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IMAGING PATIENTS WITH STABLE CHEST PAIN SPECIAL FEATURE: REVIEW ARTICLE

MRI perfusion in patients with stable chest-pain

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ABSTRACT

Perfusion-cardiovascular MR (CMR) imaging has been shown to reliably identify patients with suspected or known coronary artery disease (CAD), who are at risk for future cardiac events and thus, allows for guiding therapy including revascularizations. Accordingly, it is an ideal test to exclude prognostically relevant coronary artery disease. Several guidelines, such as the ESC guidelines, currently recommend CMR as non-invasive testing in patients with stable chest pain. CMR has as an advantage over the more conventional pathways as it lacks radiation and it potentially reduces costs.

INTRODUCTION

An abundant amount of research has been performed showing that functional information about a coronary artery stenosis is essential in the diagnosis, prognosis, and treatment of patients with coronary artery disease (CAD).^{1,2} Several non-invasive imaging modalities are accepted for the functional evaluation of CAD including positron emission tomography (PET), single-photon emission computed tomography (SPECT), stress echocardiography, and cardiovascular magnetic resonance (CMR).³ The most common approach to functional assessment of CAD is through myocardial perfusion imaging (MPI), possible with PET, SPECT, and CMR, while perfusion assessment by contrast echocardiography and CT is not yet established for clinical use.

All modalities show a high diagnostic accuracy with high sensitivities ranging between 84 and 89% with a wider range of specificities ranging from 61% for SPECT to 76 and 81% for MRI and PET.⁴ One of the main disadvantages of PET, SPECT and CT is the radiation exposure. CMR as a modality combines the absence of radiation with high spatial and temporal resolution and the ability to acquire images in any plane resulting in a similar diagnostic accuracy for CAD as for PET.⁴

A specific population of interest for perfusion-CMR is the group of patients in the stable phase of the chronic coronary syndrome (CCS), also known as stable CAD (SCAD)

patients. In this group specifically, non-invasive functional testing is particularly useful to guide patient management and treatment.^{3,5,6}

The main goal of this review is to give an overview of current guidelines, to review available perfusion-CMR technologies, and to discuss the clinical position of perfusion-CMR for the evaluation of SCAD patients.

GUIDELINES

Chronic coronary syndromes—stable coronary artery disease

Patients in this category are typically those with suspected CAD and chest pain and/or dyspnea (considered as an angina-equivalent). Additionally, asymptomatic and symptomatic patients with stabilized symptoms shortly (<1 year) after acute coronary syndrome (ACS) or after revascularization, as well as patients long after ACS or revascularization (>1 year) and patients with new onset heart failure or LV dysfunction and suspected CAD belong to this CCS group. Common for all these types of CCS is that myocardial ischemia is a major prognostic factor and thus, myocardial ischemia evaluation should be performed on a regular basis allowing continuous risk assessment and risk-driven treatment.³ A growing group of patients with CCS are those with CAD detected by screening. For these patients, however, the evidence of how to monitor and treat is sparse.

Recommendations

Guidelines reported invasive coronary angiography (ICA) as the reference standard for the assessment of CAD combined with fractional flow reserve (FFR) to quantify the functional significance of a stenosis. Information about the ischemic burden as provided by FFR is required to guide revascularization.⁷ Studies have shown that up to 60% of patients undergoing ICA, do not have functional significant CAD.⁸ With the increasing number of CAD patients, a non-invasive approach is needed to optimize patient pre-selection for invasive examination and guide treatment management and most recent guidelines were adjusted accordingly.

The ESC guidelines now state that non-invasive functional testing, in addition to anatomical CTA evaluation, is the first line diagnostic procedure recommended in patients with stable CAD before elective invasive procedures are undertaken.³ Also, the recommended range of pre-test-probability (PTP) for non-invasive imaging testing is now lower than in past guidelines, recommending testing not only at a PTP >15%, but also at lower PTP of 5–15% if additional “modulators of risk” are present in addition to sex, age, and clinical symptoms.³ Such modulators of risk are the presence of the classical risk factors, but also changes on resting-ECG (Q waves, ST-T alterations), LV dysfunction, pathological stress-ECG, and coronary calcifications (if CT performed).

