Cardiovascular Magnetic Resonance

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Cardiovascular magnetic resonance (CMR) creates images from atomic nuclei with uneven spin using radio waves in the presence of a magnetic field. Full details of the physical principles can be found elsewhere. For clinical purposes, MR is performed using hydrogen-1, which is abundant in water and fat. Radiofrequency waves excite the area of interest to create tissue magnetization that decays (relaxation) and after a short period is induced to release energy as a radio signal. These echoes are converted with Fourier transformation into images of spatially resolved radio signals. Relaxation is quantified in spatially orthogonal directions as T1 and T2, which allows tissue characterization to serve as a powerful clinical tool. A CMR scanner consists of a superconducting magnet, a radiofrequency transmitter and receiver connected to radio aerials, and gradient coils driven by powerful pulses of electricity to create transient magnetic fields. The imaging computer triggers to the ECG and runs scanning sequences that coordinate the complex processes. The spin-echo sequence yields static images with black blood, whereas the gradient-echo sequence usually acquires multiple images through the cardiac cycle that display cardiovascular function as cine loops. Preparation pulses can be used to display T1 or T2 contrast for tissue characterization. Fast and real-time sequences include fast low-angle shot, steady-state free-precession, spiral, and echo-planar imaging. Velocity and flow can be quantified with gradient-echo sequences with encoding of velocity in the signal phase.

CMR is extremely safe, which is unequivocally advantageous compared with x-rays, but special cautions apply. Ferromagnetic items become potentially dangerous projectiles in the scanner room. Although most metallic medical implants, including all prosthetic cardiac valves and coronary stents, are MR compatible, care is required with cerebrovascular clips. Pacemakers and defibrillators present problems, in particular related to wire heating, and are a contraindication for CMR, although specialist centers have described dedicated approaches for patients with pressing clinical circumstances, and approved MR compatible pacemakers are now available. The MR contrast agent gadolinium has proved extremely safe in tens of millions of patients. Recently, nephrogenic sclerosing fibrosis has been reported as a possible adverse event of the use of high doses in patients with severe renal impairment with glomerular filtration rate near zero. MR with a cyclic gadolinium is still used in renal failure because of the significant dangers of iodinated contrast agents.

The Society of Cardiovascular Magnetic Resonance and major cardiology societies have published guidelines in a number of important areas of clinical practice of CMR, which are useful reference material. They include credentialing, appropriateness criteria, training, imaging protocols, and reporting guidelines.

Volumes and Function

CMR measures ventricular volumes and mass using a simple acquisition of a 3-dimensional (3D) stack of contiguous short-axis cines with full biventricular coverage. Left ventricular (LV) and right ventricular (RV) volume and mass are determined by planimetry for each slice and summed for the whole ventricle. Commercially available software can correct for valve plane movements during the cardiac cycle and measure the ventricular mass contribution from the papillary muscles and trabeculae. The high fidelity of the ventricular volumes allows normalization of the measurements to body surface area, gender, and age. These data demonstrate that normalization is important for confident diagnosis of conditions such as early dilated cardiomyopathy (DCM) or LV hypertrophy. CMR is significantly more accurate and reproducible than other techniques, which makes it the technique of choice for longitudinal study of patients over time and for reducing sample size for drug studies. Diastolic ventricular function can be routinely assessed by CMR, although echocardiography is often preferred for this purpose.

Great Vessels

CMR is widely used for imaging great-vessel disease. Steady-state free-precession cines, with planes optimized to the location and orientation of the pathology, will often depict the lesion directly (stenosis) or signal loss resulting from phase incoherence (abnormal communication). Three-dimensional angiography with gadolinium enhancement may show the lesion more clearly in high resolution, but it also shows any associated pathology (collaterals). Velocity mapping provides reliable quantification in any direction of jet flow velocity and blood flow.
Valvular Heart Disease

CMR has a significant role in valve disease, but it usually acts as a second-line technique to assist when echocardiography with Doppler has proved problematic because of limited acoustic access, highly eccentric jets, or the need for quantification. Cine CMR is used to study valvular morphology and function. Valve leaflets are easily seen, especially with steady-state free-precession cines, allowing visualization of thickening and motion. Turbulent flow from stenosis or regurgitation causes signal loss within the jet, the size and extension of which are semiquantitative measures of lesion severity. Direct valve orifice planimetry has proved to be reliable by CMR, and imaging with thin, adjacent slices through the stenotic valve is performed. Valve stenosis can be quantified from blood flow velocity (m/s) in coherent jets using phase-contrast velocity mapping with optimized alignment guided by an iterative imaging approach with parallel and perpendicular cine acquisitions. The quantification of valve regurgitation is a strength of CMR because of its capability of measuring accurate ventricular stroke volumes from multislice ventricular planimetry and comparing this with the measurement of great vessel flow from velocity mapping. In isolated valve regurgitation, the regurgitant volume and fraction are simply calculated from the difference in LV and RV stroke volumes. Thus, isolated mitral regurgitation and aortic regurgitation result in an excess LV stroke volume, whereas tricuspid regurgitation and pulmonary regurgitation result in an excess RV stroke volume. For mixed regurgitant valve lesions, the integration of flow over time in a great vessel close to the ventriculoarterial valve provides the forward stroke volume, and further analysis allows the direct determination of antegrade and retrograde flow volumes for a direct assessment of the ventriculoarterial valve regurgitation. Comparison of flow measurements from both the pulmonary artery and aorta with RV and LV stroke volumes measured from the multislice ventricular planimetry technique enables a full quantitative solution for multivalve regurgitation, with discrimination of the regurgitant volume for all 4 individual valves.

