

## Powerlessness of a Number Why Left Ventricular Ejection Fraction Matters Less for Sudden Cardiac Death Risk Assessment

Katherine C. Wu, MD; Hugh Calkins, MD

The national burden of sudden cardiac death (SCD) remains high at an annual incidence estimated at 183 000 and continues to account for a disproportionately elevated fraction of all cardiovascular deaths.<sup>1,2</sup> Despite therapeutic advances in the treatment of coronary heart disease and heart failure and emphasis on SCD primary prevention with prophylactic implantable cardioverter defibrillators (ICDs), SCD accounts for 2.04 million or 40% to 50% of the potential years of life lost because of all premature cardiac death.<sup>2</sup> SCD exceeds all noncardiac causes of death except overall cancer and accidents.<sup>2</sup> However, it is well recognized that our current approach to SCD risk stratification that relies on a left ventricular ejection fraction (LVEF) <30% to 35% to identify primary prevention ICD candidates has limited overall societal impact. Particularly, among patients with nonischemic cardiomyopathy (NICM) with low LVEF, absolute SCD rates are declining in conjunction with comprehensive heart failure medical therapy and cardiac resynchronization therapy, as evidenced by the recently published DANISH trial (Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality).<sup>3,4</sup> In contrast, individuals with LVEF >35% account for the highest absolute number of SCDs, comprising 70% to 80% of those who experience SCD.<sup>5,6</sup>

### See Article by Pontone et al

LVEF is an inadequate surrogate for the underlying myocardial phenotype predisposing to SCD.<sup>7</sup> The same LVEF can represent multiple cardiomyopathic derangements. Although a powerful predictor of total and non-SCD mortality, it has limited specificity for SCD. No LVEF cutoff discriminates between sudden and nonsudden modes of cardiac death.<sup>5,6,8</sup> In fact, LVEF is not directly related to mechanisms of arrhythmia and can be subject to considerable spontaneous variability in individuals.<sup>5</sup>

Myocardial fibrosis is a major pathophysiologic determinant of arrhythmic propensity in both ischemic cardiomyopathy and NICM. