

Perfusion cardiovascular magnetic resonance: will it replace SPECT?

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In the USA, in 2005, about half of patients who died of a heart attack did not reach the hospital for emergency treatment, indicating the need for earlier detection of coronary artery disease (CAD). Single photon emission computed tomography (SPECT) imaging has a high diagnostic and prognostic power despite some technical limitations. Perfusion- and late-enhancement cardiovascular magnetic resonance (CMR) are not limited by such restrictions. Multicenter trials have found a high diagnostic performance of CMR for the detection of CAD, with one trial additionally showing superiority of CMR over SPECT. The advantages of CMR, eg, lack of radiation exposure, will likely promote a shift toward early CAD detection by CMR. Nevertheless, more efforts are needed to standardize the technique, train physicians and personnel, and improve access to infrastructures.

Keywords: cardiovascular magnetic resonance (CMR); coronary artery disease; infarction; ischemia; pharmacological stress; single photon emission computed tomography (SPECT); viability

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Dialogues Cardiovasc Med. 2007;12:114-122

While innovations in the treatment of coronary artery disease (CAD), eg, by the introduction of drug-eluting stents, are now entering a phase of consolidation, major changes in diagnostic imaging are still ahead of us, and most likely will occur in the very near future. This prediction is based on two major considerations: (i) newer imaging technologies will give rise to diagnostic strategies that were not available in the past; and (ii) exploitation of the information technology such as the World Wide Web will develop an increasing awareness of the need for better diagnostics through the knowledge gathered by international surveys and registries, which will direct our view from (restricted) academic settings to the population as a whole. This

article discusses point 1 in detail, but let us take a brief look at point 2, which states that better diagnostics are needed.

According to the American Heart Association (AHA) *Heart Disease and Stroke Statistics 2006 Update*,¹ approximately half of all sudden cardiac deaths in the US occur before patients reach the catheterization laboratory for emergency treatment. These data clearly demonstrate that detection of CAD is suboptimal with current diagnostic strategies. Moreover, approximately half of men and almost two thirds of women dying of a heart attack in the US did not exhibit symptoms before the fatal event, which suggests that focusing on symptoms may be inappropriate in regard to a large portion of the patients at risk.

SELECTED ABBREVIATIONS AND ACRONYMS

CAD	coronary artery disease
CMR	cardiovascular magnetic resonance
CXA	coronary angiography
LE-CMR	late-enhancement cardiac magnetic resonance
MDCT	multidetector computed tomography
MI	myocardial infarction
MR CM	magnetic resonance contrast media
MR-IMPACT	Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary artery disease Trial
PCI	percutaneous coronary intervention



	Ideal Test	Perfusion-CMR LE-CMR	SPECT
Stenosis or ischemia detection	+++	++	++
- Spatial resolution	+++	++	+
- No attenuation	+++	+++	+
- Standardization	+++	+	+++
- Mechanism		Flow-dependent distribution (first-pass) of MR CM into vascular (interstitial) space	Flow-dependent distribution of radiolabeled tracer into viable myocytes
Viability and scar detection	+++	+++	+
- Spatial resolution	+++	++	+
- No attenuation	+++	+++	+
- Mechanism		Redistribution (at steady-state) of MR CM into extracellular space (scar/necrosis)	Redistribution (at steady-state) of radiolabeled tracer into viable myocytes
Repeatability*	+++	++	(+)
Low costs†	+++	(+)	(+)
Comfort	+++	++	++
- Short study duration	+++	++	+
Test possible (no CI)	+++	++	++
- Electronic devices		no	yes
- Arrhythmias, atrial fibrillation		no	yes
- Claustrophobia		no	yes
- CI for stressor: adenosine physical stress		no (possible)	no possible

*Repeatability refers to the various risks associated with the tests (eg, side effects of contrast media, vascular injury in invasive coronary angiography, radiation, etc); it does not refer to reproducibility (which is included in the category: Stenosis or ischemia detection).

†Costs may differ considerably between different countries and centers.

Table I. Comparison of CMR and SPECT with the "Ideal Test." Evaluation of test performance considers both accuracy (area under the receiver-operator-characteristics curve) and reproducibility (intra-/interobserver/inter-test variability).