The 2019 ESC guidelines on the work-up of CCS patients include several recommendations about stress perfusion-CMR.³ In symptomatic patients in whom obstructive CAD cannot be excluded by clinical assessment alone, perfusion-CMR is recommended as a Class I indication (evidence level B), where the clinical assessment should integrate not only age, gender, and symptoms, but also the above-mentioned risk modifiers. Perfusion-CMR is also recommended as a Class I, if coronary CTA has shown CAD of uncertain functional significance or is non-diagnostic. Ischemic burden has been shown to impact the prognosis of the patient. A large study in ~1000 patients followed over 2.5 ± 1.0 years after their index stress perfusion-CMR demonstrated an excellent prognosis for cardiac death and non-fatal MI in patients with no ischemia or one ischemic segment only, while two or more ischemic segments yielded an approximately 10-fold increase of complications (cardiac death and non-fatal MI).⁹ Therefore, in patients with two or more ischemic segments on stress perfusion-CMR, revascularization should be considered.³

Importantly, a large multicenter randomized controlled trial tested the NICE guideline algorithms for the work-up of suspected CAD.¹⁰ The CE-MARC2 trial demonstrated that by integrating perfusion-CMR into the NICE-algorithm (currently based on SPECT and cardiac CT) unnecessary invasive coronary angiographies were reduced from 28% with the current algorithm to 8% ($p < 0.001$) when using CMR.^{10–12}

The USA guidelines are more conservative about stress perfusion-CMRs giving a Class IIb for patients with an intermediate to high PTP who are incapable of at least moderate physical functioning or have a disabling comorbidity.¹³ On the other hand, in these 2012 USA guidelines, standard exercise ECG is still a Class I indication for patients with suspected CAD able to exercise,¹³

while the most recent 2019 ESC guidelines rather discourage the use of stress ECG to rule-in or rule-out CAD even when other imaging tests are not available (Class IIb).³ Recently, the results of the large SPINS registry trial were reported,¹⁴ demonstrating excellent diagnostic and prognostic performance of perfusion-CMR in CAD patients, confirming the results found in the European CMR registry in 2016.¹⁵ It is expected, that the SPINS trial results will provide additional evidence for an upgrading in the US guidelines similarly to the European guidelines.

Diagnosis, prognosis and-cost-effectiveness

One of the earliest multislice approach studies on perfusion-CMR in an unselected study population comparing versus PET showed a sensitivity and specificity of 0.91 and 0.94 for the detection of CAD (defined by PET) and a sensitivity and specificity of 0.87 and 0.85, for the detection of CAD as defined by quantitative coronary angiography (stenosis >50%).¹⁶ These results were an early indicator that perfusion-CMR reliably identifies patients with CAD compared to other perfusion modalities and is able to provide information about the ischemic burden. In contrast to SPECT, these results showed that even subendocardial defects can be identified. In the meantime, other studies confirmed that contrast media doses of 0.075–0.1 mmol/kg are crucial for adequate perfusion-CMR examinations.^{17–20}

Several trials investigated the diagnostic accuracy of perfusion-CMR compared to SPECT, which is still one of the most used perfusion modalities, especially in the USA. The MR-IMPACT trial investigated the diagnostic performance of perfusion-CMR and SPECT for the detection of CAD using conventional X-ray coronary angiography as reference standard.^{19,21} While one analysis used one single sensitivity-specificity pair to compare vs SPECT (as required by the Food and Drug Administration),¹⁹ the correct full comparison using receiver operator characteristics curve analyses is shown in another publication,²¹ which demonstrated superiority of perfusion-CMR over SPECT for detection of CAD. However, the MR-IMPACT trials were performed on a selected population with relatively high PTP as all patients had to undergo all tests to avoid testing bias. Another landmark single center study, the CE-MARC trial, showed not only a higher sensitivity of perfusion-CMR compared to SPECT but also similar specificity in this large population powered for this specific purpose.²²

Recently, the large multicenter MR-INFORM study compared Perfusion-CMR and FFR in 918 patients and showed that in patients with stable angina and risk factors for CAD, perfusion-CMR was associated with a lower incidence of revascularization than FFR and was equivalent to FFR in predicting major adverse cardiac events.²³ Several meta-analyses evaluated the diagnostic accuracy of perfusion-CMR using ICA and FFR as reference with sensitivities and specificities ranging between 0.89 and 0.91 and 0.81 and 0.86, respectively.^{24–26} One of these studies showed that CMR has a higher accuracy than SPECT at both vessel and patients level and similar accuracy to PET perfusion.²⁶ Most meta-analysis are performed on the visual analysis of perfusion images, only one meta-analysis assessed the performance of (semi-) quantitative techniques and found considerable heterogeneity.²⁷

In order to allow CAD management, reliable information on patient outcome should be provided. The evidence on the prognostic power of perfusion-CMR is steadily increasing. In 9404 patients, obtained by pooling studies including >1000 patients, the mean event rate (for cardiac death and non-fatal myocardial infarction) in the patients with a normal CMR examination is 0.68%/year, thus, identifying those patients which can be safely deferred from further testing.^{9,14,15,28,29} Strong evidence, therefore, is available demonstrating that perfusion-CMR is an ideal test to exclude relevant CAD, *i.e.* to exclude prognostically relevant ischemia in patients with known or suspected CAD.

There is increasing evidence on the cost-effectiveness of perfusion-CMR. Comparisons of perfusion-CMR with several alternative non-invasive methods repeatedly demonstrated CMR as the most cost-effective.^{30,31}

The EuroCMR-registry cost-minimization study on 3647 patients with suspected CAD (59 centers from 18 countries) compared an initial perfusion-CMR, with follow-up ICA only in case of ischemia, with the combined use of ICA and FFR. It showed that the use of perfusion-CMR reduced costs by 14–34% in the German, UK, Swiss, and US context. Costs were reduced even more (59–71%) compared to the use of ICA alone.¹⁵ Another study on 1158 patients undergoing dobutamine stress-CMR confirmed that an initial CMR examination (before ICA) reduced cost, not only during the initial hospital stay but also during subsequent follow-up saving 12,466€ of hospital costs per life year.³²

An US-based registry confirmed these results demonstrating very low event rates for patients with a normal perfusion-CMR, *i.e.* 0.6% per year (cardiac death and non-fatal MI). Additionally, the follow-up costs in patients with a normal CMR were very low (<100\$/year) throughout the entire 5-year study period.¹⁴

In the MR-INFORM trial targeting higher risk patients, significantly fewer patients underwent revascularization in the CMR arm, potentially reducing costs. Publication of these results are awaited.

Protocol, sequences, and other technical issues

Perfusion protocol

The stress perfusion-CMR protocol is composed of two modules: first, the stress first-pass perfusion module, which evaluates myocardial perfusion during pharmacologically induced hyperemia, second, late gadolinium enhancement imaging (LGE) which evaluates myocardial injury, *i.e.* scar. Perfusion deficits detected in non-viable tissue, are not representing ischemic territories and thus, are not relevant with respect to revascularization. Hypoperfusion of viable, *i.e.* LGE negative myocardium, indicates a reduced capacity to increase perfusion during hyperemia and thus, ischemia will develop under physical stress conditions in these territories.

In the past, rest perfusion was recommended for patients with stress acquisitions distorted by artifacts that could mimic hypoperfusion deficits. In these patients, resting perfusion could potentially discriminate these artifacts from true hypoperfusion.

This approach is now less relevant, as better scanner hardware and software reduce this problem with artifacts. It is also important to note, that resting perfusion is not appropriate to assess tissue viability, as the acquisition conditions during first-pass are very demanding in comparison to those for LGE, with the latter acquiring data during a dynamic steady-state after contrast media (CM)-injection offering a time-window of 10–15 min for data acquisition (in comparison to 10–15 s for first-pass techniques).

Imaging sequences

Different MR pulse sequences can be chosen to optimally capture myocardial perfusion. Commonly, perfusion images are heavily T_1 weighted, allowing the visualization of perfusion defects due to the T_1 -shortening effect of gadolinium-chelates when they pass through the hyperemic myocardium. Irrespective of the pulse sequence type, it is required that it monitors CM passage through the myocardium with high spatial resolution ($1.2\text{--}1.5 \times 1.2\text{--}1.5$ mm), high temporal resolution (each stack of images is acquired every 1–2 heart beats), high cardiac coverage (3–5 slices over the LV myocardium), and high dynamic signal response (minimal signal increase of 250–300% over pre-contrast baseline tissue signal). While pulse sequences for perfusion assessment can vary in terms of read-out and in terms of acceleration, all are acceptable as long as they meet the “imaging output” criteria as mentioned above.^{19–21,33} These “imaging output” criteria can be achieved with all state-of-the-art MR scanners for a two-dimensional approach. Many efforts are undertaken to meet these criteria using three-dimensional approaches, however, less experience exist for these pulse sequences. Other concepts, *e.g.* arterial-spin-labeling or blood-oxygen-level-dependent imaging, aim to avoid the use of contrast media and remain currently in the research domain..

1.5 vs. 3.0 tesla

Perfusion-CMR can be performed with either 1.5 or 3.0 T systems. While 3 T can provide higher signal-to-noise ratio and contrast-to-noise ratio, it is also associated with more magnetic field (B_1 and B_0) in-homogeneities rendering the 3 T approach more susceptible for artifacts hampering the analysis of perfusion defects.

The use of a 3 T systems also results in a quadruple increase in RF power absorption which impedes the application of some of the 1.5 T perfusion sequences.³⁴ At 3 T, the magnetohydrodynamic distortion of the ECG-signal is increased resulting in difficulties with triggering and leading to an increase in cardiac motion artifacts. Finally, to our knowledge, all large multicenter, multivendor perfusion trials are conducted on 1.5 T systems, and such trials should form the basis for recommendations.

Stressor agent

For stress imaging, a stressor agent is used to achieve hyperemia. Several different stressor agents are available to induce pharmacological stress, adenosine currently being the most frequently used stressor agent.

The use of adenosine as a pharmacological stressor agent comes with some unwanted short-term side-effects such as potential bronchial constriction caused by the undesired activation of A_1 ,

Figure 1. The top row is an example of an ischemic perfusion defect, where the stress perfusion image shows a clear hypoperfused area (red arrows), whereas the LGE image shows no defect. The bottom row shows an infarct-related perfusion defect, where on both, stress perfusion (slightly hypoenhanced tissue, red arrows) and LGE image (strongly hyperenhanced tissue) a defect is shown (red arrows). This example of an infarct patient also demonstrates the superiority of LGE to delineate scar in comparison to the perfusion approach. In scar, the extracellular Gd-chelate contrast medium distributes in a large extracellular (fibrotic) compartment during first-pass, which increases the signal in the fibrotic tissue explaining its reduced sensitivity to detect hypoperfusion in scar. This reduced sensitivity to detect hypoperfusion is not observed in viable myocardium (with small extracellular compartment). LGE, late gadolinium enhancement.

A2B, and A3 receptors. These side-effects may be problematic in patients with reactive airway disease, a frequent comorbidity in CAD patients. The short half-life of adenosine (<10 s) allows for the abrupt discontinuation of administration and rapid disappearance of harmful side-effects, however, it also requires continuous i.v. administration.^{35–37} Regadenoson, a relatively new stressor agent, is a potent and selective coronary vasodilator with a rapid onset and longer half-life compared to adenosine. It can be administered as a fixed-dose bolus. One of the advantages of regadenoson is its A2A selectivity, making it suitable for patients with reactive airway disease (while this agent remains contraindicated in patients with asthma and second or third degree AV-block).^{38,39} Hyperemia can be achieved by either the administration of adenosine for 3–5 min with a rate of 140 µg/min/kg, or a single injection of 0.4 mg of regadenoson. As an advantage, adenosine can be safely augmented from 0.14 mg/kg/min over 3 min (=standard) up to 0.21 mg/kg/min over 7 min in case of inadequate response to the standard dose (i.e. <10 bpm increase in heart rate or <10 mmHg systolic blood pressure decrease).⁴⁰

Caffeine

Studies have reported that 5–15% of all perfusion-CMR examinations result in false-negative results, possibly due to drug

interactions and subsequent insufficient hyperemia.^{22,41,42} Caffeine interacts with the stressor agent in multiple ways hampering the induction of hyperemia possibly resulting in false-negative examinations. First, caffeine reacts with the same receptors as adenosine; and secondly, caffeine induces capillary de-recruitment by increasing the sympathetic nerve activity, both, resulting in a reduced difference in perfusion between healthy and impaired tissue. Studies have shown that adenosine is sensitive to the competing effects of caffeine, whereas regadenoson is not affected.^{37,38,43} Importantly, patients should be instructed to abstain from caffeine (coffee, tea, bananas, chocolate etc.) for preferably 24 h before the stress CMR examination.

Image analysis

Perfusion-CMRs can be analyzed using three different approaches; visual, semi-quantitative, and fully quantitative. Visual assessment is currently the most used method in clinical practice. Independent of analysis method, perfusion-CMRs are generally evaluated according to the 16-segment model (AHA 17-segment model minus the apical segment).⁴⁴

Imaging artifacts

Perfusion analyses become more complicated in the presence of imaging artifacts. Wrap-around artifacts and artifacts caused by mistriggering or respiratory motion during first-pass are easily recognizable. However, they can impede or even prevent correct assessment. Therefore, it is crucial to run a “testing” sequence without CM, to identify and fix artifacts before proceeding to the true hyperemic CM first-pass acquisition. Insufficient spatial resolution typically manifests as dark subendocardial zones during CM first-pass, often located in phase-encoding direction and lasting for a few images only.^{34,45} While cumbersome, this “dark rim” artifact (Gibbs-ring artifact) is of less concern with the advances of high-performance MR scanners with high gradient performance, sophisticated pulse sequences, and homogeneous magnetic fields. When adhering to the pulse sequence recommendations as mentioned above, dark rim artifacts are rare, but can be seen in children or females (with thin myocardial walls).¹⁴

Visual analysis

Visual analysis of perfusion-CMR depends on the visual detection of hypoperfused areas in the myocardium. The combination of stress perfusion and LGE images should always be used to assess ischemia. As a first step, LGE images are evaluated to discriminate non-viable from viable segments. In a second step, only viable segments are considered for further evaluation on the perfusion images, see Figure 1. A perfusion defect is most commonly defined as hypoenhancement of the myocardium that lasts for ≥6 heart beats (≥3 frames if the slice is acquired every other heart beat); involves ≥1/3 of the LV wall thickness (i.e. >1 pixel), and is larger than 50% of the circumferential extent of the myocardium.⁹ Hypo-enhanced areas that do not meet these criteria, e.g. short-lived dark subendocardial areas, are most likely artifacts. For consistent and reproducible reading, standardized windowing and leveling is important.⁹ In cases with borderline reading criteria, it is advised to look at an upslope map, where a slope reduction of >30% is typically associated with true ischemia.¹⁷

