

Clinical recommendations of cardiac magnetic resonance, Part I: ischemic and valvular heart disease: a position paper of the working group 'Applicazioni della Risonanza Magnetica' of the Italian Society of Cardiology

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Cardiac magnetic resonance (CMR) has emerged as a reliable and accurate diagnostic tool for the evaluation of patients with cardiac disease in several clinical settings and with proven additional diagnostic and prognostic value compared with other imaging modalities. This document has been developed by the working group on the 'application of CMR' of the Italian Society of Cardiology to provide a perspective on the current state of technical advances and clinical applications of CMR and to inform cardiologists on how to implement their clinical and diagnostic pathways with the inclusion of this technique in clinical practice. The writing committee consisted of members of the working group of the Italian Society of Cardiology and two external peer reviewers with acknowledged experience in the field of CMR.

Keywords: appropriateness criteria, cardiac magnetic resonance, ischemic heart disease, valvular heart disease

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J Cardiovasc Med 2017, 18:000–000

Received 21 June 2016 Revised 21 October 2016
Accepted 13 December 2016

Introduction

Cardiac magnetic resonance (CMR) has emerged as a reliable and accurate diagnostic tool for the evaluation of patients with cardiac disease in several clinical settings and with proven additional diagnostic and prognostic value compared with other imaging modalities.¹ This document has been developed by the working group on the 'application of CMR' of the Italian Society of Cardiology to provide a perspective on the current state of technical advances and clinical applications of CMR and to inform cardiologists on how to implement their clinical and diagnostic pathways with the inclusion of this technique in clinical practice. The writing committee consisted of members of the working group of Italian Society of Cardiology and two external peer reviewers with acknowledged experience in the field of CMR. As the first step, the writing committee discussed the topics to be covered and assigned lead authors for each section. As the second step, each lead author conducted literature searches and drafted the assigned section highlighting

indications and rating them according to the following score: score 1–3 = inappropriate (test is not generally acceptable and is not a reasonable approach for the indication); score 4–6 = uncertain (test may be generally acceptable and may be a reasonable approach for the indication, but more research and/or patient information is needed to classify the indication definitively); and score 7–9 = appropriate (test is generally acceptable and is a reasonable approach for the indication). As the third step, the writing committee reviewed each section, discussed document contents and arrived at a consensus on a document. As the fourth step, the document was sent for external peer review. Finally, the writing committee chair summarized the reviewers' comments and finalized the document for the final approval of all members of the working group.

Technical background

Clinical CMR can be performed using 1.5 or 3-T scanners with dedicated cardiac phased array coils, pulse sequences and postprocessing software.² However, 1.5-

T systems are currently used for the majority of examinations due to less flow, banding and susceptibility artifacts. Furthermore, devices that have been tested at 1.5 T may not be safe at 3 T.

It is recommended that CMR images are analyzed by a radiologist or cardiologist who holds at least level 1 accreditation of the European Association of Cardiovascular Imaging for CMR in presence of a level 3-accredited supervisor (or equivalent accreditation from other scientific Societies).

Cine images: wall motion, volumes and function

Left and right ventricular (LV and RV) volumes and functional parameters can be obtained by the acquisition of a set of ventricular short-axis views from atrioventricular plane to the apex with 6–8 mm slice thickness possibly with no gap between the slice, but the use of a 1–3 mm gap between the slice is also accepted.² A balanced steady-state free precession (bSSFP) cine images with a temporal resolution 45 ms or less and

in-plane spatial resolution of less than 2 mm has to be used. To confirm abnormal wall motion findings, cine images in standard axial long-axis views, from the diaphragm to the RV outflow tract, are also acquired. bSSFP is the method of choice for cine imaging because it provides high signal-to-noise ratio (SNR) and excellent contrast between myocardium and blood pool.³ The most basal short-axis slice should be located immediately on the myocardial side of the atrioventricular junction at end diastole prescribed from previously acquired long-axis cines.⁴ As an alternative, RV volume may be obtained using cine-bSSFP acquired in a set of axial planes from diaphragm to the outflow tract. Reference values of normality for cardiac volumes and other functional parameters were recently proposed in a multicenter, multivendor and multisoftware study (Tables 1–3).⁵

CMR has the capability of direct flow measurement using the velocity encoded phase-contrast (VEPC) pulse sequences. Technical details of VEPC were reported in a recent review by the working group on the

Table 1 Appropriateness criteria for valvular heart disease

	Appropriateness score	ESC guidelines class of indication	Pulse sequences
Aortic valve anatomy	8	I C Indicated in patients with bicuspid aortic valve when the morphology of the aortic root and the ascending aorta cannot be accurately assessed by echo	Parasagittal cine-bSSFP slice covering the thoracic aorta Cine-bSSFP radial slices placed on mitral and/or tricuspid valve Cine-bSSFP images parallel to aortic valve plane Cine-bSSFP images parallel to pulmonary valve plane
Quantification of aortic valve regurgitation	9	I C Indicated in patients with bicuspid aortic valve when the morphology of the aortic root and the ascending aorta cannot be accurately assessed by echo	VEPC images acquired orthogonally to ascending aorta at the sinotubular junction
Quantification of mitral valve regurgitation (indirect method)	7	–	VEPC images acquired orthogonally to ascending aorta at the sinotubular junction
Quantification of tricuspid valve regurgitation (indirect method)	6	–	Cine-bSSFP in short-axis views VEPC images acquired orthogonally to pulmonary artery
Quantification of pulmonary valve regurgitation	9	–	Cine-bSSFP in short-axis views VEPC images acquired orthogonally to pulmonary artery
Measurement of aortic valve planimetric area	8	–	Cine-bSSFP images parallel to aortic valve plane
Quantification of aortic valve pressure gradient	5	–	VEPC images acquired orthogonally to ascending aorta at the sinotubular junction
Quantification of mitral valve pressure gradient	3	–	VEPC images acquired orthogonally to mitral valve plane
Evaluation of pulmonary stenosis	8	–	VEPC images acquired orthogonally to pulmonary artery
Evaluation of valvular tumors	3	–	See valve anatomy
Evaluation of endocarditis	3	–	See valve anatomy

ESC, European Society of Cardiology; bSSFP, balanced steady-state free precession; VEPC, velocity encoded phase contrast. Appropriateness criteria: 1-3 = inappropriate; 4-6 = uncertain; 7-9 = appropriate.

Table 2 Appropriateness criteria for ischemic heart disease

	Appropriateness score	ESC guidelines class of indication	Pulse sequences
Coronary artery imaging	4	–	Whole heart 3D bSSFP
CABG imaging	4	–	CEMRA
Cardiac veins imaging	4	–	Whole heart 3D bSSFP
Diagnosis of reversible ischemia	9	I C, recommended whenever history suggests myocardial ischemia I A, recommended in patient with intermediate pretest probability of CAD and stable symptoms I B, recommended in patient with intermediate pretest probability of CAD without typical angina I B, recommended in presence of resting ECG abnormalities preventing accurate interpretation of ECG during stress I B, in patients with nonconclusive exercise ECG	Stress CMR with adenosine or dipyridamole First pass perfusion acquired in short-axis planes (basal, mid and apical) at rest and at maximal vasodilation Cine-bSSFP acquired in short-axis planes (basal, mid, apical) at rest and at maximal vasodilation Stress CMR with dobutamine
Prognostic stratification in CAD and IHD	9	II B, recommended for advanced cardiovascular risk assessment in asymptomatic adults with diabetes or strong family history or with high risk of CAD I B–I C, recommended in patients with stable CAD after change, deterioration or new occurrence of symptoms	Cine-bSSFP acquired in short-axis planes (basal, mid and apical) at rest and stress As above

bSSFP, balanced steady-state free precession; CAD, coronary artery disease; CABG, coronary artery bypass grafting; CMR, cardiac magnetic resonance; CEMRA, contrast enhanced magnetic resonance angiography. Appropriateness criteria: 1-3 = inappropriate; 4-6 = uncertain; 7-9 = appropriate.

‘Applicazioni della Risonanza Magnetica’ of the Italian Society of Cardiology.⁴

Precontrast tissue characterization

Black-blood Fast Spin Echo (FSE) or double-inversion recovery FSE, with proton density or T1-weighting are used to evaluate cardiac morphology and to detect fat, which shows hyperintense signal on T1-weighted images. Conventional T1 and T2-weighted FSE (or double-inversion recovery FSE) can be obtained setting a repetition time less than 1000 ms and an echo time less than 10 ms and a repetition time more than 1800 ms and echo time more than 60 ms, respectively. Myocardial edema can be identified as an hyperintense area on images obtained with a T2-weighted short tau inversion recovery (STIR) FSE pulse sequence, generally acquired with a triple-inversion recovery protocol (double-inversion recovery and the third-inversion recovery pulse with inversion time of 150 ms for a system 1.5 T); this type of sequence has the advantage to null signal from fat allowing detection of edema.⁶ Myocardial iron overload in cardiac hemochromatosis can be evaluated using T2*-weighted multiecho gradient-echo (GRE) or FSE with acquisition of a series of 8–10 images at different echo time beginning at about 2.2 ms and extending to 18–20 ms, with each echo iteratively spaced by 2.26 ms.⁷ The measurement of regional and global myocardial T2* permits the identification of iron overload (conservative cutoff T2* < 20 ms).⁸

The T1 mapping is a newer technique for tissue characterization, based on the quantification of T1 value in each voxel or in myocardial region of interest. The diagnostic and prognostic role of native (precontrast) T1-mapping in cardiac diseases is currently under investigation. However, studies suggest that native T1 signal can detect pathological processes: T1 is low in presence of fat (i.e. Anderson–Fabry disease) or iron and increases in the presence of extracellular protein deposition (i.e. amyloid), myocarditis and myocardial fibrosis.⁹ T2 mapping is another new technique for the quantification of myocardial T2. It is performed using a T2-prepared single-shot SSFP pulse sequence with different T2 preparation time.

