REVIEW

Imaging

Assessment of cardiac ischaemia and viability: role of cardiovascular magnetic resonance

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Over the past years, cardiovascular magnetic resonance (CMR) has proven its efficacy in large clinical trials, and consequently, the assessment of function, viability, and ischaemia by CMR is now an integrated part of the diagnostic armamentarium in cardiology. By combining these CMR applications, coronary artery disease (CAD) can be detected in its early stages and this allows for interventions with the goal to reduce complications of CAD such as infarcts and subsequently chronic heart failure (CHF). As the CMR examinations are robust and reproducible and do not expose patients to radiation, they are ideally suited for repetitive studies without harm to the patients. Since CAD is a chronic disease, the option to monitor CAD regularly by CMR over many decades is highly valuable. Cardiovascular magnetic resonance also progressed recently in the setting of acute coronary syndromes. In this situation, CMR allows for important differential diagnoses. Cardiovascular magnetic resonance also delineates precisely the different tissue components in acute myocardial infarction such as necrosis, microvascular obstruction (MVO), haemorrhage, and oedema, i.e. area at risk. With these features, CMR might also become the preferred tool to investigate novel treatment strategies in clinical research. Finally, in CHF patients, the versatility of CMR to assess function, flow, perfusion, and viability and to characterize tissue is helpful to narrow the differential diagnosis and to monitor treatment.

Introduction

The prevalence for coronary artery disease (CAD) in industrialized countries is high and is estimated to range between 20 000 and 40 000 individuals per million suffering from angina in Europe.[1] From large statistics in USA, it is also evident that many patients with CAD do not experience angina pectoris before their first heart attack and this fraction is ranging from ∼50% (for men) up to 67% (in women).[2] Thus, an estimated 40 000–80 000 individuals per million are at risk for a heart attack at some time during their course of CAD. Over the past years, cardiovascular magnetic resonance (CMR) emerged as a powerful technique to assess myocardial ischaemia and viability, and therefore, it may become an increasingly used technique to monitor and guide treatment in the different clinical presentations of CAD. In the chronic phases of CAD, ischaemia assessment by CMR may become the key test for risk stratification, thereby helping in guiding treatment decisions (revascularizations). In the acute phases of CAD, i.e. in acute coronary syndromes (ACS), viability assessment is most important and CMR is expected to play an increasing role in differentiating ACS from other diseases such as perimyocarditis, Takotsubo cardiomyopathy (CMP), or acute aortic diseases. Finally, in the end-stages of CAD, i.e. in chronic heart failure (CHF), CMR can contribute to patient management by assessing ischaemia and viability and also by excluding or confirming differential diagnoses.

In the first part of this review, we will focus on a potential role of CMR in the patient population at risk. In the second part, the review describes the possible contribution and the emerging role

of CMR in the setting of acute chest pain and ACS. Finally, in the third part, the role of ischaemia and viability imaging by CMR in CHF is discussed.

Ischaemia detection

A key cardiovascular magnetic resonance application for the assessment of chronic chest pain and suspected coronary artery disease

Perfusion-cardiovascular magnetic resonance

The principle of perfusion-CMR is based on the monitoring of contrast medium (CM) wash-in kinetics into the myocardium during a hyperaemic state (*Figure 1*). In territories supplied by significantly stenosed coronary arteries, the wash-in of CM is delayed and this is depicted as dark zones of tissue during CM first-pass, when utilizing T_1-weighted pulse sequences and Gd-based CM (*Table 1*).[3–8] As the CM first-pass lasts about 5–15 s during hyperaemia, perfusion-CMR is performed during a breath-hold to eliminate respiratory motion artefacts. To eliminate motion artefacts by cardiac contraction, the acquisition window should last <100 ms per slice. Although a spatial resolution of 1–1.5 mm × 1–1.5 mm is possible,[9] a minimum of 2–3 mm × 2–3 mm is required to minimize susceptibility artefacts at the blood pool–myocardial interface[5,10] (for more details, see *Table 2*). The read-out type of a pulse sequence [conventional or parallel imaging, fast gradient echo, (hybrid)-echo-planar, or steady-state free precession] is of minor importance as long as spatial and temporal resolutions are achieved as suggested in *Table 2*.[5] Here, it should be mentioned that a signal increase of 250–300% (relative to pre-contrast myocardial signal) is

required during hyperaemic first-pass to guarantee adequate diagnostic performance.[10–12] For an example, see *Figure 2*.

In comparison with $^{13}NH_3$-PET as the reference standard, sensitivity and specificity for ischaemia detection by CMR were 91 and 94%, respectively, and for detection of ≥50% diameter stenoses, sensitivity and specificity were 87 and 85%, respectively [area under the receiver operator characteristics curve (AUC): 0.91].[6] Similar results were obtained in other single-centre studies[13–16] (*Table 1*). For perfusion-CMR, CM doses of 0.10 mmol/kg (or ≥0.075 mmol/kg) are recommended.[5,10,12] The largest perfusion-CMR trial published so far is MR-IMPACT.[10] In 18 centres in Europe and USA, perfusion-CMR detected CAD with an AUC of 0.86 (sensitivity and specificity of 86 and 67%, respectively). In comparison with the entire single-photon emission computed tomography (SPECT) population, perfusion-CMR performed superior vs. SPECT (*Figure 3*). This superiority was also shown for multivessel disease CAD. Of note, SPECT performance in the MR-IMPACT was also well comparable with the results of earlier multicentre SPECT studies, which used conventional X-ray coronary angiography as the standard of references reporting sensitivities and specificities of 77–87 and 36–58%, respectively (*Figure 3*).[17–20] We would like to mention, that in the MR-IMPACT, no attenuation correction of SPECT data was performed, which is known to improve specificity. The diagnostic performance of perfusion-CMR was confirmed later in the MR-IMPACT II study performed in 33 centres in Europe and USA.[10] For both, perfusion-CMR and stress dobutamine-CMR, a moderate to high reproducibility could be shown (with interobserver κ values of 0.70–0.73[21,22] and 0.59–0.81,[21–23] respectively).