Abbreviations: CI, contraindication; CMR, cardiovascular magnetic resonance; LE-CMR, late-enhancement cardiovascular magnetic resonance; MR CM, magnetic resonance contrast media; SPECT, single photon emission computed tomography.

No identification of CAD in asymptomatic patients will be possible, however, if tests are costly and/or inconvenient and/or harmful for patients. The comparative features of an "ideal" cardiovascular magnetic resonance (CMR) and single photon emission computed tomography (SPECT) test are given in *Table I*.

Shaw and coworkers, in a large multicenter study (Economics of Non-invasive Diagnosis [END]), looked at the economic consequences of diagnostic strategies used in patients with suspected CAD.² In this study, approximately 11 000 patients

with stable angina pectoris were prospectively allocated to either invasive x-ray coronary angiography (CXA) or noninvasive SPECT imaging, the later being followed by CXA only if SPECT was positive. Over a 3-year follow-up period, 2.8 % cardiac deaths and 2.8% myocardial infarctions (MI) occurred in the SPECT arm vs 3.3% and 3.0%, respectively, in the invasive arm (statistically not significant). In the intermediate- and high-risk group, the reduction in deaths or MI with SPECT was 8% and 6%, respectively, and 16% in the low-risk group vs the invasive strategy. Interestingly, although use

of SPECT was only associated with a tendency toward lower complication rates, costs (including treatment costs during the 3-year follow-up period) were reduced by as much as 40% in the SPECT arm in comparison with the invasive arm. Studies like this one demonstrate that newer diagnostic algorithms can potentially improve outcome while reducing costs. So the obvious question is, with this and other large studies and meta-analyses³ showing an excellent diagnostic and prognostic yield of SPECT, why should CMR be considered to replace SPECT?

PERFUSION- AND LATE-ENHANCEMENT-CMR

The most salient feature of CMR is probably its versatility. CMR creates image information by modifying the local frequency and phase of signals from the body. These MR signals, ie, their evolution over time, depend on the type of tissue from which they originate, and these characteristics can be further enhanced and/or modified by magnetic resonance contrast media (MR CM). The magnetic resonance technique can visualize these different tissue characteristics, and high-end scanner hardware and software enable this information to be acquired today with excellent spatial and temporal resolution in two- (2-D) or three-

dimensional (3-D) formats. Consequently, CMR imaging provides comprehensive information on cardiac and vascular anatomy, myocardial and valvular function, blood flow, and metabolism,⁴ and in conjunction with MR CM, it delineates distribution of myocardial perfusion and viability in 2-D and 3-D high-resolution data sets.⁵

Principles of perfusion-CMR

Myocardial perfusion is typically assessed using MR CM first-pass CMR techniques. To this end, a conventional MR CM is injected as a rapid bolus into a peripheral vein and its first-pass through the myocardium is monitored by a very fast and contrast-sensitive magnetic

resonance pulse sequence.⁵ An example of this approach is shown in *Figure 1*.⁶ In this setting, a flow-limiting coronary artery stenosis causes a delayed wash-in of MR CM into the myocardium, and consequently a delayed evolution of signal in this region of the myocardium. These data are acquired with state-of-the-art equipment with spatial resolutions of 2 to 3 mm/pixel, evidencing transmural differences in perfusion^{7,8} and coverage of the heart with 3 to 7 slices. These slices are typically oriented in the left ventricular short axis for easy assignment of myocardial territories to the major coronary arteries. It is important to realize in this context, that the high nominal spatial resolution is preserved in CMR through the fact, that: (i) respiratory motion is eliminated from the data by breath-holding, since MR CM first-pass during vasodilation typically lasts less than 15 seconds; and (ii) cardiac contraction and relaxation is eliminated by ECG triggering, the use of which became very widespread over recent years thanks to the vector-ECG application now available on all CMR-systems. Unlike SPECT, CMR imaging is not associated with artifacts arising from signal attenuation or scattering (*Figure 2*),⁹ which is crucial for the technique achieving high specificity, particularly as regards the inferior wall and inferolateral wall.⁷ Furthermore, the ability to differentiate transmural gradients in perfusion by perfusion-CMR explains the high sensitivity of the method in detecting CAD, which is even able to detect completely balanced CAD (*Figure 3, page 118*). The diagnostic performance of perfusion-CMR for analysis of transmural (full wall thickness) and sub-endocardial perfusion data is also shown in *Figure 3*. Importantly, perfusion-CMR is not compromised in patients after percutaneous coronary interventions (PCI) and stenting (see