First pass perfusion

First pass perfusion is performed by the acquisition of at least three short-axis views (basal, mid-ventricular and apical) in diastole for each heartbeat for about 60 consecutive beats starting during the injection of a bolus of gadolinium-based contrast agent (dosage 0.05–0.1 mmol/kg for 0.5 mol contrast agents at 3–5 ml/s infusion velocity) using a saturation-recovery imaging pulse sequence with GRE echo-planar hybrid or SSFP readout.¹

Postcontrast tissue characterization

Late gadolinium enhancement (LGE) images are obtained using two-dimensional or three-dimensional segmented inversion recovery GRE or SSFP pulse

Table 3 Appropriateness criteria for myocardial infarction

	Appropriateness score	ESC guidelines class of indication	Pulse sequences
LV volumes and function	9	I C, if echocardiography is not feasible, CMR may be used as an alternative for assessment resting LV function after STEMI	Cine-bSSFP in short-axis views
RV volume and function	9	–	Cine-bSSFP in short-axis views
Acute myocardial damage <30 days from STEMI	7	I C, If echocardiography is not feasible, CMR may be used as an alternative for assessment of infarct size after STEMI I A, for patients with multivessel disease, or in whom revascularization of other vessels is considered for ischemia and viability is CMR indicated after STEMI before or after discharge	Cine-bSSFP in short-axis views T2 STIR images acquired in short-axis and long-axis views LGE images acquired in short-axis and long-axis views For stress CMR, see Table 2
Viability \geq 30 days from STEMI	9	I A, for patients with multivessel disease, or in whom revascularization of other vessels is considered for ischemia and viability is CMR indicated after STEMI before or after discharge	As above
Infarction of right ventricle	8	–	As above
Ventricular thrombi	9	–	Early gadolinium enhancement and LGE acquired in short-axis and long-axis views acquired
Mechanical complication of AMI	8	–	Cine-bSSFP in short-axis views T2 STIR images acquired in short-axis and long-axis views LGE images acquired in short-axis and long-axis views
Acute pericarditis post-AMI	8	–	Cine-bSSFP in short-axis views T2 STIR images acquired in short-axis and long-axis views LGE images acquired in short-axis and long-axis views
Pericardial effusion post-AMI	8	–	Cine-bSSFP in short-axis views T2 STIR images acquired in short-axis and long-axis views LGE images acquired in short-axis and long-axis views
Ischemic Mitral regurgitation (indirect method)	7	–	Cine-bSSFP in short-axis views VEPC of sinotubular junction LGE images acquired in short-axis and long-axis views For stress CMR, see Table 2

bSSFP, balanced steady-state free precession; CMR, cardiac magnetic resonance, LGE, late gadolinium enhancement; LV, left ventricular T2-STIR, short tau-inversion recovery. Appropriateness criteria: 1-3 = inappropriate; 4-6 = uncertain; 7-9 = appropriate.

sequence. The acquisition of an inversion-time scout sequence is recommended before the acquisition of LGE image to establish the appropriate inversion time. Phase-sensitive inversion recovery is recommended in laboratory performing fewer than 300 CMR examinations per year. Three-dimensional LGE protocol may be an excellent alternative when the expected SNR is sufficient in patients able to maintain long breath-hold. LGE images are acquired after at least 10 min following the injection of gadolinium-based contrast agent (dosage 0.1–0.2 mmol/kg for 0.5 mol agents or 0.1 for 1 mol).²

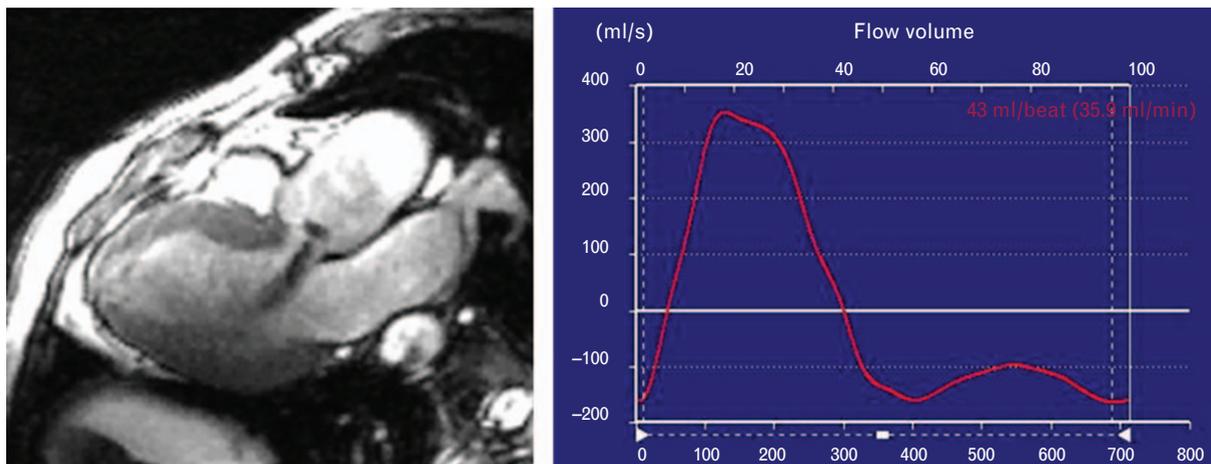
The T1 signal can be measured 15 min after contrast and used to calculate the extracellular volume (ECV). As for

the native T1, the ECV hold the potentiality to give diagnostic and prognostic information and is under investigation.