Perfusion-CMR performed at 3 T yielded similar results as was observed for 1.5 T.[24] As no multicentre data on 3 T performance are available to date, for clinical perfusion-CMR, the
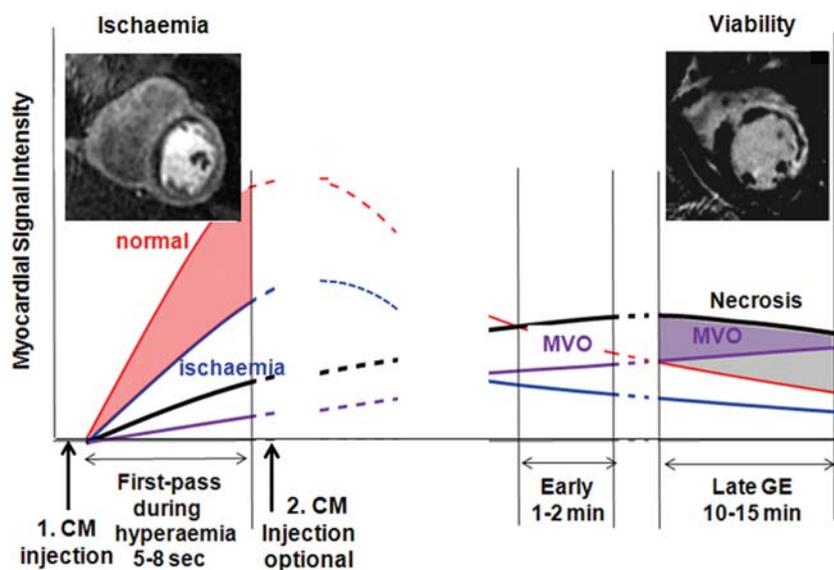
Figure 1 A schematic explains the various time points of image acquisition relative to contrast medium administration to assess ischaemia and necrosis/scar tissue. Red line corresponds to normal non-ischaemic myocardium, blue line the ischaemic myocardium, black line the necrotic tissue in the acute myocardial infarction (fibrotic tissue in chronic myocardial infarction), and purple line the tissue with microvascular obstruction (MVO).

Table I Perfusion-cardiovascular magnetic resonance and stress dobutamine-cardiovascular magnetic resonance: diagnostic performance

Study	n (n)	Reference	CM type/dose	Stress	Analysis	Sensitivity	Specificity	AUC
Perfusion-CMR								
Single[6]	57	CXA ($\geq$50%)	Gd-DTPA-BMA/0.1 mmol/kg	Dip (stress only)	Upslope subendo	87	85	0.91
Single[6]	43	PET (CFR)	Gd-DTPA-BMA/0.1 mmol/kg	Dip (stress only)	Upslope subendo	91	94	0.93
Single[7]	92	CXA ($\geq$70%)	Gd-DTPA/0.05 mmol/kg	Adeno (rest/stress)	Upslope PRI	88	82	0.91
Single[8]	79	CXA ($\geq$50%)	Gd-BOPTA/0.05 mmol//kg	Adeno (stress/rest)	Visual	91	62	—
Single[14]	84	CXA ($\geq$75%)[a]	Gd-DTPA/0.025 mmol/kg	Adeno (rest/stress)	Upslope PRI	86	87	0.92
Single[15]	104	CXA ($\geq$70%)	Gd-DTPA/0.75 mmol/kg	Dip (stress/rest)	Visual	90	85	0.90
Single[9]	51	CXA ($\geq$50%)	Gadobutrol/0.1 mmol/kg	Adeno (stress only)	Visual	—	—	0.85
Multicentre[16]	50	CXA ($\geq$50%)	Gd-DTPA/0.05 mmol/kg	ATP (stress/rest)	Visual	86	75	0.88
Multicentre[12]	80 (24)	CXA ($\geq$50%)	Gd-DTPA-BMA/0.1 mmol/kg	Adeno (stress only)	Upslope subendo	91	78	0.91
Low dose[12]	80 (29)	CXA ($\geq$50%)	Gd-DTPA-BMA/0.05 mmol/kg	Adeno (stress only)	Upslope subendo	—	—	0.53
MR-IMPACT[10]	212 (42)	CXA ($\geq$50%)	Gd-DTPA-BMA/ 0.075 mmol/kg	Adeno (stress only)	Visual	85	67	0.86
Stress dobutamine-CMR								
Single[29]	186	CXA ($\geq$50%)	—	Dobutamine	Visual	86	86	—
Single[30]	41[b]	CXA ($\geq$50%)	—	Dobutamine	Visual	83	83	—
Single[31]	22	CXA ($\geq$75%)[a]	—	Dobutamine	Visual	88	83	—
Single[32]	27	CXA ($\geq$70%)	—	Treadmill	Visual	79	85	—
Single[8]	79	CXA ($\geq$50%)	—	Dobutamine	Visual	89	80	—
Single[23c]	150	CXA ($\geq$50%)	—	Dobutamine	Visual	78	87	—
Single[33]	40	CXA ($\geq$50%)	—	Dobutamine	Visual	89	75	—
Single[34]	204[d]	CXA ($\geq$70%)	—	Dobutamine	Visual	85	86	—

n: in CM dose-finding studies (*n*) indicates participants in a specific dose group; PRI, perfusion reserve index.
[a]Area stenosis.
[b]Patients with negative dobutamine-CMR: CXA was not performed, but a follow-up of 6 months, where no cardiac death occurred.
[c]Reproducibility study: for sensitivity and specificity, means are given.
[d]Women only.