Aortic regurgitation is quantified from the excess LV stroke volume measured by ventricular planimetry. An alternative is to measure the retrograde diastolic flow, with the flow measurement taken immediately above the valve and below the coronary ostia to limit errors from coronary flow. Errors can occur in patients with a dilated aortic root because of through-plane motion, and a slice tracking technique has been developed to minimize this problem. The regurgitant fraction is obtained by dividing the retrograde flow volume by the antegrade flow. When echocardiography proves inadequate, aortic stenosis can be assessed by calculation of the aortic valve jet gradient on phase-velocity mapping or by direct planimetry of the valve area. With similar techniques, CMR is valuable in pulmonary valve regurgitation and stenosis, especially in the setting of congenital heart disease, with additional information available on the valvular or outflow tract abnormalities, the right heart, and the pulmonary circulation.

Multislice contiguous cines can be used for a full evaluation of mitral valve morphology and identification of regurgitation at scallops for surgical repair. Quantification of mitral regurgitation is commonly assessed from the difference in ventricular stroke volumes, but other approaches have been used, including the difference between forward aortic flow and LV stroke volume or mitral inflow volume, and they may be more reliable. CMR has proved useful clinically when the mitral regurgitant jet or jets are highly eccentric, which can preclude adequate assessment by echocardiography. For mitral stenosis assessment, both in-plane and through-plane velocity measurements can be used, but multiple parallel planes are again required to iterate to the correct alignment to the jet. For the tricuspid valve, CMR is usually second line to echocardiography, and Doppler is superior for the measurement of trace tricuspid regurgitation for the estimation of pulmonary artery pressure. CMR is used in Ebstein anomaly in which valvular displacement and malformation are well depicted and regurgitation RV function can be measured.

CMR can be performed safely in all prosthetic valves, although focal artifacts that can obscure small jets occur. Endocarditis lesions are best visualized by echocardiography because of erratic motion, but CMR is suitable for the identification of paravalvular abscesses.

Congenital Heart Disease

CMR is widely used to assess congenital heart disease, and when used in concert with echocardiography, the need for invasive assessment has been significantly reduced. CMR is
particularly useful for the safe, accurate, and reproducible quantification of the left-to-right shunting of blood that occurs frequently in congenital heart defects such as atrial or ventricular septal defects, patent ductus arteriosus, aortopulmonary window, and partial or total anomalous pulmonary venous return. Flow and velocity mapping is also used extensively to assess local flow in shunts after surgical repair when echocardiography may be problematic. Other valuable characteristics of CMR include the wide field of view, good reproducibility, absence of radiation for multiple serial scans, and availability of gadolinium angiography for 3D representation of the great vessels and complex anatomy. Echocardiography is usually the technique of choice in young children, but CMR becomes more valuable for older children and adults, in complex pathology, and after surgery when echocardiography may be difficult because of the presence of scar tissue, rib and chest deformity, and interposed lung tissue.

Arteries, Veins, and Conduits
CMR is considered the ideal imaging technique for the visualization of native and repaired aortic coarctation, which usually occurs as a discrete stenosis of the proximal descending aorta just opposite the insertion of the ductus arteriosus and may be associated with poststenotic dilation. Peak jet velocity across the coarctation as measured by CMR provides a useful estimate of the pressure gradient. The collateral circulation can be quantified by comparing flow proximal and distal to the coarctation and is used to determine treatment success. CMR is also ideal for long-term follow-up of coarctation repair to identify complications such as recoarctation and aneurysm. Other rarer abnormalities of the aorta such as double aortic arch are easily identified and can be followed up. Patent ductus arteriosus in newborns is assessed by echocardiography, but CMR is more reliable in older patients. CMR is valuable in abnormalities of the pulmonary circulation (both before and after repair) such as anomalies, reduced pulmonary artery flow, and systemic-to-pulmonary collaterals. Measurement of relative flow in the right and left pulmonary arteries can be useful. Systemic venous abnormalities such as left superior vena cava or interrupted inferior vena cava can easily be visualized. CMR is valuable and usually superior to echocardiography for the assessment of the pulmonary veins and any anomalies, with flow measurements allowing calculation of the shunt fraction. CMR is often superior to echocardiography after surgical repair, especially for conduits and for the RV, which is often overloaded because it functions as the systemic ventricle or because of pulmonary insufficiency. In transposition of the great arteries, both ventriculoarterial and atrioventricular discordance can be readily identified from spin-echo and cine imaging to characterize the complete or corrected forms. Most adult patients will have had early repair with either an atrium-level switch or, more recently, an arterial switch. CMR in atrial switch patients can identify systemic RV failure, systemic atrioventricular valve regurgitation, and baffle obstruction using multiple cines and flow maps. Persistent truncus arteriosus results from failure of the embryonic truncus to divide into a separate aorta and pulmonary artery, and all 3 types are well depicted by CMR, including the origin, size, and location of the pulmonary arteries, as well as conduits used in repair.

