Sudden Cardiac Death Substrate Imaged by Magnetic Resonance Imaging

From Investigational Tool to Clinical Applications

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Abstract—Sudden cardiac death (SCD) is a devastating event afflicting 350 000 Americans annually despite the availability of life-saving preventive therapy, the implantable cardioverter defibrillator. SCD prevention strategies are hampered by over-reliance on global left ventricular ejection fraction <35% as the most important criterion to determine implantable cardioverter defibrillator candidacy. Annually in the United States alone, this results in ≈130 000 implantable cardioverter defibrillator placements at a cost of >$3 billion but only a 5% incidence per year of appropriate firings. This approach further fails to identify individuals who experience the majority, as many as 80%, of SCD events, which occur in the setting of more preserved left ventricular ejection fraction. Better risk stratification is needed to improve care and should be guided by direct pathophysiologic markers of arrhythmic substrate, such as specific left ventricular structural abnormalities. There is an increasing body of literature to support the prognostic value of cardiac magnetic resonance imaging with late gadolinium enhancement in phenotyping the left ventricular to identify those at highest risk for SCD. Cardiac magnetic resonance has unparalleled tissue characterization ability and provides exquisite detail about myocardial structure and composition, abnormalities of which form the direct, pathophysiologic substrate for SCD. Here, we review the evolution and the current state of cardiac magnetic resonance for imaging the arrhythmic substrate, both as a research tool and for clinical applications. **(*Circ Cardiovasc Imaging*. 2017;10:e005461. DOI: 10.1161/CIRCIMAGING.116.005461.)**

Key Words: arrhythmias, cardiac ■ cardiomyopathies ■ death, sudden, cardiac ■ fibrosis ■ magnetic resonance imaging ■ tachycardia, ventricular ■ ventricular dysfunction, left

Sudden cardiac death (SCD) remains a significant public healthcare burden.[1] Estimated potential years of life lost because of SCD approach 2 million in men and 1.3 million in women and often strikes in the prime of life.[2] Significant progress in medical and device therapy has improved treatment of the precursors of SCD, coronary heart disease, and heart failure (HF). Clinical guideline recommendations emphasize identification of candidates with cardiomyopathy for appropriateness of primary prevention implantable cardioverter defibrillators (ICDs). Nonetheless, despite declines in overall cardiovascular deaths, there remains a disproportionately high contribution from SCD, rates of which exceed all noncardiac deaths except overall cancer and accidents.[2] SCD prevention is limited by the lack of robust approaches to identify patients at the highest risk and distinguish them from those who will not benefit from the costly therapy. Current practice guidelines for selecting candidates for ICD therapy for the primary prevention of SCD rely on left ventricular ejection fraction (LVEF) <30% to 35% as the sole LV structural abnormality.[3] LVEF, however, is an inadequate surrogate of the underlying myocardial phenotype predisposing to SCD and thus is insensitive and nonspecific.[4] The same LVEF can represent multiple cardiomyopathic derangements. Those with LVEF <35% account for <20% of all SCD events.[4] No LVEF cutoff discriminates well between sudden and nonsudden modes of cardiac death.[4] In fact, LVEF is indirectly related to mechanisms of arrhythmia and subject to considerable spontaneous variability.[4–6] A 2010 workshop highlighted this predicament and recommended that research should assess new approaches that may provide incremental information on SCD risk beyond LVEF, including new imaging methods of cardiac structure and physiology.[1] It is increasingly apparent that cardiac magnetic resonance imaging (CMR) is particularly well suited as the imaging modality of choice for SCD risk stratification, particularly compared with other modalities (Table 1).

LVEF Quantification by CMR and Impact on Decision Making

Although an LVEF <30% to 35% determines eligibility for the primary prevention ICD placement, current clinical guidelines do not specify by which imaging modality to measure LVEF. Echocardiography is the most widely used technique, both clinically and in the randomized ICD trials that inform current practice guidelines. No previous ICD trials included CMR.

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Table 1. CMR vs Other Imaging Modalities for SCD Risk Stratification

Echocardiography
Uses
Identify structural or functional cardiac abnormalities associated with increased SCD risk
Strengths
No radiation
Widely available and accessible
High temporal resolution
Relatively low cost (Medicare global payment ≈$230)
Weaknesses
Image quality highly dependent on patient factors and technician skill
Less reproducible measurements
Greater dependence on subjective assessment of LVEF
Minimal role in myocardial tissue characterization
Cardiac blood pool imaging (multigated acquisition scan)
Uses
Determination of myocardial function
Strengths
Accurate and reproducible assessment of heart function
High temporal resolution
No contraindications for indwelling devices
Imaging time <30 min
Weaknesses
Radiation exposure (≈8–12 mSv)
Costly (Medicare global payment ≈$441)
No assessment of myocardial tissue characteristics
Limited assessment of cardiac anatomy and regional wall motion abnormalities
SPECT
Uses
^{123}I-MIBG can identify cardiac autonomic innervation patterns associated with increased SCD risk
SPECT can assess myocardial viability and ischemia
Strengths
Assessment of underlying molecular, metabolic, or reversible ischemic processes predisposing to arrhythmias
Widely available
Limitations
Radiation exposure (≈11–22 mSv)
Poor spatial resolution
Prolonged imaging protocol
Very costly (Medicare global payment ≈$1108)
Positron emission tomography
Uses
Assessment of myocardial viability and ischemia
Strengths
Assessment of underlying molecular, metabolic, or reversible ischemic processes predisposing to arrhythmias
Higher spatial and temporal resolution compared to SPECT
Limitations
Radiation exposure (≈5–7 mSv)
Reduced spatial resolution compared to CMR
Very costly (Medicare global payment ≈$1285)
Computed tomography
Uses
Assessment of scar and ischemia
Strengths
High spatial resolution
Short imaging time
Weaknesses
Requires iodinated contrast
Radiation exposure (3–12 mSv)
Reduced temporal resolution for assessment of cardiac function
Costly (Medicare global payment ≈$420)
CMR
Uses
Identify structural or functional cardiac abnormalities associated with increased SCD risk
Strengths
No radiation
Accurate and reproducible assessment of structure, function, and ischemia
High spatial resolution
Exquisite myocardial tissue characterization capability
Weaknesses
Technically demanding and labor intensive for technologist, patient, and physician
Image quality can be limited by arrhythmias or patient noncompliance
Requires multiple breathholds and patient compliance
Limited/contraindicated for patients with indwelling implantable devices or ferromagnetic foreign bodies
Limited in very obese patients and those with claustrophobia
Potential for gadolinium contrast toxicity and adverse reactions
Costly (Medicare global payment ≈$557)

CMR indicates cardiac magnetic resonance imaging; ^{123}I-mIBG, Iodine-123 metaiodobenzylguanidine scintigraphy; LVEF, left ventricular ejection fraction; SPECT, single photo emission tomography; and SCD, sudden cardiac death.

However, CMR is accepted as the modality of choice for LVEF assessment because of its high accuracy and reproducibility, particularly when compared with echocardiography. Multiple studies report modest agreement and variable biases

between LVEFs quantified by echocardiography and CMR.[7] At lower LVEF, echocardiography generally overestimates CMR LVEF by at least 3% to 5%,[7,8] which may impact ICD eligibility, most notably in the intermediate LVEF range, if threshold cutoffs are used interchangeably. At higher LVEFs, echo may underestimate CMR as highlighted by the differential normal LVEF ranges for the 2 modalities. For echo, normal LVEF ranges are 52% to 74%[9] compared with 57% to 77% for CMR (excluding papillary muscles from the LV cavity).[10] How these LVEF differences affect clinical outcomes remain undetermined but highlight the lack of interchangeability among imaging modalities and the need for further investigation of modality-specific thresholds.

CMR Assessment of Myocardial Scar and Scar Heterogeneity

Myocardial fibrosis is a major pathophysiologic determinant of arrhythmic propensity in both ischemic cardiomyopathy (ICM) and non-ICM (NICM). Myocardial injury causes extensive structural and functional cardiac remodeling with resultant myocardial loss, with or without compensatory myocyte hypertrophy, and replacement of the extracellular matrix with fibrosis.[11,12] The extent and architecture of fibrosis, even in the absence of contractile dysfunction, lead to electrophysiological derangements that increase propensity for ventricular arrhythmias and SCD caused by scar-related reentry.[13,14] It is increasingly recognized that scar heterogeneity within the myocardium is especially arrhythmogenic.[15–17] The intermingling of viable myocytes and collagen produces spatial heterogeneity and anisotropy leading to slow conduction, fixed and functional conduction block, enhanced excitability, and dispersion of refractoriness, all of which promote the development and propagation of reentrant ventricular tachyarrhythmias (Figure 1).[13,18–22] Hence, identifying and characterizing the underlying arrhythmogenic substrate of myocardial scar have great potential to improve SCD risk stratification.

CMR with late gadolinium enhancement (CMR-LGE) using segmented inversion-recovery acquisition techniques has unparalleled ability to characterize myocardial tissue composition. It is increasingly used to advance our understanding of the pathophysiology, diagnosis, and treatment of ventricular arrhythmias. A growing body of literature demonstrates the strong prognostic significance of CMR scar indices, including the presence of scar, scar transmurality, total scar extent, and extent of myocardial tissue heterogeneity (gray zone).

CMR in Chronic ICM: Pathophysiologic Correlates

CMR-LGE was first utilized to quantify acute myocardial infarct (MI) size. It is based on differential T1 shortening properties of gadolinium contrast and the increased contrast volume of distribution (extracellular volume [ECV] of gadolinium) from loss of cell membrane integrity that result in demarcation of bright, hyperenhanced necrotic tissue with elevated signal intensity (SI) and differentiation from unenhanced, dark-appearing normal myocardium. Similarly, in chronic infarction, myocyte loss and replacement by collagenous scar result in increased gadolinium ECV and delayed contrast washout kinetics leading to persist hyperenhancement when imaging is performed 15 to 20 minutes after contrast injection, hence the moniker, LGE (Figure 2). Total scar extent by CMR-LGE correlates closely with pathological quantification of irreversible myocardial injury at all stages of infarct evolution beyond the acute MI period (Figure 3).[23,24] Scar size predicts major adverse cardiovascular outcomes post-MI independently of LVEF and LV volumes.[25]

In addition to total scar extent, the complex architecture of MI contributes to reentrant forms of ventricular arrhythmogenesis. The interspersion of fibrotic areas with viable myocyte myocytes and heterogeneous spatial geometry of scar underlies potentially arrhythmogenic substrate.[26] Regions of densely fibrotic tissue can be distinguished from infarct border zones with intermingled collagen bundles and viable myocytes by quantifying relative differences in CMR SI reflective of differential contrast kinetics within the scar.[27–30] Within the hyperenhanced (bright) area seen on CMR, regions of elevated SI reflecting homogeneously dense fibrosis (infarct core) can be partitioned from peripheral regions with intermediately elevated SI (peri-infarct or gray zone) reflecting a mixture of collagen bands and viable myocytes.[27] Different SI threshold definitions have been used in the literature to define infarct core and gray zone.[27,29,30] These include using an SI cutoff of

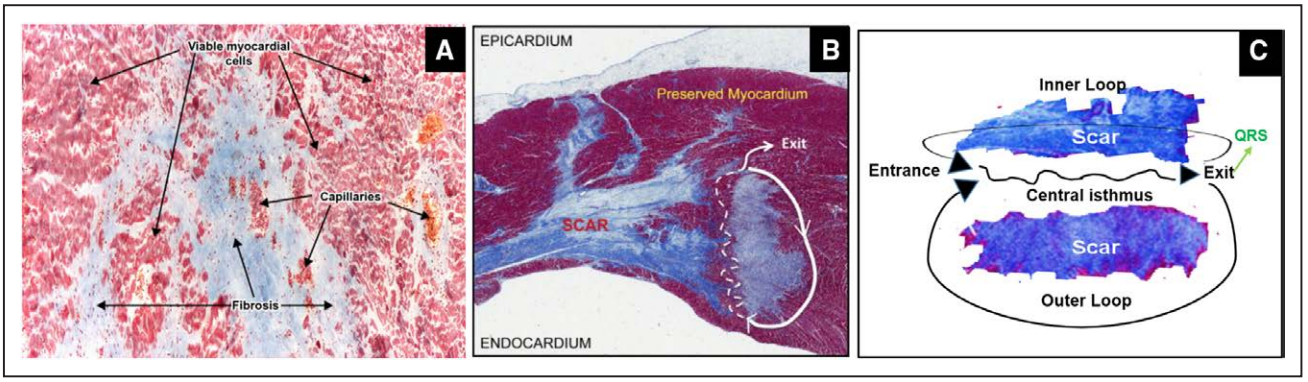

Figure 1. Mechanisms of scar reentry. Heterogeneously distributed scar not only forms electric conduction barriers but also facilitates the formation of critical isthmuses of viable myocytes that support reentrant circuits (**A** and **B**, collagen bundles shown in blue on Masson trichrome staining). **C**, Wavefronts can enter the proximal end of the isthmus (entrance), exiting from the distal end (exit), and then propagating throughout the ventricle to form the QRS complex. The wavefront can reenter the isthmus from channels within the infarct (inner loop) or via an outer loop at the border of the infarct zone with the normal myocardium. Panel A reprinted from Danciu[21] with permission of the publisher. Copyright © 2004-2016, Atlas of Pathology. Panel C reprinted from Ajijola et al[22] with permission of the publisher. Copyright ©2014, Elsevier.

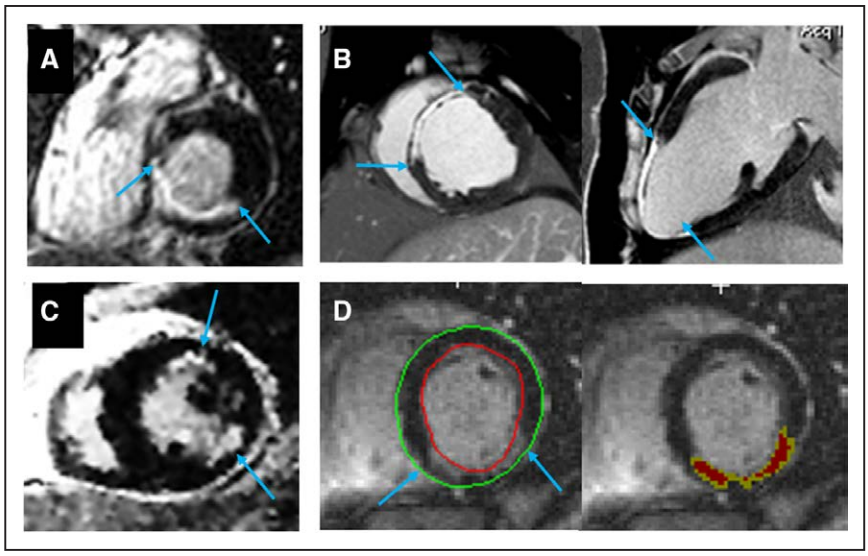

Figure 2. Ischemic scar (between arrows). **A**, Nontransmural scar of the inferior and inferoseptal walls. **B**, Thinned transmural scar in the territory of the left anterior descending coronary artery. **C**, Two subendocardial infarcts of the anterolateral and inferolateral walls. **D**, Chronic inferior infarct with wall thinning (**left**) and quantification (**right**) of core (red) and peri-infarct, gray regions (yellow) using the full-width half-maximum method.

>50% of peak SI (full-width half-maximum) within the total hyperenhanced region to define core; SI thresholds between peak normal myocardial SI and full-width half-maximum to define gray; between 35% and 50% of peak hyperenhanced SI to define gray; and SI between 2 and 3 SDs of mean SI in normal myocardium to define gray zone.

There are limited direct head-to-head comparisons of histopathology and CMR-LGE quantification of infarct heterogeneity. An ex vivo experimental swine infarct model showed that the gray, border zones, as defined by a moderate severity, histopathologic (Picrosirius Red staining) fibrosis grade of 20% to 70%, had intermediate SI by CMR-LGE. In contrast, dense core regions had distinctly elevated SI corresponding to a severe histopathologic grade of ≥70% fibrosis.[31] A patient study provided additional support for the differential contrast characteristics within infarcts.[32] Core regions (defined using full-width half-maximum) corresponded to regions with an elevated gadolinium ECV fraction of 42% compared with 25% in normal myocardium. In contrast, border regions with SI >2 SDs above mean normal myocardium corresponded to areas with intermediately elevated ECV fraction of 32%, reinforcing the concept of differential tissue composition based on CMR-LGE thresholds.

Correlations with electroanatomic voltage mapping and results of electrophysiological ablation procedures also corroborate the pathophysiologic importance of detailed infarct phenotyping by CMR-LGE. High-resolution experimental

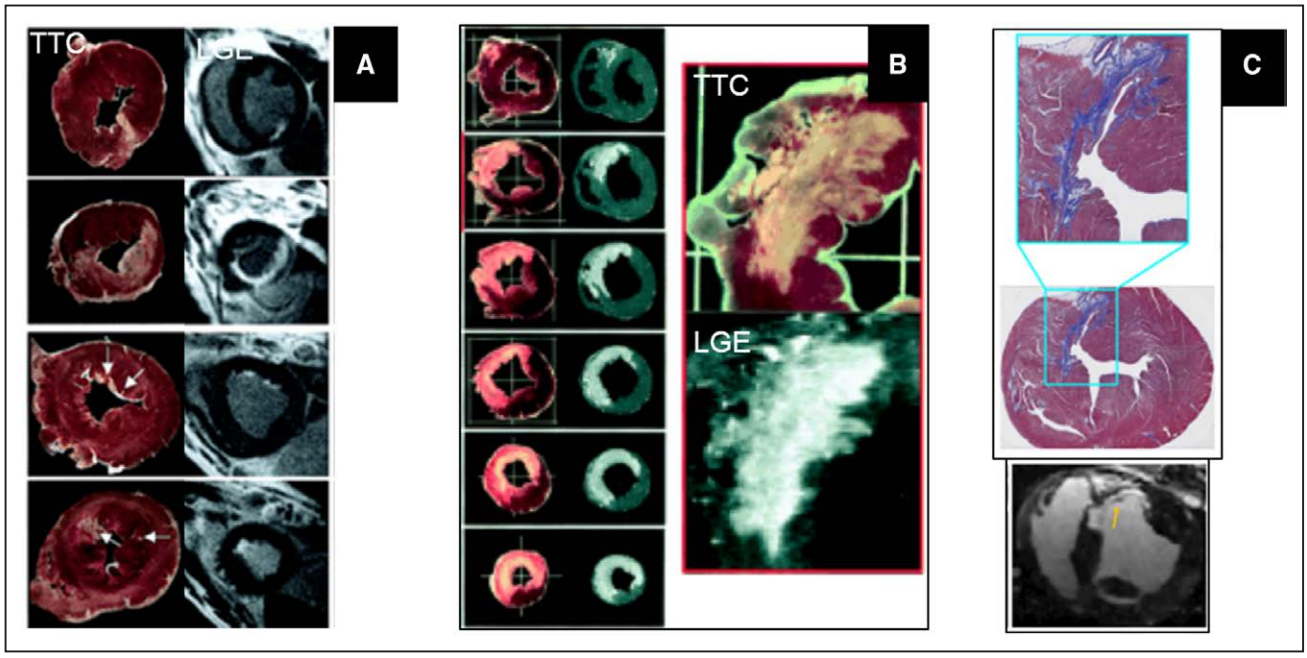

Figure 3. Pathological correlates of late gadolinium enhancement (LGE) post–myocardial infarct (MI). The region of LGE closely matches the extent of infarction determined by pathology at all stages of infarct healing. **A** (1 d post-MI) and **B** (3 d post-MI) show pathological cross sections stained with tetrazolium chloride (TTC) in which the pale regions represent regions of infarction and corresponding cardiac magnetic resonance (CMR)-LGE images. **C** (6 wk post-MI) shows Masson trichrome staining in which collagenous scar appears blue and corresponding CMR-LGE images. Panels A and B reprinted from Kim et al[23] with permission from the publisher. Copyright ©1999, Wolters Kluwer Health, Inc. Panel C reprinted from Zhang et al[24] with permission from the publisher. Copyright ©2016 John Wiley and Sons.

models of ventricular tachycardia (VT) show that critical reentrant isthmuses occur in infarct border zones.[33] Substrate mapping and targeted ablation focusing on the heterogeneous border zones result in more successful therapy of inducible VTs.[34] Subsequent patient studies also suggest the close proximity of critical VT isthmus sites to the core–gray transition zone and CMR-derived tissue characterization not only correlates with but also improves on the electroanatomic voltage mapping identification of VT ablation targets.[35,36] Other recent studies have used segmented myocardial shells to delineate layers of core as distinct from border zones and thereby locate border zone channels that correlate with VT isthmuses identified by electroanatomic pacemapping.[37,38]

CMR in Chronic NICM: Pathological Correlates

Replacement fibrosis is common in dilated NICM of unknown cause. Several patterns of focal fibrosis by CMR-LGE have been described (Figure 4). These include most commonly, midwall enhancement, sparing the endocardium; subepicardial enhancement; and patchy foci not after a coronary artery territory.[39] In some patients, an infarct pattern, that is, coronary distribution with endocardial to epicardial involvement, is seen in the absence of epicardial coronary disease. Although this may be a feature of the cardiomyopathy, it may also reflect epicardial coronary artery recanalization, spasm, or an embolic episode. Comparison between in vivo CMR-LGE and ex vivo histopathology of explanted hearts shows excellent agreement among the locations and patterns of fibrosis (Figure 5).[40–42] In patients with no LGE, histopathology confirms the absence of fibrosis.

Electrophysiological substrate mapping studies in NICM also corroborate the pathophysiologic relationship between CMR-LGE scar characteristics and arrhythmogenesis. CMR-LGE scar mapping in NICM improves the identification of critical VT components during electroanatomic voltage mapping of potential VT ablation sites.[43,44] The pattern of LGE (subendocardial, transmural, midmyocardial versus subepicardial) may be of particular utility for guiding the ablation approach (endocardial versus epicardial) in NICM.[45]

Results of Meta-Analyses in Chronic ICM and NICM

A growing number of publications and meta-analyses demonstrate the prognostic value of CMR-LGE scar presence and extent for SCD risk stratification.[46–49] A recent meta-analysis identified 19 studies comprising 2850 ICM and NICM patients who experienced 423 combined arrhythmic events (sudden death, aborted sudden death, VT/VF, and appropriate ICD therapy) with an annualized event rate of 5.3%.[47,50] The pooled odd ratio (OR) for arrhythmic events in patients with LGE above the designated study-defined thresholds was 5.62 for all patients. The OR was 5.05 in ICM and 6.27 in NICM with no significant difference in risk between ICM and NICM, suggesting similar predictive power of abnormal LGE (presence and greater extent) among ischemic and nonischemic causes.

Many subgroup analyses have been performed within the meta-analyses. Four studies specifically assessed gray zone extent (459 patients and 86 events) with a similar number of studies assessing core scar extent as a predictor.[46] Gray zone extent more strongly predicted ventricular arrhythmic events than core (relative risk 5.94 versus 3.82).[46] Studies were also grouped by mean LVEF below 30% (n=11; 1178 patients) or above 30% (n=8; 1672 patients).[47] The OR for an arrhythmic outcome for abnormal LGE findings was double for LVEF <30% compared with LVEF >30% (9.56 versus 4.48; P=0.02). However, those with LVEF >30% in existing studies tend to be secondary prevention ICD recipients that may result in survivor biases and inadequately reflect risk stratification for primary prevention.

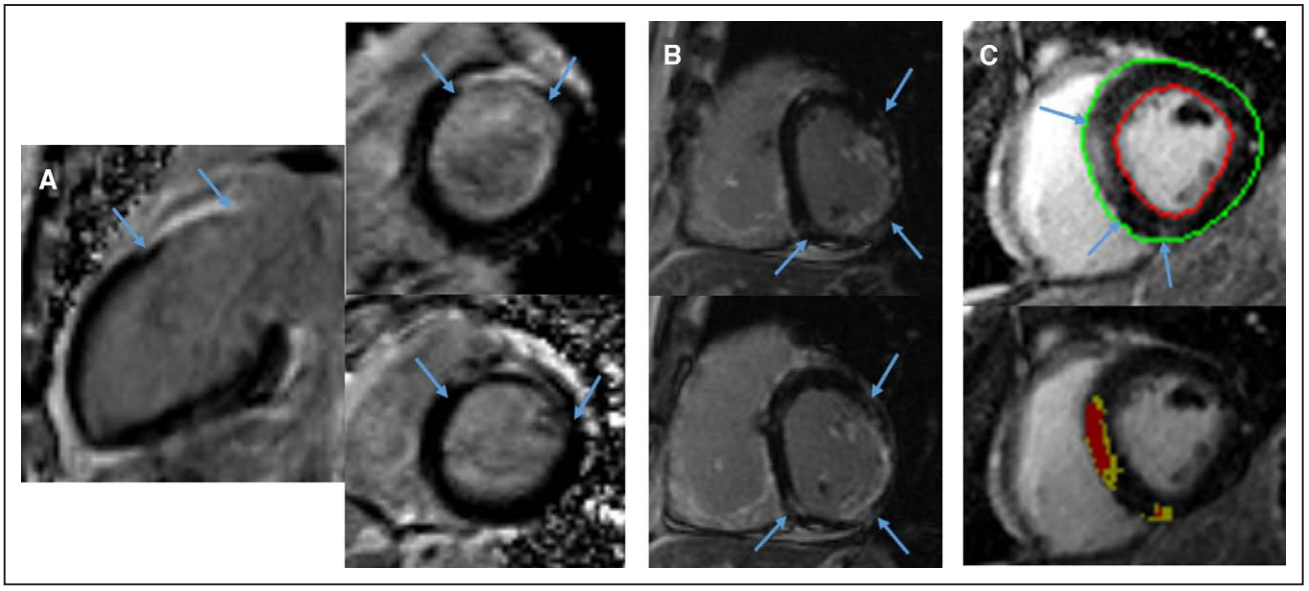

Figure 4. Nonischemic scar (between arrows). **A**, Cardiac magnetic resonance (CMR) images showing basal septal scar in a 45-y-old woman with strong family history of ventricular arrhythmia and sudden cardiac death. Electrophysiology study showed inducible monomorphic ventricular tachycardia (VT) with right bundle, inferior axis morphology. An implantable cardioverter defibrillator was placed and subsequently discharged for monomorphic VT. **B**, Patchy inferior, inferoseptal, and inferolateral late gadolinium enhancement (LGE) in a 65-y-old with non–ischemic cardiomyopathy and multiple episodes of VT. **C**, Septal and inferior right ventricular (RV) insertion LGE sparing the endocardium (**upper**) with quantification (**lower**) of core (red) and gray regions (yellow) using the full-width half-maximum method.

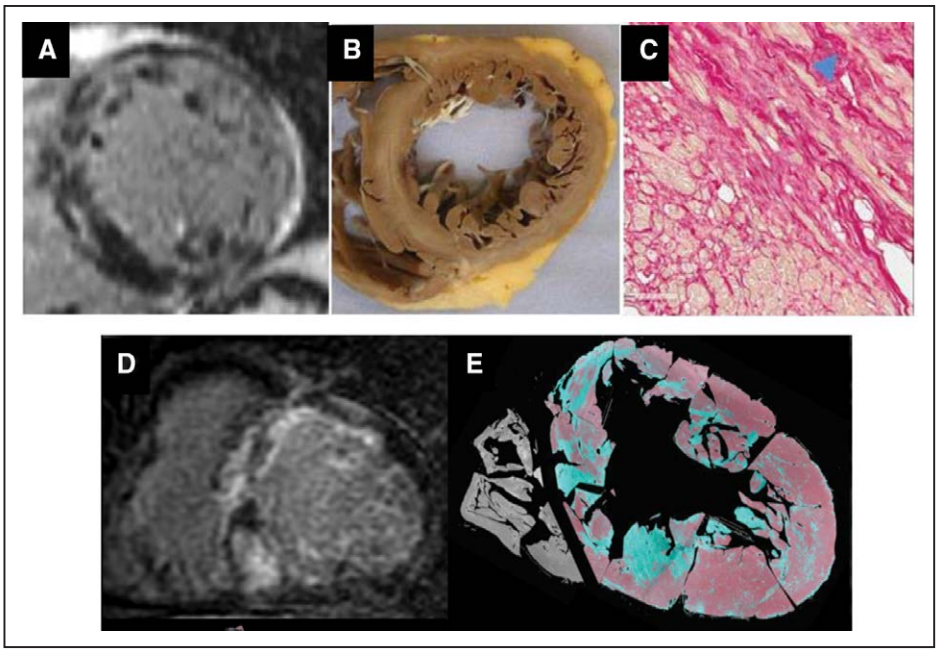

Figure 5. Pathological correlates of nonischemic scar. **A** (pre-transplant cardiac magnetic resonance imaging with late gadolinium enhancement [CMR-LGE]), **B** (post-transplant gross macroscopic cross section), and **C** (post-transplant microscopic cross section with fibrotic bundles, blue arrow) show that the LGE with a midwall, near-circumferential pattern mirrors the distribution of pathological replacement fibrosis. **D** (pre-transplant CMR-LGE) shows diffuse LGE corresponding to regions of fibrosis confirmed by Masson trichrome staining (in green) on post-transplant histopathology (**E**). Panels A, B, and C reprinted from Halliday et al[42] with permission of the publishers. Copyright ©2017, Wolters Kluwer Health, Inc. Panels D and E reprinted from Iles et al[41] with permission of the publishers. Copyright ©2014, Oxford University Press.