1.5 T equipment is recommended. Similarly, no multicentre data are available comparing visual analysis with quantitative approaches (e.g. by using upslope data). For perfusion data sets acquired with parameters as stated in *Table 2*, a high image quality will be obtained and similar diagnostic performances are likely to be achieved by both visual and quantitative approaches (*Table 1*). The relationship of data quality and acquisition strategies is currently under investigation within the European CMR registry.[25] Regarding the perfusion protocol, a high diagnostic performance was reported in several studies by analysis of the hyperaemia data only (*Table 1*), which favours a stress-only protocol.[6,9–12] Adenosine induces maximal hyperaemia at 0.14 mg/min/kg body weight (administered i.v. over 3 min), is characterized by a short half-life ($<$10 s), and is safe (1 infarction in $>$9000 examinations, no death),[26,27] and therefore, it is currently one of the most commonly used agents in pharmacological stress testing. A novel selective A_{2A} agonist regadenoson received approval for pharmacological stress testing in the USA and is likely to be available in Europe

soon. This novel drug class is easier to use (e.g. injected as a single bolus); first reports demonstrate a high safety profile, and similar diagnostic accuracy was achieved as with conventional vasodilators when combined with scintigraphy.[28]

Stress dobutamine-cardiovascular magnetic resonance
A powerful alternative to perfusion-CMR is stress dobutamine-CMR which detects ischaemia by monitoring regional wall motion during infusion of increasing doses of dobutamine. This principle is identical to stress echocardiography, but the CMR technique benefits from consistently good to high image quality in a very high percentage of patients. In a landmark paper, dobutamine-CMR performed better than stress echocardiography, where the difference in diagnostic performance was particularly evident in patients with reduced echo quality.[29] Since then, a large number of studies demonstrated the high sensitivity and specificity of dobutamine-CMR to detect CAD (*Table 1*).[23,30–34] The CMR protocol is well established,[5] the inotropic stimulation by dobutamine is following mainly that for stress echocardiography (see also *Table 2*),

Table 2 Cardiovascular magnetic resonance applications

MR modality	Types of diagnoses possible	Parameters	Time
Localizer images	Aortic dissection	fGRE sequences or SSFP sequences	1–2 min
	Aortic aneurysm		
	Pleural effusion	fGRE with and without fat saturation (to detect or exclude fatty infiltration in ARVC)	
	Large pneumonia		
	Intrathoracic masses		
	Congenital heart diseases		
	ARVC		
Cine CMR	Global LV or RV function abnormalities	Spatial resolution: 1–2 mm × 1–2 mm	5–10 min
	Regional wall motion abnormalities	Temporal resolution: 40–60 ms	
	Hypertrophic cardiomyopathy	Preferred sequence type: SSFP	
	LV aneurysms	Slice thickness: 6–10 mm, gap 0–2 mm	
	Pericardial effusion		
	Valve abnormalities (valve orifice)		
	Congenital heart diseases		
Stress perfusion-CMR	Ischaemia detection	Spatial resolution: at least 2–3 mm × 2–3 mm to minimize susceptibility artefacts along the blood pool–myocardial interface	10 min
Hyperaemia	Stress induced perfusion deficit (adenosine, dipyridamole)	Temporal resolution: 1 short-axis stack/1–2 beats	
Adenosine: 0.14 mg/kg/min for 3 min	Stress induced segmental dysfunction (cine CMR with dobutamine)	Acquisition window/slice: <100 ms to minimize cardiac motion artefacts	
Dipyridamole: 0.56 mg/kg for 4 min	Detection of CAD	Signal increase during first-pass: >250–300%	
CM: 0.075–0.10 mmol/kg injected at 5 mL/s into cubital vein	Work-up of patients with known CAD for treatment decisions	90°-preparation delay time: 100–150 ms/slice	
	Work-up of patients after CABG	Coverage: ≥3 short-axis slices	
	Risk stratification in CAD	Slice thickness of 8–10 mm	
Stress dobutamine-CMR		Sequence: see cine CMR	10–20 min
Dobutamine doses of 10/20/30/40 μg/kg (for 3 min each). Atropine up to 2 mg is added, if target heart rate (220-age) is not reached		3 short-axis and 3 long-axis acquisitions per dose of dobutamine	
Rest perfusion	Rest myocardial ischaemia/abnormal perfusion	Sequence: see stress perfusion-CMR	1 min
	Microvascular obstruction		
	Tumour (differentiation vs. thrombus)		
Early gadolinium enhancement	Microvascular obstruction	Pulse sequences: see LGE	1–10 min
	No reflow phenomenon		

Late gadolinium enhancement (LGE)	MI Myocardial fibrosis Myocarditis Various non-ischaemic cardiomyopathies Thrombus Amyloidosis	Spatial resolution: 1.5−2.0 mm × 1.5−2.0 mm Preferred sequence type: segmented inversion recovery (IR) fGRE Slice thickness: 5−8 mm, gap 0−4 mm CM: 0.15−0.2 mmol/kg i.v. Start of imaging: 10−20 min after CM injection	5−15 min
T_2-weighted CMR	Ischaemic area at risk Myocardial oedema due to inflammation Intramyocardial haemorrhage (in AMI) Myocarditis Takotsubo Differentiation of acute vs. old infarction	Preferred sequence type: segmented fast spin echo (with double inversion: dark blood) or STIR In progress: T_2-prepared single-shot SSFP for T_2 maps	5 min
MR angiography	Aortic dissection Aortic aneurysm Pulmonary embolus Congenital heart diseases	3D acquisition during breath-hold, typically untriggered Spatial resolution: 1−2.5 mm × 1−2.5 mm CM: 0.1−0.2 mmol/kg at 2−3 mL/s i.v.	10 min
MR coronary angiography	Coronary anomalies Coronary stenosis (sometimes)	Free-breathing T_2-prep. 3D navigator-gated fGRE Spatial resolution: 1 mm × 1 mm × 1.5 mm Breath-hold technique for proximal coronaries	20−30 min
CMR flow	Insufficient (stenotic) valves Shunts Congenital heart diseases	Spatial resolution: >8 pixels per vessel diameter Velocity encoding ∼120% of expected peak vel.	2−5 min
T_2*-weighted CMR	Iron overload, e.g. in thalassaemia Intramyocardial haemorrhage (in AMI)	Spoiled gradient multi-echo T_2* sequence (normal myocardial T_2* > 20 ms)	2−5 min

