reproducibility.[4]

Table 1 – Role of cardiac magnetic resonance according to current European and United States Guidelines

	Clinical scenarios	Warranty period	High-risk markers	Added benefits
ESC guidelines	Chronic IHD including: patients with an inconclusive echocardiographic test. In high-risk asymptomatic adults. To prove myocardial ischemia before revascularization.	1 year	2 or more of 16 segments with stress perfusion defects or ≥3 dobutamine-induced dysfunctional segments.	Useful to establish other etiologies (myocarditis etc.)
ACC-AHA chest pain guidelines	Acute and chronic chest pain: Intermediate-risk patients with acute chest pain and no known CAD who are eligible for cardiac testing. Suspected scar. Suspected microvascular disfunction. Acute chest pain plus intermediate risk with known CAD. Patients with an inconclusive echocardiographic test (2a). Chronic: In intermediate to high risk patients with stable chest pain and no known CAD, it is effective for diagnosis of myocardial ischemia and for estimating risk of major adverse cardiac events (1b). Patients with obstructive CAD who have stable chest pain despite optimal medical treatment (1b). Patients with known extensive nonobstructive CAD with stable chest pain symptoms (2a). Patients with persistent stable chest pain and nonobstructive CAD, with the addition of MBFR measurement (2a).	1 year		Useful to establish other etiologies (myocarditis etc). Higher diagnostic accuracy for CMR versus other non-invasive methods. CMR followed by selective ICA had projected reduced costs by □25% when compared with direct referral to ICA.

AHA/ACC: American Heart Association/American College of Cardiology; CAD: coronary artery disease; CMR: cardiac magnetic resonance; ESC: European Society of Cardiology; ICA: invasive coronary angiography; MBFR: myocardial blood flow reserve; IHD: ischemic heart disease.

There is a wealth of literature and randomized clinical trials underpinning the clinical use of CMR in patients with IHD and its inclusion in all major clinical practice guidelines.

The Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary artery disease-2 (MR-IMPACT-2) study demonstrated higher sensitivity of stress CMR than SPECT in detecting CAD.[5] The Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease (CE-MARC) trial was a head-to-head comparison of stress CMR and SPECT in patient with known or suspected CAD, using invasive angiography as gold standard. It demonstrated that stress CMR has increased diagnostic accuracy compared to SPECT, both in single and multivessel disease, as well as in males and females.[6] Further, the CE-MARC 2 trial demonstrated that the use of a functional test (SPECT or CMR) significantly reduced the probability of unnecessary coronary angiography in patients with known or suspected CAD (28% versus 7.5% and 7.1% when using stress CMR or SPECT, respectively as gatekeeper for invasive angiography).[7] Most recently, the MR Perfusion Imaging to Guide Management of Patients With Stable Coronary Artery Disease (MR-INFORM) trial randomized 918 patients with known or suspected CAD to either stress CMR evaluation or invasive fractional flow reserve obtaining similar clinical outcomes in the two groups, but the coronary revascularization rate was reduced when using CMR.[8] In terms of prognostication, data coming from the Stress CMR Perfusion Imaging in the United States (SPINS) study also proved that patients with a negative stress CMR or negative late gadolinium enhancement had very low annual rates of cardiovascular death or nonfatal myocardial infarction (< 1%) and coronary revascularization (1% to 3%) during the 5-year follow-up.[9] The non-invasive CMR-based approach has also proven to be cost-effective for healthcare systems, as demonstrated by consistent savings.[10]

Importantly, approximately half of patients with angina do not have evidence of obstructive CAD, and, if imaged