Safety considerations for gadolinium-based agents

The ‘Agenzia Italiana del Farmaco’ recommends to follow the indication of the European Society of Urogenital Radiology about contrast agents (www.esur.org/guidelines). The risk of acute reaction to gadolinium-based contrast agents is generally low. In patient at higher risk of reactions (previous acute reaction to gadolinium-based agents, asthma and allergy requiring medical treatment), actions to reduce the risk are recommended, including

Fig. 1



A case of severe aortic regurgitation. In (a), the balanced steady-state free precession image shows the jet of aortic regurgitation as a signal void for flow turbulence. The severity of aortic regurgitation is confirmed by the measurement of the retrograde flow in (b). This graph is obtained by the analysis of velocity encoded phase-contrast pulse sequence.

premedication with corticosteroids, the use of different gadolinium-based agents (in case of previous reactions) or avoidance of contrast media injection.

The nephrogenic systemic fibrosis (NSF) has been associated with the exposure to gadolinium-based contrast agents. Contrast agents identified as at high risk for NSF are contraindicated in patients with severely impaired renal function (Estimated Glomerular Filtration Rate, eGFR, < 30 ml/min) and with acute renal insufficiency and should be used with caution in patients with moderately reduced renal function (eGFR 30–60 ml/min). For contrast agents at lower risk for NSF, laboratory testing of renal function is not mandatory and renal function assessment by questionnaire may be used. However, low-risk contrast agents should be used with caution in patients with eGFR less than 30 ml/min, in pregnant or lactating women, in children less than 1 year old. However, in presence of severe renal insufficiency, we suggest to limit the injection of contrast agent for the indications in which its use is crucial for the management of the patients. Finally, at least 7 days should be left between two injections. Anyway, to assess appropriately the risk for NSF, it is suggested a laboratory testing of renal function (eGFR) in all patients with a history suspected for impaired renal function. Conversely, a laboratory testing of renal function (eGFR) in all patients with known history of impaired renal function is strongly recommended.

Valvular heart disease

Patients with valvular heart disease may benefit from CMR to identify and assess the magnitude of the disease and estimate its influence on cardiac function

(Table 1).^{10,11} bSSFP cine sequences are used to assess the anatomy and function of valves allowing a direct planimetry of the valve orifice. bSSFP sequence can also assess the presence of valvular masses (thrombi, vegetations and fibroelastomas).¹² However, small vegetations, small highly moving mass or ruptured mitral chordae may be missed by CMR.¹³

Transvalvular peak velocity may be assessed by the means of VEPC sequences, having care to avoid velocity mapping errors due to temporal resolution and artifacts from turbulent jets.¹⁴

Calculation of LV-to-RV stroke volume (SV) difference can be used to assess single-valve regurgitant disease,¹⁵ but it is not suitable in case of coexistence of multiple valvular diseases. A more accurate assessment of the regurgitation can be performed using VEPC images in combination with the measurement of ventricular SVs.⁴

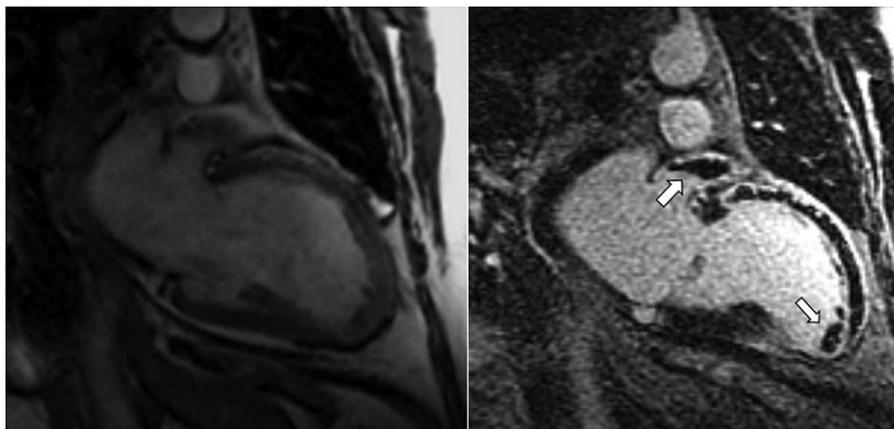
All prosthetic valves have been demonstrated to be safe in CMR, but mechanical prosthesis cause several artifacts making difficult the direct visualization of the valve itself, reducing the reliability of phase-contrast velocity-encoded measurements.

Another important ability of CMR is the direct identification of LV myocardial damage due to abnormal pre and/or after-load conditions or myocardial stretch observed in some valve heart disease as aortic stenosis and mitral valve prolapse.^{16,17}

Aortic valve stenosis

CMR provides high-resolution assessment of the anatomy of the aortic valve, aortic root and ascending aorta. Quantification of LV mass and function by CMR is

Fig. 2



Cine image (a) and late gadolinium enhancement image (b) of an anterior infarction involving the ventricular apex. Microvascular obstruction is showed as the hypointense region inside the hyperenhancement in late gadolinium enhancement images (b). An intracavitary thrombus is evident in the left ventricular apex and in left appendages (arrows).

useful to evaluate the precise effect on the LV more than measurement of wall thickness and LV diameters. CMR allows direct planimetry of the aortic valve orifice, which is the most useful technique for quantifying stenosis severity.¹⁸

Using the VEPC pulse sequence, it is possible to evaluate transvalvular peak velocity when this is difficult with echo, also though peak velocity may be less accurate compared with continuous wave Doppler echo.¹⁹ However, CMR measurement of velocity is advantageous in angulated roots in which the correct alignment of the echo beam with the ejection jet is impossible.²⁰

CMR with cine imaging has the ability to differentiate subvalvar and supra-valvar stenosis by the identification of site of velocity acceleration, detected as a signal void jet of turbulent flow.