Acute MI

Assessing arrhythmic risk in the acute MI period poses a particular dilemma. Infarct characteristics and LV remodeling evolve considerably in the initial days to weeks post-MI. Not only can LVEF recover but also infarcted regions tend to shrink as the acute edema resolves and tissue healing occurs. Current guidelines exclude routine ICD placement in acute MI patients with low LVEF within 40 days because of negative results from 2 clinical trials that showed no mortality reduction with ICDs.[51] However, SCD risk remains highest within the first 30 days post-MI across all LVEF categories although highest in those with LVEF <30%.[52] In VALIANT (Valsartan in Acute Myocardial Infarction Trial), among those with LV dysfunction or HF complicating acute MI, 19% of all SCDs or aborted SCDs occurred in the first 30 days post-MI with an absolute rate of 1.4% per month, decreasing to 0.14% per month after 2 years.[53] Thus, there remains considerable interest in better risk-stratifying these patients.

Limited studies have focused on CMR-LGE for arrhythmic risk assessment early post-MI. One multicenter study enrolled 162 patients with large reperfused ST-segment–elevation MI.[54] CMR-LGE was performed at 3 to 4 days post-MI with 24 Holter monitoring at 1 month. Size of the infarct penumbra (ie, peri-infarct, gray zone) relative to total infarct size most strongly and independently predicted Holter VT burden. Another single-center study of 440 acute ST-segment–elevation MI patients incorporated CMR-LGE at 1 week post-MI with 2-year median follow-up for SCD, sustained VT or VF documented by electrocardiography or ICD, which occurred in 2.5% of patients (n=11).[55] Mean LVEF was 52±13% with total scar size of 21±15%. On multivariate analysis, the strongest predictors of the combined arrhythmic end point were LVEF <37% combined with infarct size >30% (area under the curve, 0.87) and accounted for all but one of the arrhythmic events (n=10 of 11).

A recent clinical study highlighted changes in the temporal course of infarct tissue heterogeneity and influencing factors.[56] Twenty-one patients with reperfused ST-segment–elevation MI underwent CMR-LGE at 2 days, 3 weeks, and 6 months post-MI. Core infarct sizes declined significantly over time in both patients with and without microvascular obstruction (no-reflow). In contrast, size of the peri-infarct (gray) zone declined only in those without microvascular obstruction, remaining unchanged in those with microvascular obstruction.

CMR-LGE in Other Arrhythmogenic LV Cardiomyopathies

Hypertrophic Cardiomyopathy

Replacement fibrosis is common in hypertrophic cardiomyopathy (HCM) and detectable in 42% to 73% of patients by CMR.[57] LGE pattern in HCM (Figure 6) is heterogeneously distributed but most commonly occurs in regions of hypertrophy and tends not to follow a coronary artery territory.[58] Involvement of both the ventricular septum and free wall occurs in >30% of patients.[58] Other patterns include confinement of LGE to the free wall, septum, apex, RV–LV insertion points, RV free wall or papillary muscles or combinations, thereof.[58] CMR-LGE has been included in clinical practice guidelines as an American College of Cardiology/American Heart Association class IIb consensus recommendation since

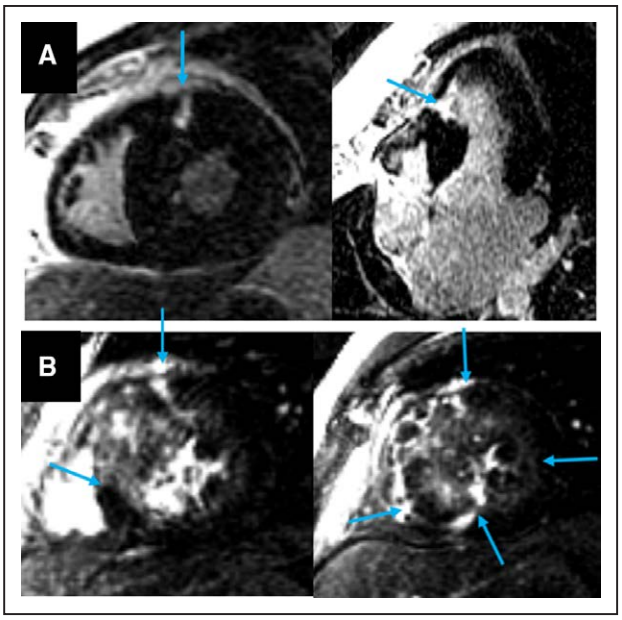

Figure 6. Hypertrophic cardiomyopathy (HCM). Two patients (**A** and **B**) with HCM. **A**, Focal fibrosis (arrows) in noncoronary territories. **B**, Extensive, diffusely distributed late gadolinium enhancement (arrows).

2011: In selected patients with known HCM, when SCD risk stratification is inconclusive, CMR-LGE may be considered in resolving clinical decision making.[59] The initial HCM-CMR data supporting this recommendation comprised 4 published studies, 1063 patients, 3.1-year follow-up with 30 SCD/aborted SCDs.[60] A more recent meta-analysis[57] confirmed these results in 5 studies of 2993 patients with median follow-up of 36.8 months and included 81 SCD or aborted SCD events. LGE and SCD were strongly associated (OR, 3.41; $P<0.001$). Larger amounts of LGE conferred a higher risk with each 10% increase corresponding to a 36% rise in SCD risk.[61] Based on these cumulative data, it has been proposed that both the presence and amount of LGE be integrated into a personalized approach to SCD risk assessment.[61]

Cardiac Sarcoidosis

Sarcoidosis is a multisystem, granulomatous inflammatory disease with variable cardiac involvement that is difficult to diagnose and may be subclinical. Ventricular arrhythmias are a common disease manifestation, and arrhythmic SCD may be the first presentation. The acute phase is characterized by myocardial inflammation of varying degree and reversibility and is modestly responsive to steroid therapy.[62] Irreversible injury with granulomatous scar formation is common and forms the basis of chronic myocardial scarring, which promotes macroreentrant ventricular arrhythmias. CMR-LGE detects chronic myocardial involvement with higher prevalence compared with nonimaging clinical diagnostic criteria such as the modified Japanese Ministry of Health guidelines.[63] The presence of CMR-LGE was added to the recent 2014 Heart Rhythm Society consensus guidelines as a criterion contributing to a probable clinical diagnosis of cardiac sarcoid.[62] Typical CMR-LGE features (Figure 7) include nonvascular territory involvement with midmyocardial or subepicardial LGE, but infarct patterns may also be seen (ie, distribution along a coronary territory with transmural or subendocardial enhancement). Basal septal aneurysm formation is a rare but specific CMR feature of cardiac sarcoid.