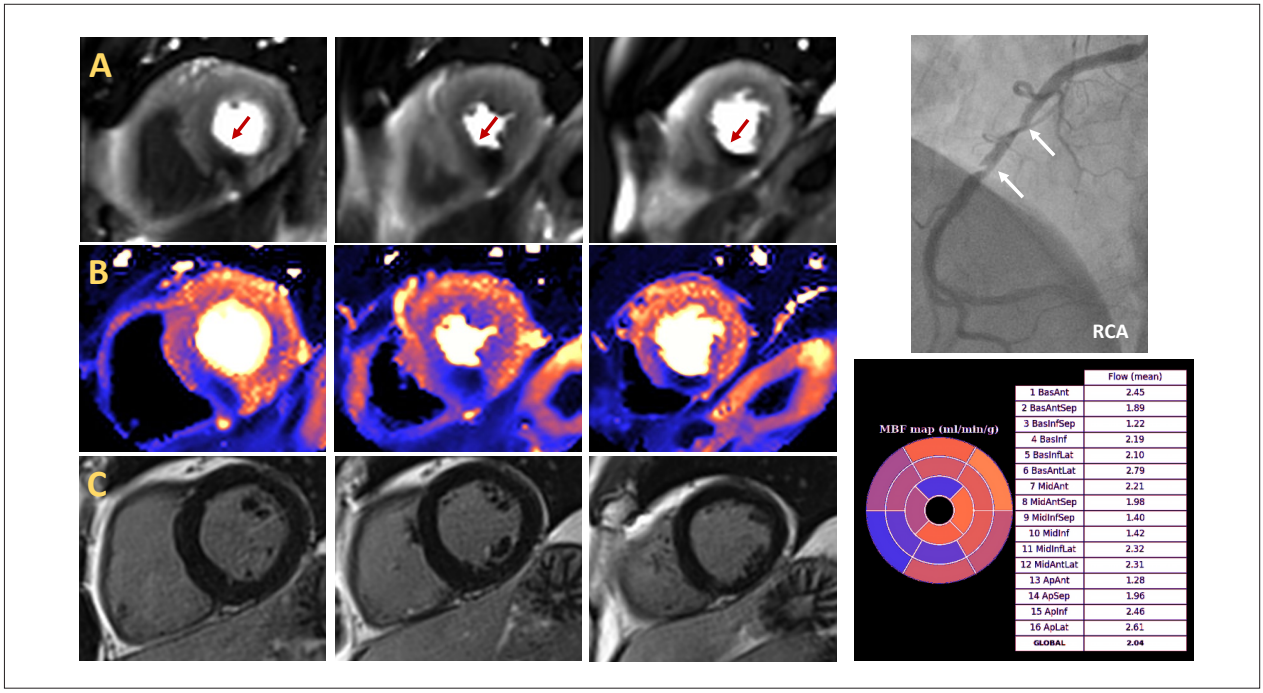

Figure 1 – *Cardiac magnetic resonance in a patient with angina. Stress first-pass perfusion images showed significant inducible myocardial perfusion defect during adenosine infusion in the RCA territory (A, red arrows). The perfusion defect was confirmed by automated in-line perfusion mapping (B, blue areas) and quantified as segmental stress myocardial blood flow (MBF map, bottom right). Late gadolinium enhancement images showed no myocardial infarction or scarring, with all segments fully viable (panel C). The patient was therefore referred for coronary angiography that demonstrated significant stenosis in the RCA. RCA: right coronary artery.*

adequately, there is demonstration of MVD.[11] This is more prevalent in women than in men and in patients with hypertension and diabetes. Quantitative stress CMR is increasingly used in patients with ischemia and unobstructed coronary arteries (INOCA) with excellent diagnostic accuracy. Recent data published by Kotecha and colleagues confirmed the usefulness of these non-invasive CMR parameters of MBF and MPR, with an additional potential role in discriminating between three-vessel disease and MVD, two conditions that are often hard to distinguish without an anatomical test.[4] A global stress MBF < 1.82 ml/g/min has in fact been proposed as a cut off to discriminate obstructive 3-vessel disease from MVD (area under the curve: 0.94; $p < 0.001$).[4]

Limitations of CMR include the relatively limited availability (although every MRI scanner has a cardiac package, often unused), high cost, limited access to existing MRI facilities, and a lack of trained CMR imaging specialists. In addition, there are some restrictions when performing CMR in patients with non-conditional devices, and the overall quality of the images acquired could be severely and unpredictably reduced in presence of metallic implants. Gadolinium-based contrast agents are relatively safe. However, caution should be used in presence of severe renal failure due to potential risk of nephrogenic systemic fibrosis and during pregnancy where a careful risk-benefit assessment is mandatory. Nevertheless, the role of CMR has evolved from mainly a research tool to a multi-purpose clinical tool with unquestionable advantages compared to other modalities. This recognized role of CMR in the recently published ESC and AHA/ACC chest pain guidelines is a testament that this technique is part of modern cardiology, and it is here to stay.