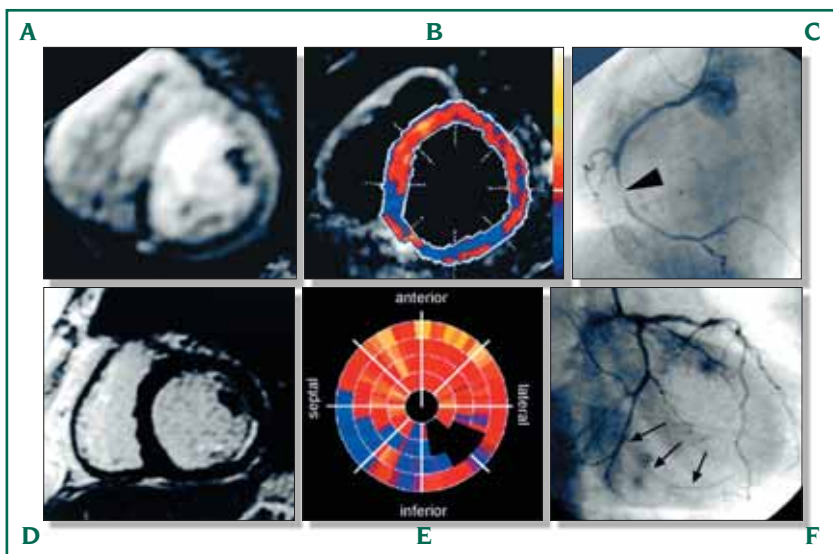


Figure 1. A combined perfusion-cardiovascular magnetic resonance (CMR) (A-C) and late enhancement (LE-)CMR (D-F) study is shown in a 48-year-old woman with atypical chest pain and dyspnea during exercise. At peak effect of first-pass contrast medium (0.1 mmol/kg Gd-DTPA-BMA, Omniscan) performed during vasodilation (adenosine: 0.14 mg/kg/min), a perfusion deficit in the subendocardial layer of the inferior wall (dark area in A) is present, which is also detected automatically and represented by an up-slope parametric map (blue area in B; threshold for colors derived from normal database). The perfusion deficit corresponds to a stenosis in the right coronary artery (arrow in C). After additional injection of 0.15 mmol/kg of contrast medium, LE-CMR is performed 15 to 20 minutes later, demonstrating a subendocardial scar as a bright area in the lateral wall (D). Perfusion and scar distribution are represented in a polar map of the subendocardial layer of the left ventricle (E). The scar is a sequel of the occlusion of a branch of the circumflex coronary artery, which fills retrogradely (arrows in F).