Two recent meta-analyses investigated the prognostic role of CMR-LGE with similar results.[64,65] One included 10 studies with 760 sarcoid patients and mean follow-up of 3.0±1.1 years.[65] The other identified 7 studies with 694 patients.[64] A composite end point was evaluated as either a primary or secondary end point: all-cause mortality, ventricular arrhythmia, ICD shock, and SCD. The prevalence of LGE ranged from 13% to 89%. Compared with those who were LGE negative, patients with LGE had a higher risk of the composite outcome (OR, 10.74; $P<0.00001$) with an increased annualized event rate of 11.9% versus 1.1% ($P<0.0001$). Data from several studies suggest that the prognostic value of LGE was independent of and stronger than LVEF and persisted among those with LVEF >50%.[64,65] The 2014 Heart Rhythm Society consensus statement[62] had previously indicated that CMR-LGE for the purpose of SCD risk stratification may be considered (American College of Cardiology/American Heart Association class IIb recommendation). Furthermore, if LVEF is in the intermediate range (36%–49%) despite optimal medical therapy and a period of immunosuppression, CMR with or without an electrophysiological study may be considered to help risk stratify these patients. The meta-analysis results support this recommendation.

Acute and Chronic Myocarditis

The natural history of acute myocarditis varies considerably. However, acute viral myocarditis may account for a large proportion of SCD in young people.[66] In the initial disease phase, active viral replication leads to direct injury and lysis accompanied by innate immune activation. The resultant myocardial damage is generally asymptomatic and most patients recover. In some, however, disease activity persists and triggers an adaptive autoimmune response with profound myocardial inflammation, causing HF and arrhythmias. Recovery occurs in resistant individuals (>90%) while progression to a dilated cardiomyopathy is seen in other susceptible people. Acutely, active myocardial inflammation is arrhythmogenic caused by triggered activity and abnormal automaticity. In chronic myocarditis, myocardial replacement fibrosis promotes reentrant arrhythmic mechanisms (Figure 8).

An early series of 32 patients with clinically suspected acute myocarditis showed the ability of CMR to diagnose myocarditis and guide endomyocardial biopsy.[67] LGE was present in 88% with typical features consisting of patchy involvement with epicardial predominance and frequent localization to the lateral free wall. At 3-month follow-up, the amount of enhanced tissue had declined in all patients who initially had LGE and completely resolved in 15%. Histopathologic analysis of the biopsy specimens obtained from LGE-positive regions showed active myocarditis in 90%. To address sampling issues with endomyocardial biopsy, an experimental model of acute myocarditis was subsequently studied. It showed close correlation between CMR-LGE and both histological severity of myocarditis ($r=0.96$; $P<0.05$) and topographical distribution of histological inflammation.

A follow-up CMR study evaluated 128 myocarditis patients with documented parvovirus B19 (PVB19) and

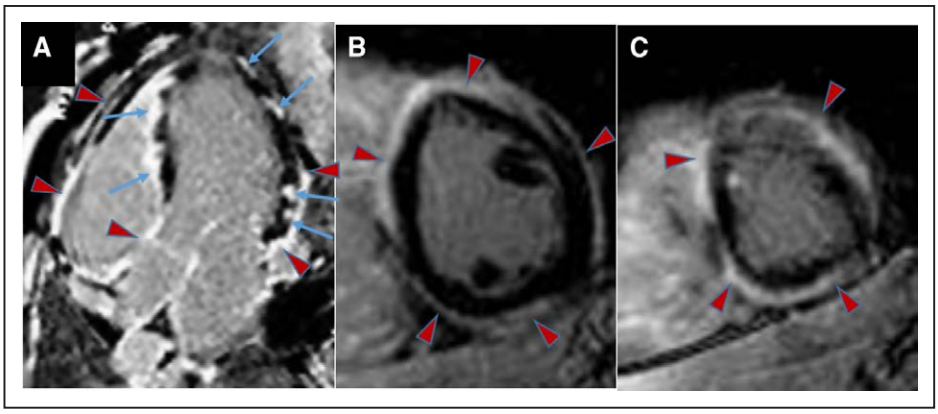

Figure 7. Cardiac sarcoidosis. A 33-year-old man who presented with the intermittent third-degree heart block and cardiac magnetic resonance imaging with late gadolinium enhancement demonstrating extensive cardiac involvement and sarcoidosis on lymph node biopsy. **A** (4-chamber apical view): patchy left ventricular (LV) lateral wall LGE and LGE of the right ventricular side of the ventricular septum with endocardial sparing (blue arrows). There is also LGE (red arrowheads) of the epicardium and pericardium of the basal to mid right ventricular (RV) free wall, atria, and LV pericardium. **B** (midventricular short-axis slice) and **C** (apical short-axis slice): extensive epicardial and pericardial (red arrowheads) LGE. Despite steroid therapy, he subsequently developed VT storm.

herpesvirus 6 (HHV6) myocardial infections.[68] Among the 87 patients with biopsy-proven active myocarditis, 95% had LGE and the LGE pattern seemed to be related to viral type: lateral wall involvement correlated with PVB19 infection and anteroseptal midwall involvement with HHV6. At average follow-up of 138 days, repeat CMR showed persistent LGE in 73%, most of whom were infected with PVB19. At initial CMR, 15 patients had evidence of healing myocarditis on biopsy with LGE in 40%. Follow-up CMR was performed in 4 healing myocarditis patients, none of whom had LGE on the second scan.

Another CMR study of 405 suspected myocarditis patients showed that LGE absence was associated with no major adverse cardiac events (cardiac death, SCD, ICD discharge, and aborted SCD) after 1591 days compared with a 5.6% event rate in those with abnormal CMR findings (reduced LVEF, abnormal LV volume, or LGE presence).[69] LGE prevalence was 28% and typically localized to the subepicardium or midwall regions. Subsequently, a study of chronic dilated NICM demonstrated that midwall fibrosis correlates with increased frequency of a secondary composite arrhythmic end point consisting of SCD or aborted SCD.[40] These patients may represent those in whom chronic myocarditis with midwall involvement progressed to a dilated NICM and forms the basis for increased arrhythmic propensity.

Future Directions

There remains a paucity of randomized control trial data using CMR-LGE to guide decision making for SCD prevention. However, there is everincreasing need to improve our