Finally, LGE permit to detect and quantify myocardial fibrosis in patients with aortic stenosis.²¹ Early reports have shown that this is associated with a worse prognosis.²² T1 mapping and ECV technique are promising techniques for the identification of diffuse fibrosis in aortic stenosis.

Aortic valve regurgitation

The evaluation of aortic valve regurgitation is the most frequent indication of CMR in valvular disease because it is often associated with ascending aorta dilation.

The quantification of aortic valve regurgitant volume and the accurate evaluation of LV volumes are the main advantages of CMR in aortic regurgitation. Aortic regurgitation may be qualitatively evaluated by the visual assessment of the regurgitation jet that is easily detected as a flow turbulence during diastole. Using the VEPC pulse technique CMR allows a direct measurement of

forward flow and retrograde regurgitant flow through aortic valve (Fig. 1). Acquisition plane must be positioned at the sinotubular junction orthogonally to the ejection jet to avoid flow underestimation. The identification of an aortic regurgitant fraction more than 33% by CMR is able to identify patients likely to develop symptoms and to predict future aortic valve replacement.²³ Moreover, the measurement of the regurgitant volume is useful to predict the reverse remodeling after valve replacement because, after the surgery, the amount of decrease of LV end-diastolic volume should be equal to the presurgery regurgitant volume.

Mitral valve stenosis

The use of CMR for the evaluation of mitral stenosis is severely limited by the frequent concomitant presence of atrial fibrillation. However, in selected cases CMR may help to have a direct measurement of planimetric mitral valve area by placing the acquisition plane in diastole.

Mitral valve regurgitation

CMR may allow the evaluation of mitral valve morphological aspect as the leaflets thickness and lengthiness, the measurement of the annulus and the coaptation area. However, transesophageal echocardiography provides superior leaflet details than CMR. As for aortic regurgitation, the main advantage of CMR is the capability to quantify mitral regurgitant volume. The preferred method for mitral regurgitation quantification is the indirect method, based on the measurement of LV SV and the measurement of the flow through aortic valve by VEPC.⁴ Briefly, in absence of shunt, the mitral regurgitant volume is equal to the difference between LV SV and the total flow measured in aorta (corrected by the aortic regurgitant volume). Recently, Uretsky *et al.*²⁴ compared the effectiveness of CMR and

echocardiography to predict reverse remodeling after correction of mitral regurgitation. Authors found that CMR was superior to echocardiography to predict reverse remodeling because of the more accurate and reproducible evaluation of regurgitant volume.

Finally, CMR may give important information about the ischemic mitral regurgitation, as the assessment of the presence of scar in the lateral wall involving the papillary muscles and the capability to quantify the severity of regurgitant volume at rest and during vasodilator stress test.

Pulmonary valve regurgitation and stenosis

The evaluation of pulmonary valve is difficult for echocardiography because of the anatomic location and orientation of flow. Also, the ultrasound estimation of RV volume and function is problematic due to the morphology and position. CMR overcomes these limitations and it is considered the gold standard for the assessment of pulmonary regurgitation and RV volumes.²⁵ CMR is the method of choice for the evaluation of pulmonary regurgitation in congenital heart disease and particularly in patients with repaired tetralogy of Fallot. Pulmonary regurgitation is directly measured by VEPC using cross-sectional plane of mid-pulmonary artery.

CMR provides evaluation of pulmonary stenosis by a direct measurement of valve planimetry and by quantification of peak flow velocities. Moreover, the evaluation of RV morphology and the identification of the origin of flow turbulence permit to differentiate pulmonary valve stenosis from subvalvular and supra-valvular stenosis.

Finally, the measurement of RV volumes and mass allows assessment of the functional effect of both pulmonary regurgitation and stenosis.

Tricuspid regurgitation and stenosis

CMR permits the study of leaflets anatomy and function, and it is used in the evaluation of Ebstein's anomaly. The visualization of regurgitant jet of tricuspid valve is difficult because of lower turbulence and velocities than for mitral regurgitation.

The quantification of tricuspid regurgitant volume is preferentially made using the indirect method as for mitral regurgitation, by the combination of RV SV and the flow through pulmonary artery.

Tricuspid stenosis is extremely rare. As for mitral stenosis, CMR is generally not used for the evaluation of this valvulopathy. However, CMR may allow direct measurement of valve planimetry and of peak velocity.

Coronary artery disease and ischemic heart disease

Coronary artery imaging

The assessment of luminal narrowing and the visualization of the coronary atherosclerotic disease is challenging

with CMR because of the small size of the vessels and the composite cardiac motion. Early reports²⁶ showed that breath-hold three-dimensional SSFP coronary magnetic resonance angiography (MRA) had acceptable specificity, but inconclusive sensitivity for diagnosing significant stenosis as compared with invasive coronary angiography. The introduction of free-breathing, noncontrast whole-heart coronary MRA can provide visualization of the coronary tree within a single three-dimensional acquisition, either by employing 1.5-T SSFP or 3-T GRE.²⁷ A prospective multicenter trial²⁸ evaluated the diagnostic ability of the abovementioned technique to detect significant coronary artery stenosis ($\geq 50\%$ reduction in diameter) proving a sensitivity, specificity and negative predictive value of 88, 72 and 88%, respectively, in a patient-based analysis as compared with the reference modality. In addition to the morphologic assessment, measurement of blood flow and flow reserve in the coronary arteries are allowed by the phase-contrast cine magnetic resonance (MR) imaging.²⁹

Despite the results of the abovementioned studies, coronary angio-CMR is not routinely used and more robust techniques such as coronary angio-computed tomography (angio-CT) are usually preferred. However, CMR remains a possible diagnostic tool for coronary anatomy, especially when other methods are contraindicated or are associated with risk (Table 2).