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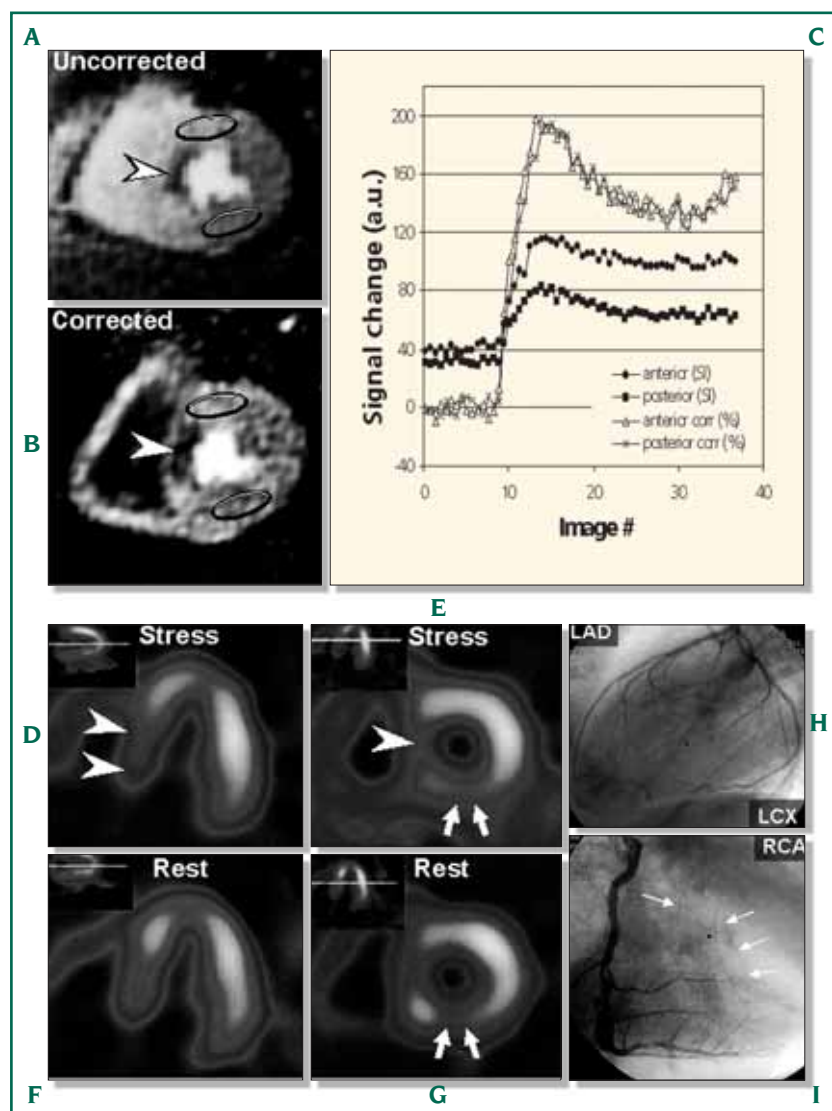


Figure 2. In a 47-year-old patient atypical chest pain developed 2 months after successful stent implantation into a stenosis of the left anterior descending coronary artery (LAD). Perfusion-CMR (cardiovascular magnetic resonance) demonstrates a perfusion deficit in the septal wall during hyperemia on an uncorrected magnetic resonance image (A, arrowhead) at peak effect of the contrast medium bolus. Uncorrected CMR signal intensity time curves (C, closed symbols) of the anterior and posterior walls (ellipses on MR images) show reduced peak signal in the posterior parts of the heart. Correction (by simple division through precontrast data) yields identical signal responses for the two regions (open symbols). In x-ray coronary angiography, the LAD stent showed no stenosis (H), but had compromised takeoff of septal branches. Contrast injection into the right coronary artery (RCA) demonstrates collateralization of the septum (arrows in I). A ^{99m}Tc -tetrofosmin single photon emission computed tomography (SPECT) hyperemic study (D,E) shows a perfusion deficit in the septal wall (arrowheads), but also reduced tracer uptake in the posterior wall in both rest and hyperemic SPECT studies (arrows) suggesting scar. Magnetic resonance excluded inferior perfusion abnormalities and x-ray coronary angiography confirmed normal RCA (I) and left circumflex coronary artery (H, LCX). This example demonstrates problematic attenuation in SPECT, which is not encountered in perfusion-CMR. Perfusion-CMR is also not limited by the presence of implanted stents (LAD territory).

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Figure 2, results of MR-IMPACT). While providing excellent information, application of the perfusion-CMR technique requires sound knowledge of cardiac pathophysiology and CMR physics, and of course access to high-end hardware and software. The challenge now is to define standards for these requirements, based on the findings from the large international multicenter trials that have confirmed the high level of performance of the perfusion-CMR technique.¹⁰ The dependence of diagnostic performance on image quality is shown in Figure 4 (page 119) derived from multicenter data.¹¹

Safety of perfusion-CMR

When assessing myocardial perfusion during hyperemia, regions of compromised perfusion reflect those developing ischemia during inotropic stress. Hyperemia testing achieved by standard adenosine infusion over 3 minutes (at 0.14 mg/min/kg) is advantageous, since ischemia (due to coronary steal) is induced only by very severe stenoses and, consequently, the test generally does not trigger angina pectoris or ischemia-induced arrhythmias, as shown in large multicenter trials using scintigraphy¹² and/or CMR.¹⁰ It should also be pointed out that

CMR does not expose the patient to ionizing radiation. For contraindications, see Table I.