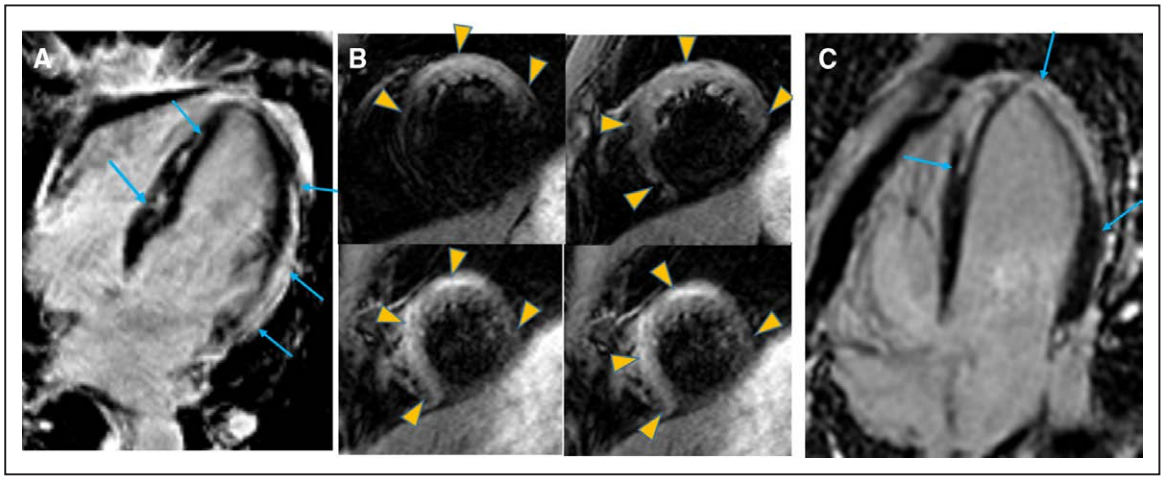

Figure 8. Acute and chronic myocarditis. **A** and **B**, Twenty-nine-year old man who presented with acute myocarditis with peak troponin-I 72 ng/mL; peak creatine phosphokinase 2742 U/L, creatine kinase-MB 331 μg/L. Left ventricular ejection fraction was mildly reduced (Movie I in the Data Supplement), but he was asymptomatic from the arrhythmia and heart failure standpoint during a 6-d hospitalization. **A**, Midseptal and lateral epicardial wall LGE (arrows) and pericardial enhancement. **B**, T2-weighted edema imaging with extensive edema (arrowheads). He died suddenly at home 2 d post-discharge. **C**, Twenty-two-year-old patient with documented acute myocarditis 15 mo previously. Cardiac magnetic resonance imaging-late gadolinium enhancement (LGE) showed LGE of the distal segments of the left ventricle (LV) with endocardial sparing (arrows) and pericardium. LV function was normal with no regional wall motion abnormalities (Movie II in the Data Supplement). Two years later, the patient developed palpitations and syncope with large burden of multifocal premature ventricular contractions on Holter (>5%). Electrophysiology study showed easily inducible monomorphic and polymorphic ventricular tachycardia. An implantable cardioverter defibrillator was implanted and subsequently fired multiple times for monomorphic ventricular tachycardia at 250 bpm.

SCD risk stratification approach, as evidenced by the recently reported DANISH trial (Danish Study to Assess the Efficacy of ICDs in Patients With Non-Ischemic Systolic Heart Failure on Mortality).[70] DANISH randomized 556 symptomatic HF patients with LVEF <36% to usual care or ICD with the primary outcome of all-cause death. After 67.6 months, there was no statistical difference in mortality among those with and without an ICD. SCD rates were relatively low overall consistent with improved outcome with comprehensive HF medical therapy and cardiac resynchronization therapy (CRT). These results further underscore the need for a more targeted approach to identifying the arrhythmogenic substrate and arrhythmically vulnerable patient. Consideration should be given to incorporating CMR-LGE into SCD prevention clinical guidelines, as has been done in HCM, based on the copious existing literature.

Ongoing studies continue to evaluate the utility of CMR-LGE for SCD risk prediction and recognize the need to incorporate multiple risk factors including CMR-LGE to significantly impact SCD prognostication. It has been suggested that improved diagnostic accuracy for any new SCD risk algorithm requires a clinically significant area under the curve level approaching 0.90.[71] No single risk factor to date has that discriminant power. For LVEF, area under the curve is 0.62. However, combining parameters, particularly those that are complementary (such as CMR-determined substrate and assessment of electrophysiological triggers) may achieve the requisite high levels of diagnostic accuracy. Because many pathologies are associated with a high prevalence of scar involvement, it is likely that increased scar extent above a certain threshold (rather than binary presence/absence) will be a better-performing risk factor. Identification of clinically meaningful cutoffs, particularly those that are disease specific, will require randomized control trials. Several randomized control trial and prospective observational studies are underway that will add to the current evidence base (Table 2).[72–74]

Early Acute MI

Observational studies suggest that the demonstration of inducible, sustained VT on invasive electrophysiology study (EPS) beyond 4 days after acute MI in patients with reduced LVEF (<40%) predicts arrhythmic risk.[52] As such, current ICD guidelines suggest that prophylactic ICD implantation may be appropriate under these conditions.[3] However, a lack of proven efficacy of such a strategy and concern with the negative predictive value of EPS have contributed to a decline in such an approach. A multicenter trial is underway to determine the efficacy of a combined EPS and CMR-guided strategy for early acute MI SCD risk stratification, the PROTECT-ICD trial (Programmed Ventricular Stimulation to Risk Stratify for Early Cardioverter-Defibrillator Implantation to Prevent Tachyarrhythmias Following Acute Myocardial Infarction).[73] Enrollment targets patients with ST-segment–elevation or non–ST-segment–elevation MI and LVEF <41% at a minimum of day 3 post-MI. Patients are randomized to EPS-directed ICD implantation versus usual care and followed up for 2 years. A cohort of 1058 patients (529 per arm) is planned with 400 patients undergoing CMR-LGE. End points include whether tissue heterogeneity or scar size by CMR predict inducible VT at invasive EPS and SCD or ventricular tachyarrhythmia at follow-up.

ICM

In addition to substrate assessment in chronic ICM, evidence supports the predictive value of determining electric irritability to identify candidates for primary prevention ICDs. The randomized controlled MUSTT (Multicenter Unsustained Tachycardia Trial)[75] showed a significant reduction in the number needed to treat when results of programmed stimulation during invasive EPS were incorporated into decision making. Inducible ventricular arrhythmia during invasive EPS remains a class I indication for ICD placement in patients with previous MI, LVEF <41% and nonsustained VT.[3] A novel proof-of-concept study recently demonstrated the potential for risk prediction based on patient-specific, CMR-derived 3-dimensional virtual heart and computational electrophysiological modeling.[76] The heart models can be noninvasively subjected to a rigorous electrophysiological stimulation protocol to determine VT inducibility. This virtual arrhythmic risk predictor strongly predicted SCD outcomes in a small retrospective cohort of 41 patients (hazard ratio, 4.05; P=0.03, which exceeded other single risk predictors). Further validation is needed and application to NICM patients in whom inducibility is also a potentially strong risk predictor.[77]

ICM and NICM With Mild-Moderate LV Dysfunction

A multicenter randomized control trial is underway in Australia and Europe targeting ICM and NICM patients with LVEF between 36% and 50% who are not currently targeted for prophylactic ICDs but comprise the majority of SCDs. CMR GUIDE (Cardiovascular Magnetic Resonance Guided Management of Mild-Moderate LV Systolic Dysfunction)[74] will test the hypothesis that a strategy of CMR-guided ICD placement reduces SCD or ventricular arrhythmia during 3-year follow-up. Patients with scar/fibrosis (n=428) will be randomized to receive ICD or an implantable loop recorder. Those without scar/fibrosis (n=521) will be followed in a registry. Results are expected in December 2020.

Hypertrophic Cardiomyopathy

A multinational prospective observational study is underway in 2750 HCM patients to assess prognostic predictors of 5-year cardiovascular outcomes.[72] All patients undergo CMR imaging for analysis of LV volumes, mass, hypertrophy distribution, LGE, and T1 mapping pre- and post-contrast. In addition to clinical data, other measured biomarkers include genomic DNA analysis and serum markers of collagen metabolism, myocardial injury, and hemodynamic stress. The primary end point is the composite of cardiac death (SCD and HF death), aborted SCD (with or without an ICD), and need for heart transplantation.