CMR provides a multimodal integrated assessment of patients with suspected CAD, possible or definite ACS, and CHF. Selection of different imaging modalities should be customized to the likely diagnoses and individualized to a given patient. Time estimates are rough estimates. ARVC, arrhythmogenic right ventricular cardiomyopathy; CABG, coronary artery bypass grafting; CM, contrast medium; fGRE, fast gradient echo; SSFP, steady-state free precession.
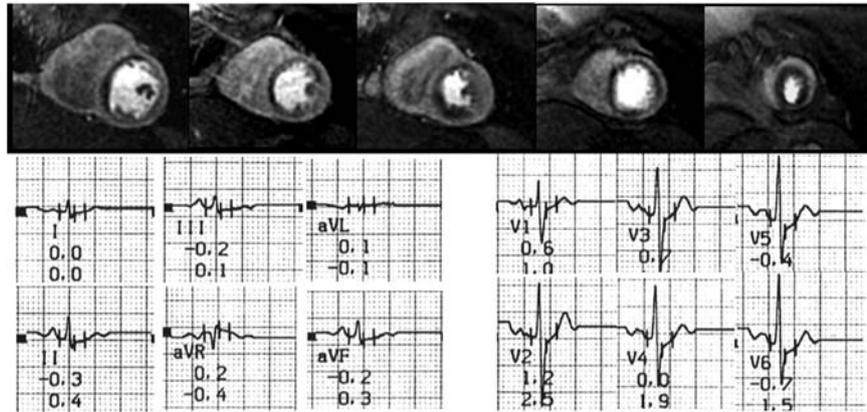
Figure 2 Example of a 70-year-old female patient with atypical chest pain and mild dyspnoea during exercise. Risk factors were hypercholesterolaemia and diabetes. The patient performed at 100% of predicted workload without symptoms and with a normal stress electrocardiogram (mildly ascending 0.07 mV ST depression) and without arrhythmias. Perfusion-cardiovascular magnetic resonance detects severe ischaemia in all vascular territories. Coronary angiography confirmed a triple-vessel disease and the patient was treated successfully by multiple stenting.
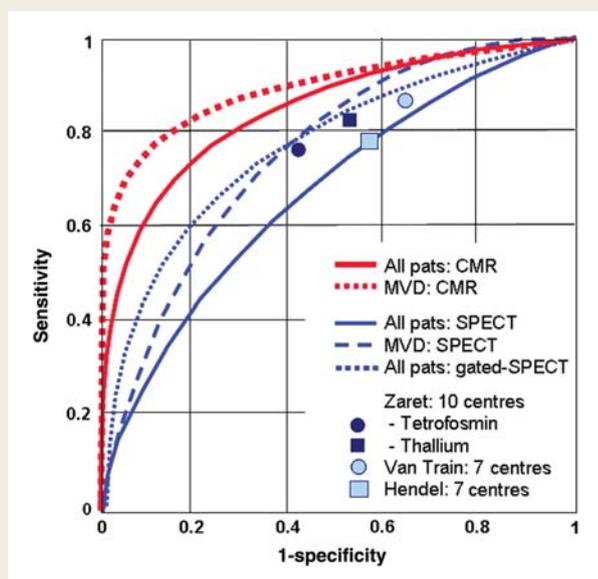

Figure 3 Diagnostic performance of perfusion-cardiovascular magnetic resonance to detect coronary artery disease (defined as ≥50% stenosis in invasive coronary angiography) in comparison vs. SPECT. Performance of SPECT in MR-IMPACT is comparable to those of previous multicentre SPECT trials (given as squares and circles) reported by Zaret et al.,[20] Van Train et al.,[18] and Hendel et al.[17] Better performance is obtained with perfusion-cardiovascular magnetic resonance vs. SPECT [$P < 0.013$, in multivessel disease (MVD) $P < 0.006$]. Modified from Schwitter et al.[10] with permission of Oxford Press.
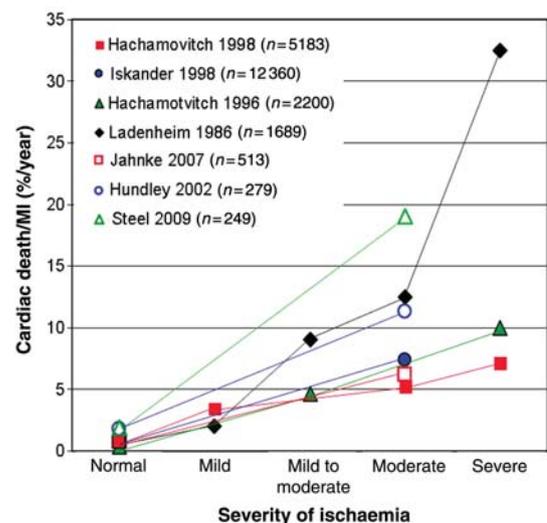

Figure 4 Prediction of cardiac death and non-fatal myocardial infarction by assessment of ischaemia in seven large studies comprising more than 20 000 patients. In patients without ischaemia, outcome is excellent.

later confirmed by other groups (*Figure 4*).[22] In a study comparing perfusion-CMR with stress dobutamine-CMR, a predictive value for major adverse cardiac events (MACE) was similar for both techniques indicating that both ischaemia tests might be similar in performance.[22]

Complication management vs. risk management: the pivotal role of ischaemia detection

Up to now, cardiologists typically concentrated on symptomatic patients and treatment was aimed to alleviate angina or to

and it is safe.[35] The consistently high image quality is also reflected by an excellent reproducibility of this test.[21,23]

Over the last few years, also outcome data after stress dobutamine-CMR could be collected demonstrating a very low event rate in patients without ischaemia,[36] and this result was

manage acute myocardial infarction (AMI) in order to reduce infarct size and to avoid cardiac death. This paradigm therefore is based on the management of complications of CAD. However, the treatment of complications of CAD such as AMI and sudden cardiac death is not always successful and it is costly. With the advent of percutaneous coronary interventions (PCI) in AMI, the death rate of AMI could be reduced in in-hospital patients, but it remains still high during the outpatient phase of AMI which underlines the need for early CAD detection.[2] As a consequence, the paradigm of a 'complications management', i.e. to treat symptomatic patients and AMI, should evolve into a 'risk management' approach, which focus on early detection of CAD and consequently on treatment and revascularization of (symptomatic or asymptomatic) CAD to prevent infarctions.[37] Updated guidelines therefore recommend to assess risk not only based on symptoms, but also on gender and risk factors, as well, and to revascularize based on the extent and severity of ischaemia.[38] High-risk patients should proceed to invasive angiography directly, whereas intermediate-risk patients with a likelihood for obstructive CAD of 20–80% (or 10–90%) should undergo ischaemia testing. In patients without ST-segment changes in the resting electrocardiogram (ECG) and which can exercise adequately, a stress ECG is still the first-line method to use.[38] Intermediate-risk patients post-exercise[5,39] are then candidates for non-invasive imaging tests such as SPECT, stress echocardiography, perfusion-CMR, or stress dobutamine-CMR to confirm or exclude ischaemia.[38] Figure 4 illustrates the prediction of cardiac death and non-fatal MI by non-invasive ischaemia detection compiled from seven large studies in more than 20 000 patients.[22,36,40–44] The evidence for the prognostic value of SPECT[40–43] is large, and a few studies are available for CMR as well.[22,36,44] These large-scale data given in Figure 4 demonstrate that in patients without ischaemia, complication rates are very low, justifying a conservative approach focusing on risk factor management.

