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.1

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 interdigititation 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

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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.

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 al9 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 arrhythmogenicity. Thus, using regional differences in CMR SI 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-
ogies 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\(^22\) 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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Katherine C. Wu

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