Cardiac Chambers
CMR identifies the atria and ventricles using characteristic morphological features, and in concert with anatomic features of the bronchus and spleen, CMR is accurate in the assignment of situs and isomerism. Atrial septal defect is well visualized with echocardiography, but CMR may be useful in older patients or those with limited acoustic windows and is preferable for quantifying the shunt and the effects on RV function. The position of the atrial septal defect relative to the atrioventricular valve and pulmonary veins can be established, and associated pulmonary venous anomalies can be shown. The size and multiplicity of the defect(s) can be demonstrated using phase-contrast cine imaging with en face views in the right atrium, which is useful for planning of percutaneous closure devices. Ventricular septal defects are seen by CMR cine signal loss in the jet, but CMR is superior to echocardiography only in complex lesions. Complex ventriculoarterial anomalies such as tetralogy of Fallot or univentricular hearts are well depicted with CMR, allowing quantification of the morphological and hemodynamic consequences. In tetralogy of Fallot, the presentation may vary from pulmonary atresia and multiple aortopulmonary collateral vessels to only mild pulmonary stenosis. In adults, surgical repair will usually have been undertaken, often with a palliative procedure to augment pulmonary blood flow with later definitive repair. CMR can assess the degree of pulmonary regurgitation and any recurrent pulmonary stenosis, RV dilatation or hypertrophy, tricuspid regurgitation, and any associated central pulmonary artery stenosis. The presence of myocardial fibrosis has been linked to impaired exercise capacity and adverse outcomes. Double-outlet right ventricle is an abnormal ventriculoarterial connection with more than half of both aorta and pulmonary artery arising from the morphological RV. CMR is useful for characterizing the relationship between ventricular septal defects and the great vessels and to assess the pulmonary arteries and any associated pulmonary stenosis or other anomaly, which assists in operative planning. CMR is also useful in single ventricles for defining the atrioventricular and ventriculoarterial connections, characterizing the interventricular communication, and defining the connections of systemic and pulmonary veins and arteries.

Valves and Atrioventricular Concordance
Echocardiography is usually preferred for depicting valve morphology, but CMR is useful for assessing valve morphology in some cases and for quantifying regurgitation and RV size and function. Valve abnormalities may be assessed by CMR, along with the associated effects on cardiac chambers, including valve atresia, Ebstein anomaly, bicuspid semilunar valve, single atrioventricular valve, and congenital mitral valve malformations. Assessment of pulmonary regurgitation after repair of tetralogy of Fallot is clinically useful in guiding the timing of valve replacement.
Ischemic Heart Disease

Myocardial Ischemia

Myocardial ischemia can be assessed by CMR from stress myocardial perfusion imaging or stress ventriculography, and both are in use clinically as alternatives to myocardial perfusion single-photon emission computed tomography (SPECT) or stress echocardiography, respectively. Stress CMR ventriculography is a relatively mature technique, with reasonably sized single-center studies showing its diagnostic accuracy and prognostic capability. Stress perfusion CMR has been assessed for technical factors in relation to diagnostic accuracy in the multicenter setting, albeit with relatively modest sample sizes. Clinical results are highly encouraging, with the multivendor Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary Artery Disease Trial (MR-IMPACT) study of 241 patients showing perfusion CMR to be either equivalent or superior to perfusion SPECT. Prognostic studies are still limited, however, and the imaging technology will mature further. The relative strengths of the 2 techniques depend on many factors, including the clinical scenario and local expertise, but there is a general perception in the CMR community that perfusion imaging will develop into an important and versatile clinical tool.

Perfusion CMR is performed at rest and again during adenosine vasodilator stress using a first-pass technique with fast intravenous injection of a gadolinium contrast agent. The myocardial signal increases in well-perfused myocardium, but this increase is impaired in regions of myocardial ischemia. Three short-axis slices are usually imaged per cardiac cycle, allowing 16 myocardial segments to be analyzed, excluding the apical cap. Ischemic myocardium in coronary disease affects the subendocardium, and the transmural extension defines the severity of the ischemia. The resting study is needed only to identify endocardial artifacts and to quantify perfusion (absolute perfusion \[\text{mL} \cdot \text{g}^{-1} \cdot \text{min}^{-1}\]) and perfusion reserve. Validation of perfusion CMR by microspheres shows a good linear relationship without the roll-off at high perfusion that is typical of the nuclear tracers, which suggests that perfusion CMR may be more sensitive for identifying moderate coronary stenosis. The optimal CMR perfusion sequence is not yet fully defined. The commercially available ultrafast sequences are being enhanced with parallel imaging, which improves resolution and reduces artifacts. Potential developments include a new tracer that binds to myocardial collagen and allows perfusion CMR to be undertaken in the equilibrium phase, greatly simplifying the imaging; improved image quality at 3 Tesla; and noncontrast agent perfusion techniques such as T2* Blood Oxygen Level Dependent (BOLD). Perfusion CMR for diagnosis performs well against invasive coronary angiography or positron emission tomography as the gold standard, and the absence of perfusion abnormalities carries a good prognosis. Perfusion CMR is also used to investigate microvascular dysfunction in syndrome X and hypertrophic cardiomyopathy (HCM).

Stress CMR ventriculography uses incremental doses of dobutamine with additional atropine when needed to reach the target heart rate, is safe, and is operationally similar to stress echocardiography. Induction of new regional wall motion abnormalities is assessed on short- and long-axis cine images acquired at each stage of stress. Diagnostic accuracy is good compared with invasive angiography and superior to echocardiography if acoustic access is suboptimal. Low cardiac event rates are associated with normal stress CMR, and increasing risk is seen with increasing extent of ischemia. Stress CMR can be combined with tagging to quantify myocardial strain, which improves diagnostic accuracy, reduces observer variability, and can be combined with perfusion imaging.