Conversely, coronary MRA can accurately visualize the origin and the path of anomalous coronary vessels and should be preferred to coronary angio-CT in young patients.³⁰

Coronary artery bypass and coronary vein imaging

Coronary MRA allows the visualization of bypass grafts with good image quality as these are motionless and larger as compared with the native coronary arteries. The numerous technical approaches include both spin-echo and GRE sequences. In a head-to-head comparison³¹ between multisection true fast imaging with bSSFP and gadolinium-enhanced MRA, the former showed more false-positive findings for occlusion and reduced visualization of arterial grafts. Coronary bypass graft MRA assessment presents common limitations related to local signal voids due to susceptibility artifacts that are caused by metallic objects (metallic clips along the course of grafts, sternal wires, possible coexistent prosthetic valves and graft stents).

The importance of the assessment of the coronary venous system has been progressively developing in parallel with the growth of resynchronization therapy. The acquisition of both anatomic details and myocardial scar information may help in adequate LV lead implantation. In particular, three-dimensional MR coronary vein angiograms can be overlaid onto the live radiograph fluoroscopy to improve the lead catheter implantation.³²

However, CMR is not routinely used for evaluation of both coronary artery bypass grafting (CABG) and coronary veins in clinical practice.

Stress cardiac magnetic resonance for diagnosis

The assessment of LV behavior under stress condition is clinically important, as it is evident that the presence of inducible ischemia is the 'conditio sine qua non' to pose a strong indication for myocardial revascularization. The employment of gradually increasing dosage of dobutamine (at the highest dosage of 40 mg/kg/min) is useful to induce wall motion abnormalities in territories supplied by stenotic coronary arteries.^{33,34} The detection of wall motion abnormalities by dobutamine stress CMR has shown to provide a significantly higher diagnostic accuracy than dobutamine stress echocardiography.³⁵ The addition of tagging³⁶ to high-dose dobutamine stress CMR allows the use of quantitative methods and may improve overall accuracy. Despite this, tagging technique is not routinely used during dobutamine stress CMR in clinical setting. However, the use of dobutamine stress imaging is limited by the longer time of execution, the need to reach target heart rate that may alter image quality and the most frequent complications than vasodilator stress.

In clinical practice, single photon emission CT (SPECT) and positron emission tomography represent standardized techniques for the assessment of myocardial perfusion. Advantages of first pass perfusion CMR with vasodilator stress using dipyridamole or adenosine include the lack of ionizing radiation and high spatial resolution (2–3 mm in plane), thus allowing determination of transmural and subendocardial perfusion defects. Moreover, vasodilator stress CMR testing, providing both myocardial perfusion and regional kinesis information in a one-stop shop fashion, has demonstrated its high diagnostic accuracy in coronary heart disease and its superiority over SPECT in terms of sensitivity and negative predictive value.^{37–39} In addition, low-dose dobutamine and vasodilator stress CMR may answer the important need of identifying viable myocardium to predict a functional improvement after revascularization procedures Table 2.⁴⁰

The main limitation of the vasodilator stress test is that the maximal vasodilation is not obtained in all the patients using the conventional dosage.

Stress cardiac magnetic resonance for prognosis

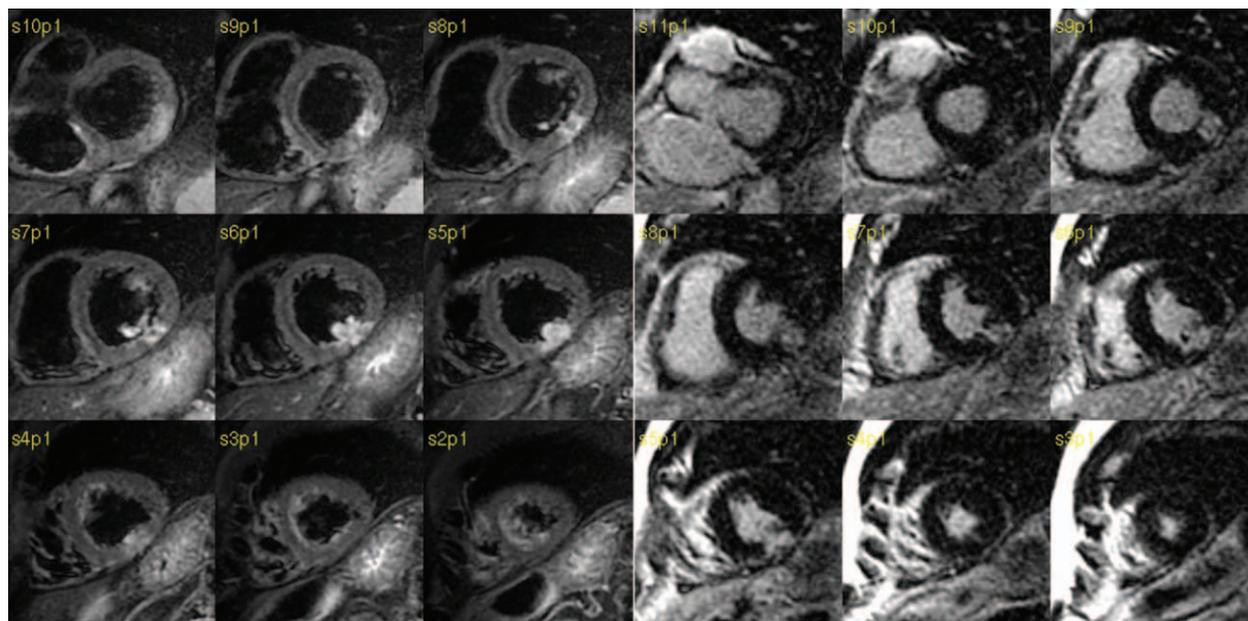
Over the past several years, numerous studies adopted stress CMR to assess the prognostic value of inducible perfusion defects and wall motion abnormalities (WMAs) in patients with known or suspected coronary artery disease (CAD). Recently, Shah *et al.*⁴¹ studied a cohort of 815 consecutive patients and showed that stress CMR reclassifies 91.5% of patients at moderate pretest cardiovascular risk (65.7% to low risk; 25.8% to high risk) with