Perfusion- and late-enhancement-CMR in combination

Once myocardial regions of compromised hyperemic perfusion are mapped within the left ventricular wall (Figure 1A,B), it is crucial for further clinical decision making to determine whether the perfusion abnormality is due to scar formation (which does not require revascularization) or whether it resides in viable myocardium, which would

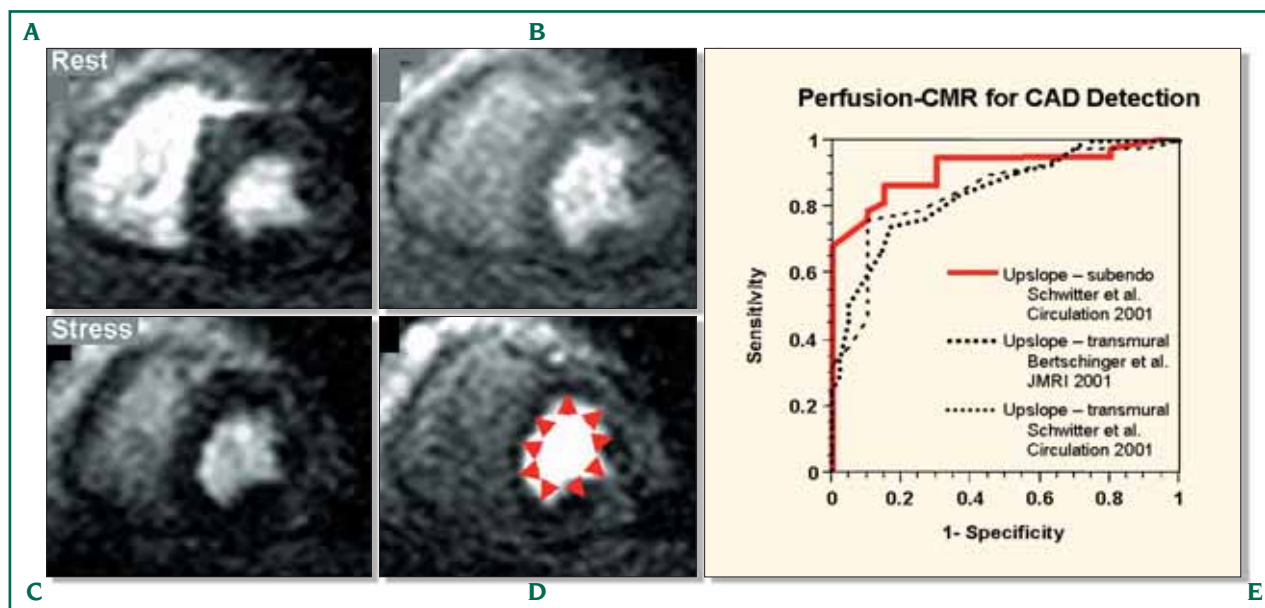


Figure 3. Perfusion-CMR (cardiovascular magnetic resonance) provides high spatial resolution of perfusion information. In resting conditions, contrast medium (0.1 mmol/kg Gd-DTPA-BMA, Omniscan) first enters the left ventricular cavity (A) and reaches peak homogeneous concentration in the myocardium a few seconds later (B). During hyperemia (adenosine: 0.14 mg/min/kg), however, in this patient with a stenosis in the left anterior descending coronary artery (LAD), contrast medium shows delayed wash-in into the subendocardium of the perfusion territory of the LAD. In this patient, the large LAD extends into the inferior wall and thus supplies the entire apex serving as a model of completely balanced hypoperfusion of the apex, which is readily detected by CMR through visualization of a transmural gradient of perfusion in the wall (D). In E, receiver-operator characteristics curves show a better diagnostic performance of analysis of the subendocardial upslope data compared with upslope data calculated from full wall thickness (= transmural).