Myocardial Infarction

Myocardial infarction is detected with very high sensitivity by imaging some 10 minutes after the injection of gadolinium contrast. Kinetic and volume of distribution effects result in high gadolinium concentration in abnormal myocardium, which is bright on T1-weighted CMR. This technique of late gadolinium enhancement (LGE) yields high-resolution images of infarction (acute and chronic), fibrosis, and infiltration that have excellent longitudinal reproducibility. LGE has been shown to have high accuracy for the detection of infarction in both the acute and chronic setting in a substantial multicenter trial of 566 patients. LGE has revolutionized the study of infarctions because CMR is considerably more sensitive than perfusion SPECT and wall motion abnormality. Thus, previously unrecognized infarctions have been shown to have important prognostic importance over and above conventional risk measures in patients with clinical suspicion of coronary disease but no previous infarction; microinfarction after complex percutaneous coronary interventions can be demonstrated; and confident exclusion of infarction can be made in acute coronary syndromes. Quantification of infarct size has also shown in vivo the shrinkage of acute infarcts over time in both volume and transmural extent.

However, considerable additional information is available through the use of supplementary techniques in acute infarction. Some acute infarcts have a central dark zone with gadolinium enhancement, which represents microvascular obstruction, where gadolinium penetration is very slow, being limited by diffusion. This is best imaged by early gadolinium enhancement imaging at 1 to 2 minutes after injection. Infarcts with microvascular obstruction have a poorer prognosis, which is a predictor that is independent of ejection fraction. Microvascular obstruction slowly shrinks over weeks and is not seen in chronic infarctions. T2-weighted CMR is used in acute infarction to identify cellular edema, which allows clear differentiation of acute from chronic infarction and reversible from irreversible ischemia. Edema imaging also allows identification of the area at risk in acute infarction, and by subtraction of the infarct size determined by LGE, the area of salvaged myocardium can be measured. CMR has been validated against SPECT to assess the area at risk. Because the high signal on T2 edema CMR is persistent after the reversible ischemic insult, this can be measured hours or days after a primary angioplasty, which makes research studies of adjuvant techniques for revascularization much easier than the previous gold standard technique of immediate radioactive technetium injection at pre-
sensation with SPECT, which needs to be performed within 6 hours. T2* CMR has been shown to identify myocardial hemorrhage in acute infarction. Early gadolinium enhancement is also superior to echocardiography for the identification of ventricular thrombi, which appear as dark filling defects on the endocardial surface of enhanced infarcts. Myocardial fiber microstructure remodeling after infarction can also be studied with diffusion tensor tractography.

CMR has been used in patients presenting with possible acute coronary syndrome to image resting wall motion, resting perfusion, and infarction enhancement to determine whether invasive investigation is required. The sensitivity and specificity for detecting acute coronary syndrome were 84% and 85% for CMR when performed within 12 hours of presentation and was superior to ECG, troponin, and Thrombolysis in Myocardial Infarction risk score. Additional T2-weighted imaging for edema associated with only reversible injury may be helpful in the acute setting in identifying patients requiring invasive coronary angiography. Low-risk patients may be assessed by stress testing, and CMR has good diagnostic accuracy for detecting >70% stenosis. Normal adenosine perfusion CMR in the emergency room identifies patients without subsequent diagnosis of coronary artery disease who have a good prognosis. A majority of patients presenting with acute chest pain with elevated troponin but normal coronary arteries can be shown to have an alternative diagnosis by CMR, the most common cause being myocarditis.

Myocardial Viability

Using CMR to predict recovery of function after revascularization has been achieved with both LGE and low-dose dobutamine stress ventriculography. The transmural extent of LGE predicts the likelihood of recovery of regional function, and when >20% of the myocardium is hibernating, improvement of ejection fraction is likely. However, low-dose dobutamine stress CMR may be more sensitive. LGE may show nontransmural scar that fails to recover function after adequate revascularization. This may relate to incomplete revascularization, structural hibernation requiring a longer-than-expected recovery period, or limitation of functional recovery to wall motion improvement which is apparent only at stress. Overall, LGE CMR has a negative predictive value of ≥90% of no functional recovery in segments with >50% transmural infarction and a positive predictive value of ≥80% of recovery in segments without infarction. Larger infarctions also predict a reduced likelihood of ejection fraction response to β-blockers in patients with heart failure.

Cardiomyopathy

Dilated Cardiomyopathy

The structural and functional abnormalities of both ventricles in established DCM are shown well by CMR, and changes over time or with treatment can be monitored serially because of high longitudinal reproducibility. However, in patients newly presenting with large heart, the main issue is differentiating the diagnosis of DCM from the sequelae of coronary artery disease. Many centers routinely perform coronary angiography as a gold standard, but it has significant limitations because of the inability to adequately characterize whether infarction has occurred (coronary stenosis often exists without downstream infarction, and infarction commonly occurs in relation to nonobstructive plaques). LGE CMR is valuable as a noninvasive alternative. A study of patients labeled as having DCM who had normal coronary angiography showed no LGE in 59% and patchy or circumferential enhancement in the midwall in 28%, which established that myocardial infarction was not the cause of ventricular dysfunction. The final group of 13% of patients had LGE showing often extensive infarction, which suggested that these patients has been incorrectly assigned DCM after “normal” coronary angiography, probably because of coronary recanalization after infarction and untreated ventricular remodeling. The midwall LGE seen in DCM patients matches the fibrosis found at postmortem, is linked to diastolic dysfunction, and is an important predictor of major adverse cardiac events, including sustained ventricular tachycardia and sudden cardiac death. This predictive value appears to be independent of more conventional markers of risk such as ejection fraction. The amount of LGE also correlates with the likelihood of inducible ventricular tachycardia during electrophysiological testing. It has been shown with CMR spectroscopy that a low ratio of phosphocreatine to ATP can predict an adverse outcome.