corresponding changes in the observed major adverse cardiac event (MACE) rates (0.3%/year and 4.9%/year for low and high posttest risk, respectively). Buckert *et al.*⁴² demonstrated in 1229 consecutive patients with stable CAD that the evidence of reversible perfusion deficit on adenosine perfusion CMR was the strongest independent predictor for the combined endpoint of cardiac death, nonfatal myocardial infarction (MI) and stroke with a three-fold increased risk. The consistency and robustness of prognostic stratification by adenosine stress CMR seem to be preserved regardless of the patient's sex.⁴³ The meta-analysis by Lipinski *et al.*,⁴⁴ including 19 studies (14 vasodilator, four dobutamine and one both) and involving 11 636 patients followed up for 32 months, showed that the combined outcome of annualized cardiovascular death and MI rates were 0.8% for negative and 4.9% for positive study. In addition, the evidence of LGE was significantly associated with a worse prognosis as well. In a separate meta-analysis, stress CMR has proven a very high negative predictive value for MACE, and the absence of inducible perfusion defects or wall motion abnormalities demonstrated a similar capability to identify low-risk patients with known or suspected CAD.⁴⁵ Finally, Pontone *et al.*⁴⁶ showed how the stress CMR with dipyridamole provides additional prognostic value by the detection of both components of ischemic cascade (perfusion and wall motion abnormality).

Cost-effectiveness of magnetic resonance imaging in coronary artery disease and ischemic heart disease

Available analyses regarding the cost-effectiveness of CMR are relatively few. A comparison between the cost-effectiveness and utility of CMR with SPECT in patients with suspected CAD was performed employing a mathematical model based on Bayes' theorem.⁴⁷ In patients with low-to-intermediate pretest probability of CAD, CMR was consistently more cost-effective than SPECT and showed lower costs per quality-adjusted life-year gained. The likelihood of CAD exceeding 0.60 represented the watershed beyond which proceeding directly to invasive coronary angiography was found to be the most cost-effective strategy. A parallel evaluation was published extrapolating data from CE-MARC Study.⁴⁸ CMR was included as part of the optimum diagnostic strategy when it followed a positive or inconclusive treadmill test. Very recently, Genders *et al.*⁴⁹ tried to determine the cost-effectiveness of different imaging strategies in patients with stable chest pain and low-to-intermediate probability of CAD. For this purpose, the authors developed a simulation model analyzed from the perspective of the United Kingdom, the United States and the Netherlands health systems. The strategy that maximized the Quality Adjusted Life Years with the highest cost-effective included coronary angio-CT as first step, continued with cardiac stress imaging if coronary

Fig. 3



A patient with acute myocardial infarction involving the inferolateral wall and the respective papillary muscle [late gadolinium enhancement images in (a), T2-short tau inversion recovery images in (b)].

angiography found at least 50% stenosis in at least one coronary artery. Differences among the cardiac stress imaging tests were trivial, but stress echocardiographic strategy resulted the best when compared with SPECT or cardiac CMR.

Myocardial infarction

The study of acute ischemic myocardial damage has to consider the complexity of events occurring in the evolving MI. An acute infarct goes through a series of inflammatory and healing stages with replacement of the dead myocardium by collagenized scar tissue.⁵⁰ It follows that any imaging modality aiming to study acute MI has to take into account the dynamic and rapid changes in the infarcted tissue as well as the maladaptive modifications of LV geometry, morphology and function.