be considered for revascularization. Thus, for a comprehensive workup of patients with CAD, it is obvious that perfusion-CMR and late enhancement-CMR (LE-CMR) should be performed in combination, at least in patients with wall-motion abnormalities. For viability assessment, CMR exploits the fact that conventional MR CM are excluded from myocytes with intact cell membranes. Thus, in acute myocyte necrosis, where cell membrane integrity is lost,¹³ or in chronic scar tissue, where extracellular space is large,¹⁴ conventional MR CM accumulate and induce a high signal (Figure 1D), when probed with appropriate pulse sequences. Thus, LE-CMR relies on the redistribution of MR CM from the intravascular compartment into the enlarged extracellular space (acute necrosis or scar), analogous to viability imaging with SPECT, which also relies on redistribution, in this case however, of tracer from the blood pool into viable myocytes. Thus, at

steady-state after redistribution, LE-CMR shows scar and necrosis as bright areas, whereas SPECT after redistribution shows these regions as dark, ie, cold spots.

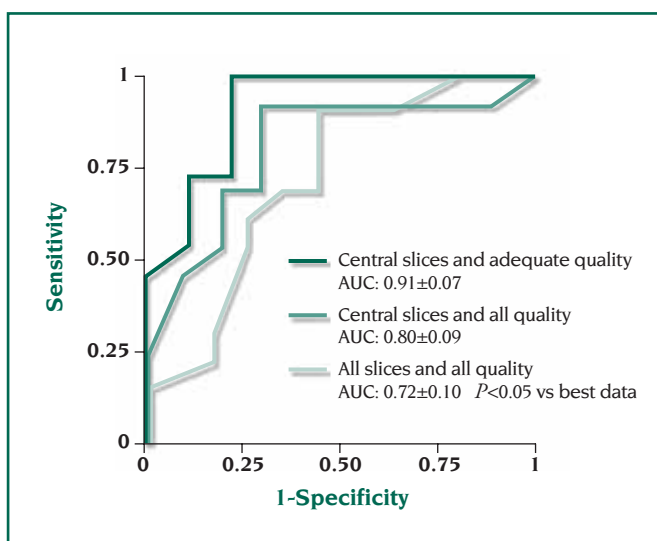
While both techniques rely on redistribution, LE-CMR acquires these data during a breath-hold with ECG-triggering, thereby preserving the nominally high spatial resolution of CMR. Since MR CM exchange between blood pool, intra-, and extra-cellular compartments at steady-state is considerably slower than first-pass kinetics, LE-CMR imaging is performed over a period of several minutes, resulting in even higher spatial resolutions (compared with perfusion-CMR) in the order of 1-2×1-2 mm² in 2-D or 3-D formats. Thus, scar tissue as small as 0.5 gram is reliably detectable with LE-CMR¹⁵ and recovery of function after revascularization is predictable when considering the transmural extent of scar and thickness of viable rim tissue.^{14,16}

Perfusion-CMR performance

In a single-center study, a stress-only perfusion-CMR protocol yielded a sensitivity and specificity of 87% and 85%, respectively, for detection of CAD (defined as ≥50% diameter stenosis in at least one coronary artery in quantitative coronary angiography) corresponding to an area under the receiver-operator characteristics curve (AUC) of 0.91. A comparison with PET perfusion data as standard of reference in these patients yielded even higher sensitivity and specificity of 91% and 94%, respectively, for perfusion-CMR (AUC: 0.93). Excellent results were also reported from other groups using perfusion-CMR at rest and stress with sensitivities and specificities of 88% to 90% and 84% to 90%, respectively.¹⁷⁻¹⁹ Finally, a multicenter, single-vendor study yielded a sensitivity and specificity of 91% and 78%, respectively, for CAD detection with an AUC of 0.91 using a semiautomatic analysis approach

Figure 4. Image quality is crucial for a reliable diagnostic performance. In this multicenter study,¹¹ image quality was read blindly, and 14% of the studies were deemed nonevaluable (score >4). Furthermore, for this particular pulse sequence, the central slices showed better signal behavior than the peripheral slices (data not shown). When the central slices were analyzed from examinations with adequate quality, excellent performance was achieved with an area under the receiver-operator characteristics curve (AUC) of 0.91. When all quality scores entered the analysis, AUC decreased to 0.80, and finally by adding all slices into the analysis, AUC further decreased to 0.72. These data demonstrate the importance of data quality for test performance, thus emphasizing the importance of protocol optimization, and the need for training of physicians and technicians, as well as the utilization of high-end MR systems.