Hypertrophic Cardiomyopathy

HCM is usually diagnosed by echocardiography with increased ventricular wall thickness in the absence of pressure overload. CMR also has a role in diagnosis because the comprehensive myocardial coverage is superior in identifying regional hypertrophy, particularly in the basal regions. Apical variants of HCM are also better identified by CMR. CMR can show the other features of HCM such as small cavity, dynamic resting function, RV involvement, outflow tract obstruction, and systolic anterior motion of the mitral valve and mitral regurgitation. The good discrimination of blood from myocardium allows accurate CMR measurements of not only wall thickness but also ventricular mass, which has been shown to be normal in 20% of patients with HCM phenotype and is a more sensitive marker of outcomes in HCM than maximal wall thickness. LGE CMR also has an important role in HCM in identifying myocardial replacement fibrosis. This may be limited to the superior and inferior insertion junctions of the RV (considered a benign finding) or can be extensive scarring. Scarring is typically, but not always, in the region of maximal wall thickness. There is an association between the extent of scarring and the development of the late dilated phase of HCM with heart failure, and in patients >40 years of age, there is an increased prevalence of markers of sudden death. The fibrosis may therefore affect both systolic and diastolic function and act as a focus for reentrant tachycardia. The link to arrhythmia has recently been confirmed and appears to be an independent predictor for new-onset atrial fibrillation. No data currently exist relating the use of LGE to guide defibrillator implantation. LGE is also used to assess the location and extent of therapeutic septal myocardial infarction. The accuracy of CMR in identifying HCM is helpful for the screening of relatives of probands.
Other CMR techniques are used in the assessment of HCM, although clinical utility remains to be established. Stress perfusion CMR shows microvascular dysfunction related to wall thickness and fibrosis and may be an early marker of disease\(^8^3\) and an adverse prognosis. CMR tagging shows abnormal strain, shear, and torsion in dysfunctional hypertrophy, which may be useful for differentiating HCM from athletic hypertrophy or hypertension. CMR spectroscopy of ATP shows a bioenergetic defect in HCM, suggesting that inefficient energy use may underlie the clinical manifestations of HCM.\(^8^4\) Fiber disarray may also be imaged directly by CMR with diffusion-weighted tractography; this may find diagnostic application in patients with borderline phenotype, particularly with confounding pathology such as hypertension.\(^8^5\)

**Fabry Disease and Amyloidosis**

About 4% of patients presenting with an HCM phenotype actually have Fabry disease,\(^8^6\) in which \(\alpha\)-galactosidase activity is reduced, causing accumulation of glycosphingolipid GB3. In many cases, CMR shows midwall LGE of the basal lateral wall,\(^8^7\) which is unusual for HCM and not typical for myocarditis. The cause for this distribution may be increased wall stress. CMR can assess the efficacy of enzyme replacement treatment.\(^8^8\) Other patients with hypertrophic heart have the restrictive cardiomyopathy amyloidosis, with diastolic dysfunction, ventricular hypertrophy, and interatrial septum thickening. The distinction from other forms of hypertrophy can be problematic in the early stages. Pericardial and pleural effusions are common in amyloidosis. However, LGE in amyloid infiltration is distinctive; it has a global subendocardial enhancement pattern that results from interstitial amyloid deposition in the endocardial layer.\(^8^9\) Patchy amyloid deposition is also seen. Another characteristic finding is a dark blood pool with LGE imaging, which is caused by abnormal gadolinium-handling kinetics. LGE had good diagnostic accuracy\(^9^0\) and predicts death; in 1 study, it was superior to other conventional predictors.\(^9^1\)

**Iron Overload (Siderotic) Cardiomyopathy**

Siderotic cardiomyopathy occurs mainly in transfusion-dependent patients such as those with thalassemia major. Heart failure from myocardial siderosis is the biggest cause of death in thalassemia\(^9^2\) because free labile iron damages cell membranes and impairs mitochondrial function. When the iron storage capacity is exceeded, micromagnetic particles of ferrithridite (hemosiderin) form that disturb the magnetic field and lower the CMR signal that can be measured using the T2* relaxation parameters.\(^9^3\) Normal myocardial T2* is 40 ms; the lower limit of normal is 20 ms.\(^9^3\) Myocardial T2* <10 ms indicates a high risk of toxic heart failure\(^9^4\) that can rapidly spiral into death and is superior to liver iron and serum ferritin in assessing prognosis.\(^9^4\) Studies show that the prevalence of myocardial siderosis is \(\approx 50\%\), which indicates that all thalassemia major patients require direct myocardial iron assessment for evaluation of risk.\(^9^5\) Asymptomatic LV dysfunction is common in thalassemia but is underdiagnosed because of the higher-than-normal ejection fraction and cardiac output caused by the chronic anemia. Decompensated heart failure is a medical emergency in myocardial siderosis, and immediate treatment with continuous intravenous deferoxamine is required.\(^9^6\) with later conversion to subcutaneous deferoxamine combined with deferiprone.\(^9^7\) In less severe myocardial siderosis, deferiprone monotherapy or combination therapy is effective.\(^9^8,9^9\) Using T2* CMR with tailored cardiac treatment has been associated with a 71% reduction in UK cardiac deaths.\(^9^2\)

