Sudden cardiac death (SCD) is most commonly precipitated by malignant ventricular tachyarrhythmias and readily prevented by insertion of implantable cardioverter-defibrillators (ICDs). However, our ability to identify which individuals are at highest risk for SCD and thus candidates for ICDs remains inadequate. Current clinical guidelines for selecting patients who have yet to experience clinical evidence of sustained ventricular arrhythmias target those with reduced global left ventricular (LV) function (LV ejection fraction [LVEF] <30–35% with or without heart failure) as meeting criteria for primary prevention ICDs.1 Patients who have survived a cardiac arrest episode, in the absence of a reversible cause, generally meet criteria for secondary prevention ICDs, as may individuals presenting with sustained ventricular tachyarrhythmias, particularly those with structural heart disease.1 Using an LVEF threshold focuses on subpopulations with the highest incidence of SCD and originates from the results of previously published ICD and antiarrhythmic trials that preferentially included only these higher-risk cohorts. However, as was first noted by Myerburg et al2 in 1992, the highest absolute number of SCD events in the population as a whole occurs in patients without systolic LV dysfunction or established heart disease and few to no cardiac risk factors (see Figure 1; Zipes et al).3 Hence, many patients who are at risk for SCD are not being identified as candidates for ICDs. This deficiency in risk stratification practice was articulated in a recent National Heart, Lung, and Blood Institute and Heart Rhythm Society workshop publication, which concluded that “Current methods of clinical risk prediction are inadequate and there is increasing recognition that employment of the LV ejection fraction as a risk predictor is effective in only a small subgroup of patients.”3

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In the majority of cases, the pathogenesis of ventricular arrhythmias involves the interplay between an abnormal myocardial phenotype and a triggering agent.4 Myocardial scar, with its interdigitation of collagen and bundles of viable myocytes, provides the tissue heterogeneity that predisposes to the electrical inhomogeneities required to initiate and propagate reentrant ventricular arrhythmias.5–7 SCD may also occur in the setting of nonischemic etiologies of cardiomyopathy, including hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular dysplasia (ARVD), and acute and chronic myocarditis, in which myocardial fibrosis, inflammation, and/or fatty infiltration contributes to arrhythmogenesis. With the evolution of techniques such as cardiac MRI (CMR), which allow identification of previously unrecognized myocardial abnormalities, there is increased interest in examining whether or not CMR is useful for risk stratification beyond global LV function. In the current issue of Circulation: Cardiovascular Imaging, single-center studies by White et al8 and Appelbaum et al9 lend further support to the potential value of myocardial substrate imaging by CMR when evaluating patients for SCD risk, even when LVEF is preserved.

White et al8 performed CMR imaging in 82 patients presenting to their institution with resuscitated SCD or sustained monomorphic ventricular tachycardia (VT), in the absence of an established ischemic etiology. In addition to cine imaging, both T2-weighted and delayed enhancement (DE) sequences were performed to assess for myocardial edema and scar/fibrosis. In patients suspected of having ARVD (those presenting with VT with left bundle-branch morphology), T1-weighted imaging with a double inversion recovery fast echo sequence was also performed to evaluate for intramyocardial fat. An investigator blindly adjudicated the clinical reports of all non-CMR imaging, and, based on the results, judged whether or not an etiology could be determined as causing the arrhythmia, assigning 1 of 7 predefined diagnostic categories. The same was done in a blinded fashion after review of the CMR images. In both cases, a summary of the clinical presentation and relevant ECG findings were provided for clinical context. The majority of patients had relatively preserved LVEF (mean±SD of 51±19% for the entire cohort; 60% with LVEF ≥50%). The CMR results led to reclassification of 50% (n=41) to a new or alternative diagnosis, including 20 patients (24% of the entire cohort) in whom non-CMR imaging had shown no significant myocardial disease and 18 (22% of the entire cohort) in whom non-CMR imaging suggested an idiopathic cause. Seven patients (9%) were found to have LV dysfunction by CMR, not detected by the non-CMR imaging methods, presumably due to limitations such as inadequate acoustic windows in echocardiography. The etiologic causes...
of prospective studies having sufficient size and follow-up duration. Nonetheless, because DE is so commonly seen in HCM, the positive predictive value of DE presence alone is likely to be low and may not ultimately be the best risk factor. The current work by Appelbaum et al shows that the extent of DE, both intermediate and high SI, was higher in patients with ventricular arrhythmias, consistent with the results of a prior study using high SI only. Moreover, the diagnostic performance of intermediate SI was the highest (area under the curve, 0.72) compared with high SI (area under the curve, 0.65) and total SI (area under the curve, 0.68).