Assessment of LV Remodeling

Although CMR accurately and reproducibly quantifies LV dimensions, CMR volumes and masses are not strong independent discriminants of SCD outcomes, particularly when

Table 2. In-Progress Studies of CMR for SCD Risk Stratification

Study Title	No. of Patients and Sites	Patient Cohort	Study Design	CMR Metrics	Follow-Up
HCMR[72]	n=2750	Established or new HCM diagnosis	Prospective observational registry	LV and RV volumes and function	5 y for composite end point:
	44 international sites	18–65 y old		LV and RV mass	Cardiac death
				Hypertrophy	Aborted SCD
				LGE	Need for heart transplant
				T1 for diffuse fibrosis	
PROTECT-ICD trial[73]	n=1058, 400 with CMR	2–40 d after first or repeat acute MI with LVEF ≤40%	RCT with randomization to electrophysiology study-guided ICD	LV size	2 y for combined end point of
	25–30 international sites		Secondary aim to relate CMR with electrophysiology study results and outcomes	LV function	Nonfatal ventricular arrhythmia
				Myocardial edema	SCD
				Infarct size	
				Peri-infarct injury	
				T1 times and ECV	
CMR GUIDE[74]	n=949	LVEF 36%–50% because of coronary artery disease or NICM	RCT with randomization to ICD or ILR in those with scar by CMR-LGE	LV volumes and function	3 y for composite of
	23 sites in Australia and Europe			LV mass	SCD
				T1 mapping	Ventricular arrhythmia
				Infarct size	
PROSe-ICD	n=600	ICM or NICM undergoing first ICD pulse generator change	Prospective observational registry	LV and RV volumes and function	5 y for appropriate ICD firing or SCD
Extension	3 US sites			LV mass	
PROSe-ICD Extension				Extent of scar and scar heterogeneity	

CMR indicates cardiovascular magnetic resonance; CMR GUIDE, Cardiovascular Magnetic Resonance Guided Management of Mild-Moderate LV Systolic Dysfunction; ECV, extracellular volume; HCM, hypertrophic cardiomyopathy; HCMR, Hypertrophic Cardiomyopathy Registry; ICD, implantable cardioverter defibrillator; ICM, ischemic cardiomyopathy; ILR, implantable loop recorder; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarct; NICM, non-ICM; PROSe-ICD, Prospective Observational Study of the ICD in Sudden Cardiac Death Prevention; PROTECT-ICD, Programmed Ventricular Stimulation to Risk Stratify for Early Cardioverter-Defibrillator Implantation to Prevent Tachyarrhythmias Following Acute Myocardial Infarction; RCT, randomized control trial; RV, right ventricle; and SCD, sudden cardiac death.

compared with LGE scar. However, the ability to quantify LV shape indices by CMR that may better identify phenotypically high-risk individuals, particularly in ICM, is promising.[78] A recent proof-of-concept study reported differences in regional LV curvature by CMR that were associated with increased SCD risk despite similar global LV volumes and masses.[79]

CMR further has the potential to predict and track the temporal course of cardiomyopathy. Both positive and negative LV remodeling, due either to the natural history of the myopathic process or resulting from therapeutic interventions, may significantly impact SCD risk. Baseline CMR scar extent before ICD insertion was recently shown to predict subsequent LVEF trajectory with a trend toward fewer arrhythmic outcomes in those with improved LVEF.[5] The advent of protocols to safely image patients with indwelling ICDs and CRT devices and reduce device-related artifacts[80] provides additional opportunities. Scar imaging seems to predict less effective cardiac resynchronization and increased SCD risk when the LV lead is positioned over regions of scar.[81] CMR can potentially be used to further monitor response to CRT as defined by improvement in dyssynchrony and LVEF and reduction in chamber sizes and mitral regurgitation, all of which may reduce subsequent SCD risk. CMR can also be potentially used to investigate suboptimal lead positioning post-implantation in nonresponders and explore mechanisms to better understand the phenomenon of CRT-induced proarrhythmia.[82] An observational study is underway to examine the association between temporal changes in scar extent and characteristics as well as LV chamber remodeling and subsequent arrhythmic risk in ICD and CRT-D recipients undergoing their first ICD generator change. Repeat CMR-LGE will be performed in patients originally enrolled in the

PROSe-ICD (Prospective Observational Study of the ICD in Sudden Cardiac Death Prevention) who have not yet had an appropriate ICD shock (NCT00733590).

New CMR Techniques for SCD Risk Assessment

T1 Mapping

The CMR-LGE technique relies on detecting relative differences in SI and requires a region of normal remote myocardium. Hence, although highly accurate and reproducible for identifying focal regions of scar or fibrosis, it is insensitive to diffuse fibrosis, which is common in NICM. The T1 mapping technique, both native, noncontrast and after contrast administration, measures extracellular matrix expansion and thus better detects diffuse fibrosis.[83,84] Small studies have reported correlation coefficients of 0.49 to 0.98 between histological assessment of ECV fraction and that of T1 mapping for quantifying fibrosis associated with valvular heart disease and cardiomyopathy.[84] A recent study of 131 ICM and NICM patients performed T1 mapping and CMR-LGE before ICD implantation with average follow-up of 425 days for appropriate ICD discharges or sustained ventricular arrhythmias.[85] Both gray zone assessment and native T1 mapping independently predicted the outcome with respective net reclassification improvements of 62.5% and 43.9% in the primary prevention ICD cohort. Native T1 mapping has the advantage of lack of contrast requirement. Further studies are needed to establish standardized, reproducible protocols and normative values as well as compare the diagnostic accuracy of T1 mapping over and above existing LGE indices.

Edema Imaging

Myocardial edema imaging combined with CMR-LGE may help differentiate myocardial necrosis from reversible inflammation in inflammatory cardiomyopathies. Existing techniques improve the diagnosis of myocarditis and sarcoidosis. Whether a combined imaging approach improves identification of SCD risk remains uncertain.

Conclusions and Comments

Progress in SCD risk stratification remains impeded by a one-size-fits-all approach with over-reliance on LVEF, lack of patient-specific personalization, and failure to incorporate pathophysiologically driven risk factors.[7] CMR is a powerful and ideal technique to address these limitations with the potential to transform the field. Current constraints to widespread CMR implementation include the lack of consensus on quantitative infarct and tissue heterogeneity standards as well as definitive outcome studies. It is thus perhaps timely to consider a prospective randomized controlled trial of purely CMR-guided decision making for primary prevention ICD insertions across a wide range of LVEF values, including both ischemic and nonischemic causes, to challenge the current concept of a low LVEF threshold.[7] Such a trial would require long-term, adjudicated arrhythmic outcome assessment. In the interim, there would seem to be sufficient published data to support the incorporation of CMR metrics in SCD risk stratification in clinically indeterminate situations, similar to that done with HCM. This will require expert consensus for inclusion in clinical practice guidelines.

Disclosures

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SUPPLEMENTAL MATERIAL – Video Legends

Video 1

See also Figure 8, Panels A and B. Cine MR images in the 4 chamber apical view of a 29-year-old who presented with acute myocarditis. LVEF was mildly depressed at 52% with subtle mid-anterolateral and very proximal septal wall hypokinesis with otherwise low normal regional wall motion. RV systolic function was normal. The cine findings underestimate the extent of myocardial involvement due to extensive inflammation and necrosis which are evident on the LGE (Figure 8, Panel A) and T2 images (Figure 8, Panel B) and do not follow a typical coronary artery distribution, consistent with a non-ischemic process. The patient died suddenly 2 days following hospital discharge.

Video 2

See also Figure 8, Panel C. Cine MR images in the apical long axis view of a 22-year-old with chronic myocarditis. The cine findings show normal biventricular systolic function with no regional wall motion abnormalities and are not sensitive to the extensive fibrosis seen on the LGE images (Figure 8, Panel C).