How does this statement relate to the theory that often non-obstructive plaques are vulnerable? Here, it appears important to note that not all plaque ruptures result in infarctions.[45,46] The repeated rupture of vulnerable plaques is most likely the mechanism of disease progression, whereas plaque rupture *with consequent vessel occlusion* is the event that directly drives outcome (such as cardiac death and non-fatal MI).[45–47] As can be seen in Figure 4, ischaemic patients with haemodynamically relevant plaques are at a particularly high risk for infarctions, i.e. for plaque ruptures that cause acute vessel occlusions. Also, an invasive study in more than 4000 patients with stenosis of <50% diameter reduction yielded an event rate for cardiac death/non-fatal MI as low as 1.1%/year,[48] whereas an increasing degree of stenosis on invasive coronary angiography was associated with an increasing risk for infarctions.[49,50] These data and particularly those from non-invasive imaging (Figure 4) clearly confirm that ischaemia (i.e. its extent and severity) is a most powerful predictor for future infarctions,[22,36,41–44,51] and ischaemia detection takes a central position in the current guidelines.[38,52]

Since CAD is a chronic disease with relatively stable phases that can be interrupted by episodes of disease progression (plaque ruptures) and complications (plaque ruptures with occlusions), the monitoring of disease activity requires a test, which can be repeated whenever a disease progression is suspected. Cardiovascular magnetic resonance can be repeated theoretically whenever needed since it is not exposing patients to any ionizing radiation. This is an important advantage of CMR over SPECT or multidetector computed tomography (MDCT). Perfusion assessment by CMR requires one CM administration during hyperaemia, which results in short examination times of <1 h. In addition, perfusion-CMR is not hindered by stents in the coronary arteries, so that patients can be monitored after PCI. As PCI are associated with X-ray exposures, and most patients will also need other X-ray-based examinations during their life time, it is most reasonable to avoid X-ray exposure in these patients whenever possible.[53,54] Cardiovascular magnetic resonance is entering now the routine work-up of patients as shown in the European CMR registry data with >11 000 patients included, where CMR findings changed diagnosis and consequently further work-up and/or treatment in ~60% of the cases.[55]

Viability assessment

Although a successful risk management strategy should avoid MI, this concept will not always prevent CAD complications, and as a consequence, viability assessment will then be required.

Cardiovascular magnetic resonance applications in ST-segment elevation myocardial infarction: impact on clinical management and on research

The diagnosis and management of ST-segment elevation myocardial infarction (STEMI) is well established,[56] and in general, there is no routine need for non-invasive imaging in STEMI during early phases of presentation, except, for example, in suspected aortic dissection, where echocardiography, CT, or CMR is required. Echocardiography is also helpful in suspected cardiac tamponade or mechanical complications of AMI and CMR is also valuable in detecting intracardiac thrombus complicating AMI (Figure 5).

Since CMR is an excellent tool for tissue characterization, it offers unique applications in the field of AMI and, in particular, in AMI research. Necrosis can be visualized by CMR with excellent contrast and with submillimetre resolution allowing for detection of microinfarcts well below 1 g of mass.[57,58] This late gadolinium enhancement (LGE) technique[59] is now widely accepted as an excellent way to assess viability in both acute and chronic MI. The current-generation gadolinium-based CM (with one exception) are described as extracellular agents. This means that the gadolinium chelates rapidly distribute within the intravascular and interstitial space but are excluded from the intracellular space (Figures 1 and 6). Because the cell membranes of infarcted myocardium can no longer exclude the contrast from the intracellular space, over the course of 10–20 min, acutely infarcted myocardium enhances to a much greater extent than viable myocardium (Figures 1 and 6A and C).[60,61] Thus, LGE imaging quantifies the extent and severity of myocardial injury after acute reperfused infarction.[60,62–65] Recently, phase-sensitive strategies for LGE imaging were introduced (phase-sensitive inversion recovery) that further improved the robustness of CMR viability imaging. In
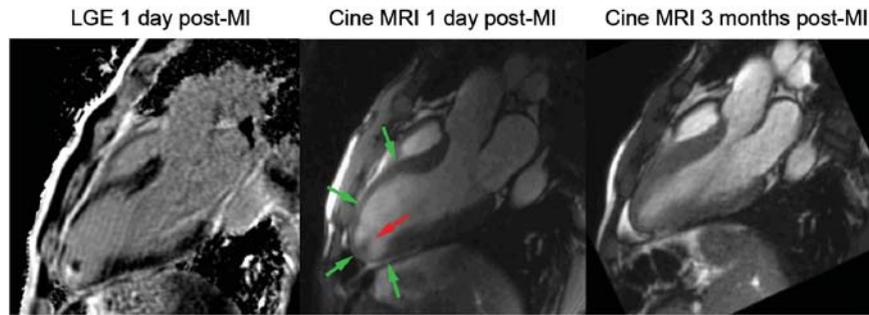
Figure 5 Viability assessment by late gadolinium enhancement (A) demonstrates the absence of necrosis (lack of bright tissue) in the hypo-akinetic anterior wall [end-systolic image in (B)]. As expected, the follow-up assessment by cardiovascular magnetic resonance demonstrates a major recovery of contractile function in the anterior wall [(C) end-systolic images at follow-up]. The late gadolinium enhancement technique is also sensitive for detection of thrombus, which is attached to a small necrotic (=bright) area in the apex of the left ventricle (A).
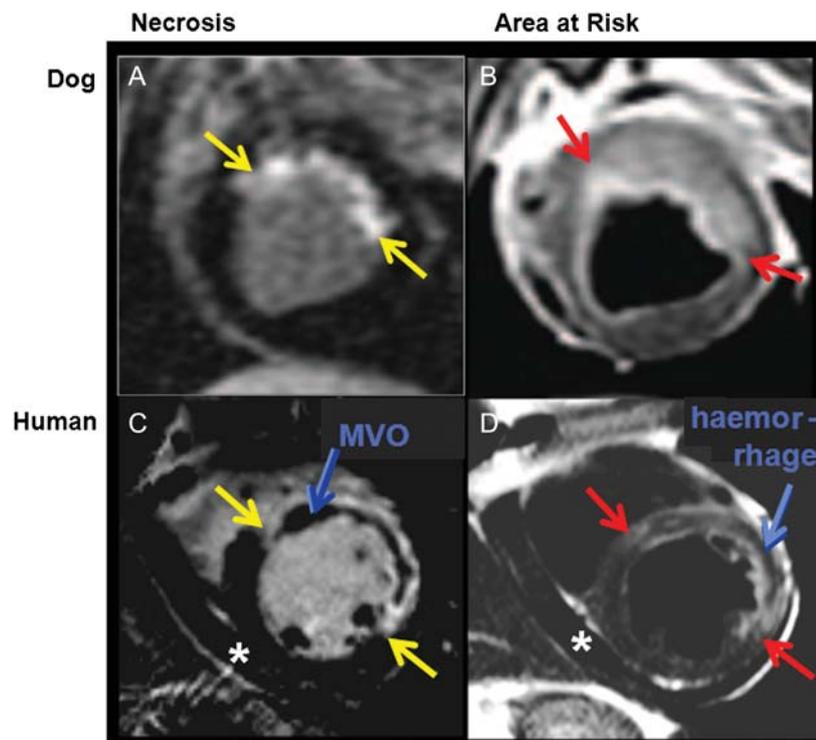