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(Figure 4).¹¹ Fewer data are available regarding the prognostic value of perfusion abnormalities detected by CMR. Ingkanisorn et al studied 135 patients with chest pain in the emergency department, in whom acute MI was excluded. Perfusion-CMR had a 100% sensitivity and 93% specificity (AUC 0.97) to predict survival without new detection of CAD or complications such as new MI or death, during a follow-up of 1 year.²⁰ Taken together, perfusion-CMR and LE-CMR yield highly accurate myocardial perfusion and viability information in different myocardial layers such as the subendocardium. These data are acquired during a safe and short (approximately 1 hour) examination and yield high sensitivity and specificity for CAD detection. Not surprisingly, preliminary data also suggest that this information is predictive for future cardiac events.

SPECT IMAGING

SPECT imaging in combination with ^{99m}Tc-tracers is a powerful technique for the detection of perfusion abnormalities during hyperemia induced by pharmacological or physical stress and it also allows assessment of viability.²¹ In the early 90s, the first applications of ^{99m}Tc-tracers

yielded sensitivities and specificities for the detection of angiographically documented CAD of 81% and 90%, respectively.²² For dual-isotope rest ²⁰¹Tl/stress ^{99m}Tc-sestamibi SPECT protocols, sensitivities and specificities of 91% and 75% were reported, respectively.²³ The performance of diagnostic SPECT is also well established in disease states such as complete left bundle-branch block (sensitivity and specificity of 79% and 81%, respectively²⁴) or diabetes (sensitivity and specificity of 86% and 56%, respectively²⁵). In women, who are more prone to attenuation artifacts in the anterior myocardium due to breast tissue, gender-specific diagnostic SPECT performance achieves a sensitivity and specificity of 72% and 71%, respectively.²⁶ Slightly lower performances were reported from multicenter trials with overall sensitivities in the range of 77% to 85% and specificities of 36% to 58%.²⁷⁻³⁰ While attenuation artifacts represent a substantial limitation for SPECT imaging, attenuation correction algorithms can mitigate this problem, albeit at the expense of some reduction in sensitivity.²⁷ Another improvement is provided by gated-SPECT, which was shown to increase three-vessel disease detection (typical perfusion/function abnormality pattern in 25% of pa-

tients with gated-SPECT vs typical perfusion abnormality pattern in only 10% of patients with ungated SPECT), while specificity was not altered, with 72% vs 69%, respectively, for gated- vs ungated SPECT.³¹ Since assessment of diagnostic performance typically requires invasive coronary angiography as the standard of reference, these studies are often restricted to smaller patient groups. Considerably larger studies are available for the assessment of prognostic performance with SPECT³ than with CMR.²⁰ Despite the technical restrictions for SPECT imaging mentioned above, this technique was shown to discriminate patients with preserved prognosis vs those with complications in studies involving thousands of patients.³ In summary, single-center and particularly multicenter studies show adequate SPECT performance for the detection of CAD. Limitations in sensitivity may arise from suboptimal spatial resolution of the technique, as well as from attenuation artifacts. For perfusion-CMR these two types of limitations are less of a concern, which explains its high diagnostic performance in CAD detection. With this in mind, studies were undertaken to directly compare perfusion-CMR and SPECT imaging.