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This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the Management of Acute Myocardial Infarction in Patients Presenting with ST-Segment Elevation: The Task Force for the Management of Acute Myocardial Infarction in Patients Presenting with ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39(2):119-77. doi: 10.1093/eurheartj/ehx393.
2. Gulati M, Levy PD, Mukherjee D, Amsterdam E, Bhatt DL, Birtcher KK, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2021;78(22):e187-e285. doi: 10.1016/j.jacc.2021.07.053.
3. Kramer CM, Barkhausen J, Bucciarelli-Ducci C, Flamm SD, Kim RJ, Nagel E. Standardized Cardiovascular Magnetic Resonance Imaging (CMR) Protocols: 2020 Update. J Cardiovasc Magn Reson. 2020;22(1):17. doi: 10.1186/s12968-020-00607-1.
4. Kotecha T, Martinez-Naharro A, Boldrini M, Knight D, Hawkins P, Kalra S, et al. Automated Pixel-Wise Quantitative Myocardial Perfusion Mapping by CMR to Detect Obstructive Coronary Artery Disease and Coronary Microvascular Dysfunction: Validation Against Invasive Coronary Physiology. JACC Cardiovasc Imaging. 2019;12(10):1958-69. doi: 10.1016/j.jcmg.2018.12.022.
5. Schwitter J, Wacker CM, Wilke N, Al-Saadi N, Sauer E, Huettle K, et al. MR-IMPACT II: Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary artery disease Trial: perfusion-cardiac magnetic resonance vs. single-photon emission computed tomography for the detection of coronary artery disease: a comparative multicentre, multivendor trial. Eur Heart J. 2013;34(10):775-81. doi: 10.1093/eurheartj/ehs022.
6. Greenwood JP, Maredia N, Younger JF, Brown JM, Nixon J, Everett CC. Cardiovascular Magnetic Resonance and Single-Photon Emission Computed Tomography for Diagnosis of Coronary Heart Disease (CE-MARC): A Prospective Trial. Lancet. 2012;379(9814):453-60. doi: 10.1016/S0140-6736(11)61335-4.
7. Greenwood JP, Ripley DP, Berry C, McCann GP, Plein S, Bucciarelli-Ducci C, et al. Effect of Care Guided by Cardiovascular Magnetic Resonance, Myocardial Perfusion Scintigraphy, or NICE Guidelines on Subsequent Unnecessary Angiography Rates: The CE-MARC 2 Randomized Clinical Trial. JAMA. 2016;316(10):1051-60. doi: 10.1001/jama.2016.12680.
8. Nagel E, Greenwood JP, McCann GP, Bettencourt N, Shah AM, Hussain ST, et al. Magnetic Resonance Perfusion or Fractional Flow Reserve in Coronary Disease. N Engl J Med. 2019;380(25):2418-28. doi: 10.1056/NEJMoa1716734.
9. Kwong RY, Ge Y, Steel K, Bingham S, Abdullah S, Fujikura K, et al. Cardiac Magnetic Resonance Stress Perfusion Imaging for Evaluation of Patients With Chest Pain. J Am Coll Cardiol. 2019;74(14):1741-55. doi: 10.1016/j.jacc.2019.07.074.
10. Moschetti K, Kwong RY, Petersen SE, Lombardi M, Garot J, Atar D, et al. Cost-Minimization Analysis for Cardiac Revascularization in 12 Health Care Systems Based on the EuroCMR/SPINS Registries. JACC Cardiovasc Imaging. 2022;15(4):607-625. doi: 10.1016/j.jcmg.2021.11.008.
11. Mileva N, Nagumo S, Mizukami T, Sonck J, Berry C, Gallinoro E, et al. Prevalence of Coronary Microvascular Disease and Coronary Vasospasm in Patients With Nonobstructive Coronary Artery Disease: Systematic Review and Meta-Analysis. J Am Heart Assoc. 2022;11(7):e023207. doi: 10.1161/JAHA.121.023207.