Figure 6 Tissue characterization by cardiovascular magnetic resonance. On the left-hand side (A and C), late gadolinium enhancement is applied to delineate tissue necrosis as bright areas (red arrows). In the canine experiment, a small subendocardial necrosis is detected, whereas in the patient with acute myocardial infarction (C), a dark core in the centre of necrosis is indicating the presence of microvascular obstruction. On the right, T_2-weighted images show increased signal in the myocardium, indicating the presence of oedema, which corresponds to the area at risk. In the patient (D), dark areas in the centre of oedematous tissue indicate haemorrhage. The oedematous tissue [bright on T_2-weighted images in (B) and (D)], i.e. the area at risk minus the necrotic tissue [in (A) and (C), respectively] yields the amount of salvaged myocardium.

large infarcts, particularly when non-reperfused, microvascular obstruction (MVO) is visualized by the LGE approach as a dark core residing within a bright infarct zone.[66–68]

Several studies have validated LGE vs. biomarker release such as CK, CKMB, and troponin in the setting of acute or subacute MI.[57,67,69,70] The amount of LGE is inversely related to the eventual left ventricular (LV) ejection fraction and the transmural extent of infarction predicts the likelihood of recovery of regional wall motion (Figure 5). Comparative studies with SPECT[58,71] and PET[72–74] suggest significant advantages for CMR due to the

increased spatial resolution of CMR compared with nuclear methods. Furthermore, LGE has excellent sensitivity and specificity even in the difficult setting of multicentre trials.[75,76]

Thus, in the field of AMI research, CMR is becoming increasingly important as it allows for accurate and reproducible quantification of global and regional LV function, and also for the quantification of necrosis/scar tissue and MVO (Table 2 and Figure 6). Recently, an elegant approach was proposed to assess the amount of myocardium at risk. By means of T_2-weighted CMR, Aletras et al.[77] demonstrated a close relationship between the amount of tissue oedema in the myocardium and the area at risk as assessed by microspheres (Figure 6A and B). Novel pulse sequences are available now to increase the robustness of T_2-weighted oedema imaging by means of T_2 maps.[78] By subtracting necrotic tissue from the tissue at risk, a myocardial salvage index can be calculated, which was successfully applied to demonstrate that the amount of salvaged myocardium in AMI patients is inversely related to the time delay from pain onset to PCI.[79] This index was also shown to predict MACE.[80] Another type of tissue injury, intramyocardial haemorrhage, can be visualized. Haemorrhage influences the T_2 properties of tissue and consequently low signal areas on T_2-weighted images were shown to correspond to haemorrhage on histology.[81,82] An example is given in Figure 6D. A heterogeneous distribution of the various degradation products of haemoglobin also modify local magnetic field properties and T_2^*-weighted sequences might be even more sensitive for the quantification of haemorrhage.[83] The presence of haemorrhage in the core of the infarcted area might influence the healing processes and Ganame et al.[84] could observe an adverse remodelling of the LV in patients after PCI, when haemorrhage was present in the infarct core.

Cardiovascular magnetic resonance in acute chest pain patients and in acute coronary syndromes

Although STEMI diagnosis is straightforward in emergency departments (ED), a relatively small fraction, typically <10%, of the patients with chest pain actually have STEMI and/or an ischaemic ECG and the great majority does not have ACS.[85] Thus, the ED physician is faced with a daunting task of separating life-threatening diseases such as ACS, aortic dissection, and pulmonary embolism from other aetiologies that might not require immediate hospitalization. In acute chest pain, the ACCF/AHA Guidelines on ACS[86] recommend a non-invasive approach in patients with severe co-morbidities and in those with a low likelihood for ACS. Similarly, the ESC guidelines recommend non-invasive imaging in acute chest pain with repetitive negative troponins and normal or undetermined ECGs.[87] As shown in Figure 7, non-invasive imaging can improve sensitivity of detecting unstable angina/non-STEMI (NSTEMI) and other causes of chest pain. The first major clinical trial assessing the diagnostic performance of CMR in the ED (in patients with 30 min of chest pain and no ST elevation) detected MI with a sensitivity and specificity of 100 and 79%, respectively, and many of those false-positive cases turned out to have unstable angina.[88] The primary endpoints, NSTEMI and unstable angina, were detected by CMR with a sensitivity of 84%
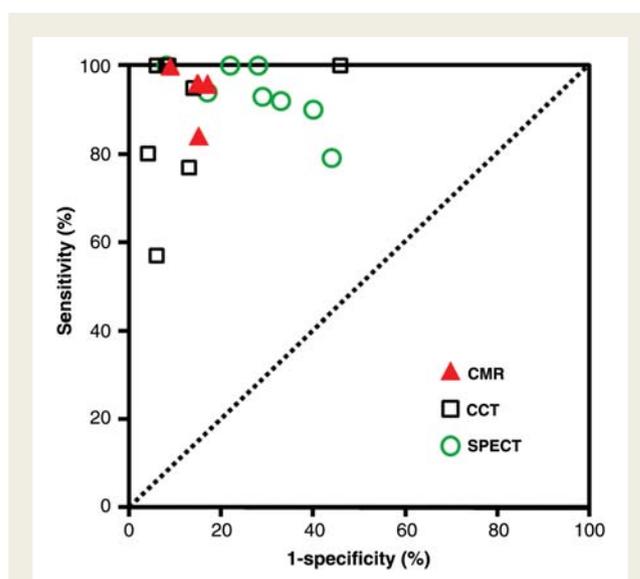