Although the findings of both these studies highlight the diagnostic potential of CMR, the authors note as important limitations that they did not examine whether the CMR results led to significant changes in the clinical management of these patients or predicted prognosis, which are essential questions when assessing comparative effectiveness of imaging strategies. Moreover, future studies will need to address the issue of cost effectiveness of adding CMR to SCD risk stratification algorithms and this may require targeting CMR to distinct cohorts in a tiered approach. The data from White et al suggest that it may have a vital role in 2 particular subgroups who present with ventricular arrhythmias, those of patients in whom non-CMR imaging suggests a structurally normal heart or an idiopathic etiology. In these 2 subgroups, CMR changed the diagnosis in 57% of cases and could affect the subsequent management. As is evident by the CMR-determined etiologies (Table), tailoring of the CMR examination to include specific sequences based on pretest clinical suspicion will be critical, such as when ARVD is suspected from the morphology of the presenting VT, other ECG abnormalities, and/or evidence of right ventricular abnormalities by non-CMR imaging. In fact, current guidelines for the diagnosis of ARVD already incorporate specific CMR findings into the major and minor criteria. Also in support of a tiered diagnostic approach, CMR imaging with DE was recently added to HCM guidelines as a class IIb indication:

“In selected patients with known HCM, when SCD risk stratification is inconclusive after documentation of the conventional risk factors, CMR imaging with late gadolinium enhancement may be considered in resolving clinical decision-making.”

Standardized methods of quantifying DE and the importance of differentiating intermediate from high SI regions remain unresolved issues in CMR. The mere presence versus absence of DE is unlikely to be adequate as a single risk stratifier, and quantification of DE probably is needed to improve diagnostic performance. Pathophysiologically, scar characteristics do contribute to how arrhythmogenic a heart will be, and spatial heterogeneity in terms of admixtures of normal myocytes with collagen bundles are what support reentrant ventricular arrhythmias rather than densely confluent fibrosis. Thus, using regional differences in CMR SI (presumably reflecting different contrast volumes of distribution and kinetics) to evaluate for areas of tissue heterogeneity and distinguish them from homogeneously scarred regions make sense. Validation of SI thresholds for defining myocardial heterogeneity remains a challenge, particularly since there is a limited histopathologic basis in nonischemic etiol-

identified by CMR in the reclassified cases are listed in the Table. In 3 cases (4%), the CMR diagnosis was incorrect.

The genetic disorder HCM has a fairly high prevalence of 1 in 500 and is the most common cause of SCD in individuals younger than 35–40 years old, despite preserved LVEF. Clinical markers of SCD risk (syncope, family history of SCD, nonsustained VT, extreme ventricular hypertrophy, and nonsustained VT) have relatively low predictive value, and thus improved risk stratification is needed. The study by Appelbaum et al investigated whether or not the presence of ventricular arrhythmias (nonsustained VT, ventricular couplets, and PVCs) was related to the amount of tissue heterogeneity reflected by regions of intermediate signal intensity (SI) versus high SI areas. One hundred forty-five HCM patients with qualitative evidence of myocardial DE were studied, and as is usually observed, LVEF was preserved in all (70 ± 11%). The concept of tissue heterogeneity has been previously described in patients with chronic myocardial infarction, in whom regions of intermediate SI (gray zone), postulated to reflect admixtures of scar/fibrosis with viable muscle bundles, have been associated with increased arrhythmogenesis and poor cardiovascular and all-cause mortality. In nonischemic cardiomyopathies such as HCM, heterogeneity in SI can be visually observed as well. In fact, a histopathologic-CMR correlation study of HCM observed that gradations of SI occurred in regions of DE and as SI increased, there were associated increases in collagen involvement on a segmental basis, supporting differential gadolinium kinetics. Scar is a common feature in HCM, occurring in up to 70–80% of patients regardless of symptoms. Although the presence of total scar by CMR has been associated with increased event rates, including for ventricular arrhythmias and SCD, its discriminant ability as a single risk factor has yet to be established because of the lack

Table. Causes of Reclassification

<table>
<thead>
<tr>
<th>CMR Diagnosis</th>
<th>Normal by Non-CMR Imaging (n=20 of 40)</th>
<th>Unexplained LV Dysfunction (n=13 of 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myocarditis</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Healed myocarditis</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Acute MI</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Healed MI</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>LV noncompaction</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>ARVD</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Sarcoid</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

CMR indicates cardiac magnetic resonance; LV, left ventricular; MI, myocardial infarction; and ARVD, arrhythmogenic right ventricular dysplasia.
ogy such as HCM, but at the minimum, any method should correlate visually with what is observed. The “best” thresholds may be those that predict outcomes with the highest diagnostic accuracy and will need to be demonstrated in large, adequately powered, prospective studies.

Finally, the results of these 2 studies support the hypothesis that myocardial scar may be a potential predictor of SCD over and above that of LVEF because it directly defines the abnormal substrate associated with increased SCD risk. Although it did not assess SCD or cardiac mortality, a recent multicenter, largely retrospective, observational study\textsuperscript{22} of 1560 consecutive patients referred for cardiac CMR (cine and DE) found that both CMR LVEF and the amount of DE were independent predictors of all-cause mortality at a median of 2.4-year follow-up. Notably, even among the 721 patients with LVEF $\geq$50\%, DE measuring above the median value predicted increased all-cause mortality. Thus, the unique ability and strength of CMR to characterize myocardial tissue are increasingly evident and deserving of continued investigation. The full potential of CMR with DE as a clinical tool for SCD risk stratification has yet to be realized, and, while changing current paradigms will be difficult, the rate of return may be high.

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Disclosures

None.

References


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Assessing Risk for Ventricular Tachyarrhythmias and Sudden Cardiac Death: Is There a Role for Cardiac MRI?
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