Historically, T2-weighted STIR imaging has been used for the detection and quantification of infarct-related myocardial edema, depicted as an area of hyperintense myocardial signal. This technique may serve as a useful diagnostic marker in patients with unstable angina or evolving MI in the emergency department, as well as for the retrospective quantification of myocardium at risk.^{51–53} Several experimental and clinical studies support the utility of T2w imaging for the determination of myocardium at risk up to 7 days after an acutely reperfused ST-segment elevation MI.^{52,54,55} The myocardium at risk represents the ischemic tissue nourished by the infarct-related artery, potentially

salvageable by the reperfusion strategies, and it is one of the major determinants of final infarct size also in reperfused MIs.^{56,57} Accordingly, the correction of infarct size for myocardium at risk allows the determination of myocardial salvage, which represents an ideal metric for testing the efficacy of novel reperfusion strategies due to its potentially lower inherent variability.⁵⁸ T2w imaging is also useful for the depiction of intramyocardial hemorrhage, which appears as hypointense signal within the hyperintense edematous myocardium.⁵⁹ Postinfarction myocardial hemorrhage invariably denotes structural damage of coronary microvasculature as a consequence of severe ischemia/reperfusion injury.⁶⁰ However, it has to be acknowledged that the clinical and research applicability of T2w imaging for quantification of infarct-related myocardial edema have several important limitations: highly dynamic pattern of myocardial edema in the early post-infarction phase, difficulty in the edema quantification on T2w images based on SI algorithms, technical constraints of T2w sequences (inherent low SNR, susceptibility to motion and slow-flow artifacts), the influence of cardioprotection therapies on the severity of myocardial edema and the unsolved discussion about the robustness of T2w images in the depiction of reversibly ischemic myocardial damage.^{61–63} The novel native T1-mapping and T2-mapping techniques are likely to overcome some of the abovementioned limitations as well as to shed new light on the mechanisms implicated in the reversibly ischemic myocardial damage.⁵⁴

CMR with LGE technique is an accurate modality to visualize and quantify irreversible ischemic damage (Figs. 2 and 3).⁶⁴ This consists in performing T1w inversion recovery segmented gradient echo sequence between 10 and 20 min after a bolus of gadolinium-based contrast agent (Table 3). The use of phase-sensitive inversion recovery imaging eliminates the necessity to precisely choose the optimal inversion time and allows consistent signal and contrast across the scanning range, allowing a more reproducible imaging protocol because it is not dependent on accurately setting the inversion time.^{65,66,67} Acute myocardial necrosis causes an increase in distribution volume due to membrane rupture of myocytes, resulting in an expanded ECV, which translates into a high gadolinium concentration, thus shortening T1 relaxation and hyperenhancement.⁶⁸ However, LGE technique may overestimate myocardial necrosis of about 10% in the very early phase when the volume of the infarcted tissue tends to increase due to other causes, such as hyperemia, edema and inflammation cells infiltration. Experimentally, the infarcted tissue reduces its volume of about three to four-fold between 4 and 28 days after infarction,⁶⁹ and clinical studies showed about a 40% decrease of infarcted tissue measured a mean of 7 days to 4 months after MI.⁷⁰ In patients with an acute MI, infarct transmural thickness decreases significantly between 1 and 7 days, being stable afterward. Therefore, infarct transmural thickness measured at 7 days is comparable with that measured at 1 year after MI.⁷¹ According to the authors, it is the dynamic and rapid shrinkage of the infarcted tissue to represent the major concern for the assessment of myocardial viability in the early postinfarction phase. Postcontrast imaging has also a great value for the depiction and quantification of microvascular obstruction and detection of intracavitary thrombi.^{68,72–74}

In recent years, several clinical studies have evaluated the prognostic value of CMR in patients with acute MI.^{75,76} These studies were mainly limited by the low number of patients included (214–738 patients), low event rate (range 19–52 events) occurring during short follow-up (mean duration 12 and 38 months). Eitel *et al.*⁷⁷ have shown that more than 70% of major adverse cardiovascular events occurred in patients with LV ejection fraction 47% or less, an infarct size at least 19% and microvascular obstruction at least 1.4% of LV mass. Based on C-statistic, infarct size and microvascular obstruction may provide an incremental prognostic value above clinical risk assessment and LV ejection fraction. At multivariate analysis, patients with microvascular obstruction at least 1.4% of LV mass had a 3.6-fold increased likelihood of experiencing an adverse event during 12-month follow-up. Recently, van Kranenburg *et al.*⁷⁸ published a meta-analysis on the prognostic value of CMR parameters in 1025 patients with acute ST-elevation myocardial infarction. Over a median follow-up of 12 months, microvascular obstruction and LV ejection

fraction 40% or less, but not an infarct size at least 25% of LV mass, were independent predictors of MACE (death, hospitalization for heart failure and reinfarction). Although these findings are attractive, it has to be kept in mind the several limitations inherent to meta-analysis, the short follow-up (median 12 months, interquartile range 4–21 months) and the rather wide time range (14 days) between the acute infarction and CMR as an inclusion criterion. Accordingly, further large, prospective multicenter studies with long-term follow-up and hard-clinical end points are warranted to prove the prognostic value of CMR parameters beyond the clinical-based risk stratification in patients with acute MI.

Finally, it is important to recognize the excellent diagnostic capacity of CMR in detecting possible mechanical complications in patients with MI: late rupture of LV free wall, pericardial complications (cardiac tamponade, pericardial effusion and acute pericarditis) and, less frequently, interventricular septal rupture and papillary muscle infarction/rupture. Moreover, CMR has excellent diagnostic accuracy for the detection of ventricular thrombosis and the infarction of the RV.⁷⁹ However, the use of CMR for the evaluation of mechanical complications of MI may be limited only to hemodynamically stable patients.

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