**Arrhythmogenic RV Cardiomyopathy**

CMR has been widely used in arrhythmogenic RV cardiomyopathy because of good RV visualization, quantitative RV function analysis,\(^1^0^0\) and limitations of echocardiography as a result of the proximity to the sternum. Arrhythmogenic RV cardiomyopathy is now recognized as a disorder of intercellular connections called desmosomes, and many gene defects that affect desmosomal proteins such as desmplakln and plakoglobin are now known. Therefore, arrhythmogenic RV cardiomyopathy is now recognized as a disease of injury and consequent repair with fibrofatty replacement, with dominant expression in the RV presumably only because of lower structural strength. However, LV involvement is also well recognized, appearing in up to 25% of cases.\(^1^0^1\) Recent data show how imaging and plakoglobin protein expression from myocardial biopsy can be combined to augment diagnosis in arrhythmogenic RV cardiomyopathy.\(^1^0^2\)

CMR contributes to the identification of diagnostic criteria for arrhythmogenic RV cardiomyopathy such as morphological abnormality, regional wall motion abnormality, increased volumes (including progressions over time), and fibrofatty infiltration. Expert scan interpretation is needed, however, because of the wide range of normal RV findings, and specificity can be problematic in a population with a low incidence of disease. In particular, identification of fatty infiltration has high interobserver variability and can occur as a normal variant. Instead, LGE of the RV has been used to identify the fibrous replacement, but the thin RV wall makes this technique difficult. The best use of CMR is to ensure that evaluations are made in conjunction with recognized task force criteria. CMR is currently being evaluated to identify risk of sudden cardiac death.\(^1^0^3,1^0^4\)

**Myocarditis**

CMR is now established as the first-line imaging technique to diagnose myocarditis.\(^1^0^5\) Three CMR techniques are used. First, T1-weighted spin-echo myocardial signal may be increased in acute myocarditis 1 to 2 minutes after gadolinium injection, indicating hyperemia, and signal quantification of global myocardial enhancement relative to skeletal muscle may be increased.\(^1^0^6\) Second, T2-weighted spin-echo myocardial signal may be raised, indicating myocardial edema. Third, LGE may be present, especially in the epicardial portion of the lateral wall or septum, indicating myocardial necrosis.\(^1^0^7\) The location of LGE predicted the viral pathogen and can be used to guide myocardial biopsy for improved histological diagnosis. The extent of LGE and its presence in the septum are predictors of adverse long-term ventricular remodeling.\(^1^0^8\) Myocarditis has been shown to be a common differential diagnosis of patients presenting with acute chest pain but normal coronary arteries.\(^6^5\) These CMR techniques
used in myocarditis have also proved to be useful in the diagnosis of transplant rejection.109

Other Cardiomyopathy

Cardiac sarcoidosis is reported in \( \approx 25\% \) of autopsy hearts in sarcoid patients with extracardiac involvement. Endomyocardial biopsy has low accuracy resulting from sampling error because cardiac involvement is usually patchy and affects mainly the LV. Changes in the ECG can be indicative. LGE CMR shows myocardial abnormalities in presumed areas of fibrosis in sarcoidosis; they are typically distributed in a noncoronary manner and may be punched out or bizarre.110 T2-weighted CMR may identify areas of active myocardial inflammation. Some work suggests that CMR may have value as an indication for steroid treatment.111 Noncompaction results from incomplete maturation in embryonic endomyocardial development with persistence of spongy myocardium. Marked trabeculation typically affects the lateral wall and apex, with deep intertrabecular recesses and a thin epicardial layer. Progressive ventricular dysfunction, arrhythmias, and systemic embolism may occur. The diagnosis can be made by echocardiography, but CMR shows the abnormality well with comprehensive ventricular coverage if there is limited involvement, and LGE can demonstrate underlying fibrosis.112 A ratio of noncompacted to compacted myocardial of \( > 2.3 \) in diastole is used as a quantitative criterion for diagnosis.112 CMR also shows LGE in Chaga disease, which is endemic in some parts of the world and a major cause of morbidity and mortality.113

Coronary Arteries

CMR is widely used for visualizing the lumen of arteries and veins throughout the body, but the technical difficulties of imaging the small, tortuous coronary vessels on the curved surface of the moving heart make robust coronary imaging difficult.114 Invasive coronary angiography has higher spatio-temporal resolution and currently is the only means to place coronary stents. A number of special CMR techniques are used to mitigate the problems: Imaging is performed when diastole limits cardiac motion; a 3D volume captures tortuous vessels; respiratory gating with navigator echoes reduces breathing-induced blurring; parallel imaging accelerates acquisition; and contrast agent or prepulses improve coronary-to-background contrast. Whole-heart sequences are promising, but coronary CMR currently cannot replace invasive coronary angiography, and its overall diagnostic performance is inferior to computed tomography.115 Coronary CMR has proven clinical utility in congenital coronary anomalies, however,116 because the technique easily resolves the origin and proximal coronary course in relation to the aortic root and pulmonary trunk. CMR is the first-line choice in children and young adults in whom x-rays should be avoided when possible and may be used in the follow-up of coronary aneurysms in Kawasaki disease.117