Figure 7 Performance of different imaging techniques to detect acute coronary syndromes in acute chest pain patients. Data are derived for cardiovascular magnetic resonance from references,[88–91] for computed tomographic angiography from references,[106–111] and for SPECT from references.[103,112–118]

and a specificity of 85%. Cury et al.[89] incorporated T_2-weighted imaging into the protocol to differentiate acute from chronic wall motion abnormalities, which improved the overall results to a sensitivity of 85% and a specificity of 96%.

Ingkanisorn et al. studied 135 patients with acute chest pain who had MI excluded by serial ECG and troponin-I. In these patients, adenosine perfusion-CMR, performed within 72 h of presentation, yielded the highest sensitivity and specificity (100 and 93%, respectively) of any single CMR protocol component.[90] In addition, no patients with a negative CMR scan had any cardiovascular outcomes in a 1-year follow-up. A large percentage of patients with an abnormal perfusion-CMR had the diagnosis confirmed by other testing, required revascularization, or suffered from an MI during follow-up. Plein et al.[91] studied NSTE-ACS and adenosine perfusion-CMR, performed within 72 h of presentation, yielded the highest sensitivity and specificity for significant coronary stenosis detection of 88 and 83%, respectively, which increased to 96 and 83%, respectively, by using images of diagnostic quality only. Recently, CMR was shown to reduce the overall cost of evaluating patients with intermediate-risk chest pain.[92]

With regard to feasibility of using CMR in the ED setting, in the study by Kwong et al.,[88] a total of 11% were excluded (5% because of claustrophobia). Weight and body size are not significant limitations in centres with high-performance wide-bore scanners. There remain other significant barriers to the use of CMR in the routine assessment of chest pain in the ED including limited ability to accommodate emergency studies, limited availability of infrastructure needed to perform the relatively complex cardiac CMR scans, and limited availability of experienced technologists and physicians.

Differential diagnoses of acute coronary syndromes

Cardiovascular magnetic resonance is very useful to exclude or confirm conditions that can mimic NSTE-ACS or unstable angina. In these patients with chest pain and troponin elevations, but normal coronary angiography, CMR could yield findings typical for myocarditis in 30–50% of the cases.[93–95] In Takotsubo CMP characterized by anginal symptoms, ECG changes, and normal coronary anatomy, echocardiography or CMR can demonstrate the typical akinetic or dyskinetic motion of the apex. In addition, in Takotsubo CMP, the LGE technique can demonstrate tissue viability and exclude myocarditis, which consequently predicts the well-preserved prognosis in these Takotsubo patients.[96–98] In addition, oedema formation was found in these patients by T_2-weighted CMR imaging.[99]

Finally, CMR can be applied to detect or exclude acute diseases of the aorta such as dissection, penetrating ulcers, or intramural hematoma.[5,100] However, it should be mentioned that CT is the primary method for the assessment of acute diseases of the aorta or for the 'triple-rule-out' strategy due to its speed and the ease of utilization.

In patients with acute chest pain, echocardiography can detect regional wall motion abnormalities and, when combined with CM, can detect perfusion abnormalities. The sensitivity of wall motion abnormalities in patients with AMI range from 88 to 92% which is generally lower than thresholds desired by ED physicians.[101,102]

Single-photon emission computed tomography imaging can also be used to evaluate patients with chest pain syndromes in the ED. Multicentre clinical trials support the conclusion that SPECT imaging adds a diagnostic value above clinical evaluation[103] and reduce the cost of evaluation compared with short hospitalizations to evaluate low-risk patients.[104] At the same time, these studies also document the imperfect sensitivity for short-term cardiac events defined as emergency revascularization, MI, or death.[103,104] Even in a relatively low-risk population, SPECT missed 3% of AMI in the ED.

Multiple MDCT angiography studies have shown sensitivities and specificities for CAD detection that exceeds generally accepted statistics for any of the stress test modalities.[105] Although studies that used MDCT angiography to evaluate patients with acute chest pain reported a sensitivity of 90–100% and a specificity of 86–96%,[106–110] certain limitations need to be considered. When non-diagnostic scans are taken into account, sensitivities in some of these studies may result as low as 57–77%.[107,108]

Overall, the diagnostic performance of CMR[88–91] to detect ACS in the ED (Figure 7) is comparable to that of MDCT angiography[106–111] or SPECT,[103,112–118] even though comparative studies are lacking.