(Semi-) quantitative analysis

Semi-quantitative and quantitative analysis of perfusion-CMR is performed using the myocardial signal intensity (SI) time curves

Figure 2. The top row represents a stress perfusion image with a defect in the inferior wall. The bottom row shows the AIF and TAC curves, visualizing the in- and outflow of contrast media. It is demonstrated that ischemic myocardium (blue) curves show a lower TAC compared to normal myocardium (green). The dashed lines represent the measurements needed for semi-quantitative analysis; the maximum AIF value and the maximum TAC upslope. AIF, arterial input function; TAC, tissue attenuation curve.

obtained in different myocardial segments or even in different myocardial layers. In quantitative perfusion imaging, two SI-time curves are contracted out of the image data set, the arterial input function (AIF) and the tissue attenuation curve (TAC). The AIF describes the wash-in and wash-out of CM in the aorta or LV cavity based on the SI measured over time, whereas the TAC represents the wash-in and wash-out of CM in the myocardium, see [Figure 2](#).

Semi-quantitative

Semi-quantitative analyses assess the TAC in the myocardium, while the AIF is not measured or only approximated. Accordingly, the most commonly used semi-quantitative method is the upslope method where myocardial blood flow (MBF) is estimated based on the maximal upslope of the TAC and maximal value of the AIF ([Figure 2](#)).^{27,46} Such upslope maps are nowadays made readily available by most vendors. Other semi-quantitative markers are the peak-enhancement index, contrast-time arrival index, maximal upslope, time to peak.²⁷

Quantitative

Fully quantitative analysis of perfusion-CMR is performed using a model-dependent deconvolution technique, using the full AIF for MBF calculations. For this purpose, two major obstacles have to be addressed. First, the conversion of signal intensities into CM concentrations, and second, identifying the best model describing the CM kinetics during the first pass.

With CMR-CM concentrations are not measured directly but through the SI, making it necessary to convert the SI-curves to contrast concentration curves. However, the relationship

between SI and gadolinium concentration is non-linear, *i.e.* at high CM concentrations, the SI-time curve becomes saturated.^{47,48} Dual-bolus techniques and in particular, the elegant dual pulse sequence approach, can deal with this, providing look-up tables taking into account the specific pulse sequences features and CM types and doses.^{49,50}

More evidence through larger studies and randomized controlled trials will be needed to assess the diagnostic performance of such quantitative analysis versus visual analysis. Therefore, these quantitative perfusion-CMR techniques cannot yet be recommended for application in clinical routine. While quantitative PET data are used to calculate coronary flow reserve and cardiovascular risk, regional ischemia detection by PET is typically achieved by visual non-quantitative evaluations. If quantitative perfusion CMR becomes feasible and robust, its contribution to the current CMR-based work-up of CAD patients will need to be defined. Nevertheless, perfusion CMR will potentially offer quantitative perfusion information at lower cost than PET MPI, without exposing the patient to radiation.

FUTURE PERSPECTIVES

Perfusion-CMR imaging has been shown to reliably identify patients with suspected or known CAD, who are at risk for future cardiac events and thus allows for guiding therapy including revascularizations.

Current and upcoming economic studies will hopefully impact on decision makers in the health care systems in order to improve the

access to perfusion-CMR.⁵¹ For the near future, patient management by CMR will be based on the visual analysis of the perfusion. Large prospective trials are needed to assess the additional value of quantitative imaging over visual analysis.

An alternative MRI technique is evolving, the so-called hyperpolarized MRI, which increases the polarization of spins for several orders of magnitude. It produces signals that are proportional to the metabolite concentrations⁵² yielding quantitative real-time

information on metabolic activity⁵³ and perfusion. Initial clinical studies have been reported in humans using standard MR scanners.⁵⁴ Such techniques are expected to enhance our understanding of myocardial perfusion and metabolism substantially.

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