Other Conditions

Cardiac Tumors

Intracardiac masses are uncommon, and their diagnosis can be challenging. Although other imaging is usually performed first, CMR often yields significant additional value in characterizing the tissue and detailing the relation of the mass with surrounding tissue and organs.118 Visualization of a mass is first performed with simple spin-echo and cine sequences. Tissue characterization can be approached with a number of additional sequences: T1- and T2-weighted spin-echo imaging is used to identify melanoma metastasis (high T1 signal because melanin shortens T1)119 and fibroelastoma (typically located on the aortic valve with high T2 signal);120 fat suppression is used to identify atrial lipomatous hypertrophy and lipoma; first-pass perfusion imaging identifies increased vascularity in benign tumors (hemangioma, myxoma) and in malignant tumors, especially angiosarcoma in the anterior atrioventricular groove; early hypoenhancement at 1 to 2 minutes after injection of gadolinium identifies thrombus;121; and late enhancement at 10 minutes after gadolinium shows expanded interstitial space in fibroma. Other important diagnostic features include the shape, location, and containment of the mass, particularly whether tumor extension or invasion of tissue planes has occurred. Malignant tumors often have typical features with associated findings such as pleural or pericardial effusion. Another important role of CMR is the identification of normal variants, which can be mistaken for tumors, including false tendons, persistent venous valves, and the crista terminalis.

Pericardium

CMR shows the pericardium with good resolution, usually as a thin dark line over the heart of \( < 4 \) mm, although the pericardium can show up as the 2 visceral and parietal layers if pericardial fluid is present. CMR is useful in a wide range of pericardial abnormality.122 Pericardial thickness can be visualized over the entire heart, which offers advantages over echocardiography, and therefore is useful for showing total or partial absence of the pericardium, which is diagnosed by the unusual position of the heart and absent pericardial layers. CT is superior for identifying pericardial calcification and may yield better image quality in sick patients with dyspnea and arrhythmias. The pericardial thickness is very often increased in constriction. The diagnosis of constriction is difficult to make if this cannot be demonstrated, but constriction can rarely occur without thickening, or localized thickening may be missed. In addition, pericardial thickening does not always indicate constriction. Therefore, it is always important to demonstrate the physiological sequelae of constriction, which is done with real-time short-axis cine CMR during respiration. During inspiration, intrathoracic pressure falls, increasing venous return to the right ventricle; in constriction, this causes the interventricular septum to bulge into the left ventricle. This simple technique is effective and very useful clinically. Pericardial fluid, depicted as a high-signal-intensity space between the pericardial layers, is reliably detected. Clinical experience suggests that CMR is superior to echocardiography in this regard, especially over the inferior wall. Tamponade resulting from pericardial fluid is readily recognized with diastolic chamber collapse. Rare causation of tamponade with fat in egregious atrial lipomatous hypertrophy can be diagnosed with fat-suppression sequences. Gadolinium enhancement of acutely inflamed
pericardium is useful diagnostically in pericarditis such as Dressler syndrome because the pericardium becomes bright. LGE imaging in pericarditis may show myocardial involvement of the underlying subepicardium with patchy necrosis. Pericardial cysts are identified from their typical location in the pericardiophrenic angle, encapsulation, and characteristically high T2 signal with intermediate T1 signal. Recently, CMR has been used to quantify pericardial fat as a risk factor for coronary disease and its relation to other fat stores.123

Future Clinical Developments in CMR

Atherosclerosis

CMR is used routinely to assess the luminal consequences of atherosclerosis, but there is considerable interest in direct assessment of the arterial wall structure and function. Most work has been performed in the carotid artery because of its superficial position, but coronary imaging has also been attempted at lower resolution. Arterial sclerosis can be assessed by measuring the arterial wall volume, which acts as a useful measure of atheroma burden. Multiple contiguous slices of the carotid artery are acquired above and below the bifurcation with 2D or 3D techniques, and the wall volume in a single slice is simply obtained from the difference between the luminal and adventitial boundaries. This is summed over all slices to obtain the total vessel volume. However, this varies according to body size, and for comparisons between patients, the total wall volume is normalized to the outer wall volume, yielding the ratio of wall to outer wall. In normal subjects, this ratio and the wall volume increase with age,124 and they are increased in atherosclerosis. CMR measurement of wall volume is reproducible, which makes it useful for demonstrating atherosclerosis regression with treatments such as statin.125 Multispectral CMR is also used to characterize arterial plaque using, in particular, proton density and T1- and T2-weighted sequences.126 The known plaque characteristics associated with vulnerability and plaque rupture are the presence of lipid pool, the thickness of the fibrous cap, and plaque inflammation; these features can all be assessed by CMR. Lipid pools have low signal on T2-weighted images and can be detected with novel fluorine-based contrast agents.127 The fibrous cap is visualized as a continuous line by CMR. Lipid pools have low signal on T2-weighted images and can be detected with novel fluorine-based contrast agents.128 Plaque inflammation can be assessed with iron oxide particles ingested by activated macrophages in vulnerable plaques, causing identifiable MR signal loss, and this macrophage activity can be reduced through statin treatment.129 Thrombus in the plaque or on the luminal surface shows up as a high signal in T1 imaging because of paramagnetic enhancement effects from products of hemoglobin breakdown. T2* plaque imaging shows intraplaque iron content and has been linked to outcome.130 CMR can also image coronary plaque, and arterial remodeling has been shown.131

Arterial Function

CMR can measure endothelial function with flow-mediated dilation (endothelium dependent) and glyceryl trinitrate (endothelium independent).132 CMR assesses changes in the arterial area, which has advantages over ultrasound measurements of arterial diameter, especially in noncircular vessels. Validation studies in humans suggest that CMR has improved reproducibility, which reduces sample sizes for trials.132 Endothelial dysfunction has been demonstrated by CMR in smokers and in patients with transfusional iron loading, which normalizes with iron chelation treatment. Coronary endothelial function can also be assessed by CMR with high-resolution cross-sectional coronary imaging in response to glyceryl trinitrate vasodilation.133 CMR can assess arterial function by measuring aortic compliance and pulse-wave velocity, which become abnormal in early atherosclerosis and predict cardiac events.