Congestive heart failure

Chronic heart failure in the setting of ischaemic heart disease

Patients after ACS or AMI are at increased risk for future cardiac events, and thus, ischaemia testing is reasonable to perform, for example, by utilization of perfusion-CMR or stress dobutamine-CMR or any other established ischaemia test, and ischaemia testing should be combined with a viability assessment. Since the collagen scar has relatively little intracellular space and a large interstitial space, the volume of distribution of gadolinium chelate is much higher than in the normal myocardium, resulting in a bright scar and viable myocardium appearing nulled or dark (Figures 1 and 5). In a landmark paper, Kim et al.[119] demonstrated the ability of CMR to predict the recovery of segmental contractile function post-revascularization in relation to the transmurality of scar tissue in dysfunctional segments. After revascularization, segments with ≤25% transmurality of scar recovered function in about 80%, whereas <10% of segments recovered when transmurality exceeded 50% of wall thickness.[119] These results were confirmed by others.[68,71] Another study stressed the finding that a scar thickness of ∼4 mm or more is associated with a very low likelihood of functional recovery due to tethering, whereas a viable rim of ∼4 mm is required to allow for recovery of function.[73] In addition to tissue characterization, low-dose dobutamine-CMR can be performed as well to assess the likelihood of functional recovery. Thus, patients with CHF and substantial hibernating or stunning myocardium can be readily detected by CMR and benefit from revascularization. Both scar mass[120] and detection of MVO[120–122] predict the outcome. In patients without MVO, MACE-free survival was ∼90% at 18 months, but decreased to ∼50% in patients with MVO. The presence of viable and scar tissue was shown to predict responsiveness to cardiac resynchronization therapy (CRT) using nuclear techniques.[123] Novel CMR-based models propose to integrate viability data into maps of dyssynchrony to predict CRT responsiveness.[124]

Cardiovascular magnetic resonance is also very sensitive in detecting intracardiac thrombi that complicate infarctions in up to 20–30% of the cases.[125–127] In a comparative study of 361 patients with surgical or pathological confirmation of intracardiac thrombus, CMR had a better sensitivity for thrombus detection than transoesophageal and transthoracic echocardiography while all three modalities had excellent specificities of 99, 96, and 96%, respectively.[126] In another comparative study, contrast echocardiography nearly doubled sensitivity to detect LV thrombi vs. non-contrast echocardiography, but was inferior in comparison to LGE, which was particularly powerful for mural and small apical thrombi.[127]

Chronic heart failure in non-ischaemic heart disease

In CHF, hibernation, stunning, ischaemia, or scar is not always the substrate of dysfunction. A variety of differential diagnoses exist and CMR can considerably contribute in this situation, as the identification of different aetiologies leading to CHF is a prerequisite for a targeted CHF treatment. In dilated CMP, typically no localized endocardial scars are detected, but zones of fibrosis in the mid-wall of the interventricular septum and at the LV–RV insertion points are frequently present,[128] whereas ischaemia is absent. Again, in dilative CMP, the amount of LGE is strongly related to prognosis.[93] Another important differential diagnosis

in CHF to consider is myocarditis. Inflammatory involvement of the myocardium is in general progressing from the subepicardial layer towards the endocardium and most frequently locates in the lateral and inferior walls of the LV.[95,129–134] If inflammation results in irreversible myocyte damage, the LGE technique delineates inflammatory tissue with high spatial resolution allowing to recognize the typical pattern of lesions and also enables accurate follow-up studies to assess responsiveness to treatment. T_2-weighted non-contrast- and T_1-weighted contrast-enhanced CMR sequences, which are sensitive for tissue oedema, may add additional diagnostic information.[135,136] Cardiac amyloidosis is another entity that can cause CHF. Conventional gadolinium-based CM exhibit a high affinity to the amyloid material, which results in specific CM kinetics. These CM kinetics can easily be assessed by the LGE technique[137,138] and yield sensitivities and specificities for the diagnosis of cardiac amyloidosis of 80 and 94%, respectively.[139]

Cardiovascular magnetic resonance applications are helpful in the differential diagnosis of many other cardiac diseases that can lead to CHF.[5] Although many of them cannot be mentioned here, it is worthwhile to recognize that iron overload, e.g. in thalassaemia patients, is the most frequent reason causing death in this large population. Cardiovascular magnetic resonance T_2^* measurements can be applied in a few breath-holds and are now generally accepted as the method of choice to guide chelation therapy as this approach could dramatically decrease the global and cardiac death rate.[140,141]

Safety aspects of cardiovascular magnetic resonance

Electronic devices such as pacemakers, defibrillators, infusion pumps, and others are considered as absolute contraindications.[142] There is up to now one pacemaker type which obtained approval from regulatory authorities to be MR compatible, and other manufacturers will certainly follow soon with similar products. Preliminary experience shows an overall preserved image quality with this MR-compatible pacemaker with only minimal artefacts along the leads. In general, implanted devices such as heart valves, occluders, and stents[143] are compatible with MR, at least up to 1.5 T (for further information, several websites are available for detailed listing).[5] Claustrophobia is present in up to 5% of the cases and the administration of a tranquilizer is usually very effective.[144] Concerning the administration of CM, the cases of nephrogenic systemic fibrosis (NSF) were described where the skin and in severe cases also internal organs develop a fibrosis which can lead to death.[145] This NSF is documented in some 350[146]–500[145] cases worldwide for linear gadolinium chelates (out of up to 200 million administrations), whereas macrocyclic gadolinium chelates are considered of very low risk (with <10 unconfounded cases reported so far).

Outlook

As CMR is now entering the clinical arena, it will be crucial to monitor its performance in daily practice. Also, prognostic data on CMR are rare. The European Registry on CMR was started with a pilot in 2008 and is now active in many European countries and will deliver valuable insights regarding the prognostic yield of ischaemia and viability CMR.[55,58] New CMR techniques are at the horizon in the field of metabolic imaging using hyperpolarized ^{13}C compounds[147,148] and for tissue characterization, detection of inflammation,[149] and cell tracking using fluorine-based CMR.[146] In the future, metabolic CMR and fluorine CMR will be fused with the 'conventional' function, perfusion, and viability CMR information in order to study the myocardium in depth.[147,149]

Conclusions

Cardiovascular magnetic resonance has developed considerably in the past years, and in particular, function, viability, and ischaemia imaging are now an integrated part of the diagnostic armamentarium in cardiology. By combining these CMR applications, CAD can be detected in its early stages and this allows for interventions with the goal to reduce complications of CAD such as infarcts and, at a later stage, heart failure. As the CMR examinations are robust and reproducible and do not expose patients to radiation, they can be repeated without harm to the patients, which is important as CAD is a chronic disease and patients therefore should be monitored over several decades.

Cardiovascular magnetic resonance also progressed recently in the setting of ACS. In this situation, CMR allows for important differential diagnoses and it also delineates precisely the different tissue components in AMI such as necrosis, MVO, haemorrhage, and oedema, i.e. area at risk. With these advantages, CMR might become the preferred tool to investigate novel treatment strategies in clinical research.

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