Comparison of CMR and SPECT performance

Ishida and coworkers reported on a single-center comparison between perfusion-CMR and SPECT for the detection of CAD in patients without prior MI.¹⁸ Perfusion-CMR performed significantly better than SPECT, with an AUC of 0.89-0.91 vs 0.71-0.75, respectively, ($P < 0.001$). The overall high performance of perfusion-CMR for the detection of angiographically defined CAD^{7,11,17-18} was the basis for a large multicenter, multivendor perfusion-CMR trial in order to determine the optimum MR CM dosage for perfusion-CMR and for its comparison with SPECT.¹⁰ The MR-IMPACT (Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary artery disease Trial) was conducted in 18 centers in the US and Europe in 234 patients with known or suspected CAD. Three blinded readers each assessed the perfusion-CMR and SPECT images at rest, and stress and quantitative coronary angiography was used as the standard of reference (with diameter stenoses $\geq 50\%$ in at least one coronary artery of ≥ 2 mm diameter defining CAD). A total of 4.8% and 5.3% of the perfusion-CMR and SPECT studies, respectively, were not evaluable. At the dose of 0.1 mmol/kg of a conventional MR CM (Gd-DTPA-BMA, Omniscan, GE Healthcare), perfusion-CMR yielded an excellent AUC for the detection of CAD, of 0.86 (sensitivity and specificity: 91% and 67%), which was significantly superior to SPECT, with an AUC of 0.67 (sensitivity and specificity: 74% and 57%). Similarly, perfusion-CMR was also superior to SPECT for the detection of multivessel disease (AUC: 0.89 vs 0.70). This large multicenter, multivendor trial confirmed the impressive performance of perfusion-CMR, particularly when considering the number of participating

centers and the multivendor design. This led to an even larger clinical phase 3 trial, MR-IMPACT II, being carried out in 34 centers in Europe and US, the first results of which were presented in late 2006, further confirming the superiority of perfusion-CMR.³²

PERSPECTIVES OF CMR AS A COMPONENT IN FUTURE DIAGNOSTIC ALGORITHMS

The prevalence of CAD is expected to increase in the next decades due to the older age of the population and an increase in other risk factors such as diabetes and obesity. As economic resources may not develop in parallel, cost-effectiveness will become an increasingly important issue. Since costs for CAD treatment by PCI and surgery are substantial and drug therapy typically lasts for many decades, accurate diagnosis is crucial for appropriate allocation of expensive treatments. CMR provides a comprehensive assessment of patients with suspected or known CAD and is also helpful for the diagnosis of cardiomyopathies, myocarditis, valvular heart disease, and congenital heart disease in the adult. Perfusion-CMR and LE-CMR are ideally suited for the detection and workup of CAD and will most likely become a "backbone" diagnostic modality in cardiology of the future, where patients at risk should be detected earlier than with current diagnostic algorithms. This active strategy will make it possible to treat CAD earlier and hence will hopefully reduce the high rate of fatal MIs in the prehospital phase.¹ To this end, the diagnostic strategy should be expanded from the "very high risk" to the "high-intermediate risk" population.³³ In this population, however, with a lower incidence of CAD, tests must not cause any harm to patients, and avoiding ion-

izing radiation of CMR is important, considering that 10 mSv of exposure induces cancer in about 1 per 1000 expositions.³⁴ While radiation exposure is 6 to 8 mSv for SPECT (depending on tracers and protocols), approximately 15 mSv is required for Multidetector CT (MDCT) coronary angiography,³⁵ which is increasingly utilized for exclusion of CAD. In comparison, in a recent multicenter single-vendor MDCT coronary angiography trial (n=11 centers), 42% of all patients were excluded from analysis due to inadequate quality, yielding a sensitivity and specificity of 80% and 70%, respectively, for CAD detection in the remaining population.³⁶ The multicenter single-vendor CMR study yielded a sensitivity and specificity of 91% and 78%, respectively, after exclusion of only 14% of patients.¹¹ In MR-IMPACT (n=18 centers and multivendor), sensitivity and specificity were 91% and 67%, respectively, after exclusion of only 5% of the CMR studies.¹⁰

Currently, CMR examinations are still demanding with respect to cardiological and imaging knowledge, and also with respect to infrastructure, as demonstrated by the recent multicenter CMR trials. Based on these trials, perfusion-CMR and LE-CMR, in experienced centers, may be considered as a valuable alternative to SPECT for the workup of patients with suspected CAD or post revascularization. Considering the advantages of CMR over SPECT a shift toward CMR is expected in the near future. However, before this transition occurs, it appears wise to put major effort into standardizing CMR protocols, training physicians and technical personnel, and improving the accessibility of CMR units.

Juerg Schwitter is Consultant of GE-Healthcare and Primary Investigator of the MR-IMPACT program.



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