Electrophysiology

The interface between CMR and electrophysiology has advanced significantly in recent years.134 The 2 main areas of advancement have been the prediction of arrhythmia related to LGE and the assessment of patients before and after atrial fibrillation ablation. In coronary disease, the size of scar assessed by LGE is related to the risk of future ventricular tachycardia and is a better predictor than ejection fraction.135 Further work showed that the size of the gray zone of admixed viable and fibrotic tissue at the border zone of infarction is also a powerful predictor of ventricular tachycardia.136 or defibrillator shocks.137 Recently, myocyte fiber tracking with diffusion tensor CMR has shown fiber remodeling in the epicardial viable rim of infarctions with nodes of orthogonal myofiber intersection or contact, which are potential sources of arrhythmia in this region.138 In cardiomyopathy, the presence of LGE has also been linked to outcomes. In DCM, midwall LGE predicted sudden cardiac death and ventricular tachycardia and was superior to ejection fraction,71 findings that have now been replicated.72,73 LGE in DCM may be useful in planning LV ablation.139 In HCM, LGE is also associated with arrhythmias.80,81,140 CMR has started to become established in the management of atrial fibrillation. Pulmonary vein and left atrial anatomy are shown well by CMR and can be merged into the mapping systems for improved guidance for ablation.141 The extent of left atrial scarring shown by LGE before ablation predicts the recurrence of atrial fibrillation after ablation.142 Recurrence is also predicted by incomplete isolation of pulmonary veins shown by left atrial LGE,143 suggesting that this technique may prove useful for periprocedural assessment of patients after ablation.

Cardiac Resynchronization Therapy

Cardiac resynchronization therapy improves LV function and outcomes in heart failure patients with dyssynchrony. The accurate prediction of which patients will respond to pacing, however, remains problematic, and new CMR methods show promise in this regard. The presence of inferolateral LV scar shown by LGE is an important predictor of failure of clinical response to cardiac resynchronization therapy and adverse outcomes,144 as is the overall LV scar burden.145,146 Location of the LV pacing lead in the coronary sinus can be optimized by CMR of the coronary venous system.147 Novel CMR-based measurements of dysynchrony have been developed,148 and the tissue synchronization index has been shown...
to be an independent predictor of mortality and morbidity after cardiac resynchronization therapy. The addition of LGE to dysynchronous assessment improves the predictive value of CMR.

Interventional CMR
There has been substantial interest in the development of invasive CMR in which specially developed MR-compatible devices are used to catheterize patients and to perform interventions. The clinical advantages include visualization of the soft tissues during interventions, online CMR assessment of the procedural success, and reduced x-ray exposure. Clinical indications currently remain limited, but procedures in children are the most likely to emerge first. Other clinical applications may be seen in electrophysiology, valve replacement, and accurate placement of myocardial stem-cell injections for myocardial regeneration.

Novel Contrast Agents
The value of the conventional extracellular gadolinium contrast agents has been enormous for CMR over the last decade. However, contrast agents with high specificity for targeted epitopes are under development. Several approaches have been made, including highly flexible constructs linked to F(ab') fragments carrying high gadolinium loads and labeled short peptides found ex vivo to bind to a target protein. Complex nanoparticles with tunable magnetic properties have been developed that might allow MR of multiple agents with simultaneous color discrimination of different targets. Targeted molecules may also permit new solutions to established techniques such as a recently described agent targeted to collagen that allows high-resolution MR of myocardial perfusion, which has potential to replace the currently used and more technically demanding first-pass method. There seems to be little doubt that important developments can be expected in this field.

Hardware Developments
High-field CMR (3 T) has started entering clinical practice because of its increased signal-to-noise ratio, which results in improved spatial or temporal resolution, and has useful application for perfusion imaging, angiography, and vascular wall imaging. However, the ECG is harder to acquire, artifacts are more common, and some restrictions are necessary to limit heating effects from the radiofrequency energy. Accelerated imaging with multichannel coils and sophisticated postprocessing techniques has allowed a substantial reduction in imaging time, which combines well with high-field CMR. Fundamental design changes to magnetic resonance scanners remain possible, and a recent development attracting interest is the use of traveling wave systems in which the radiowave transmitter is based outside the magnet bore. This generates a greater field of view, especially for high-field systems, and increases the effective bore size, which can be used to alleviate claustrophobia and lower magnet price.

Conclusions
CMR continues to develop across a broad range of clinical applications, and much can be expected of this technology in the future. Assessment of the role of CMR relative to other cardiac imaging techniques remains difficult in this fast-paced technological landscape where little remains constant over the period of any comparative study, the results of which may be rendered obsolete by the time of publication. The challenge is to identify as clearly as possible the unique capabilities of each technique and to develop algorithms for their best integration into patient care pathways. Unnecessary duplication of investigations must be avoided for cost-effective healthcare delivery. Likewise, payers need to recognize that technological advances in imaging may result in more expensive but more effective investigations with longer-term healthcare benefits not seen at the time of imaging that are difficult to prove. Modern cardiology is becoming increasingly reliant on cardiac imaging, and this trend seems certain to continue.

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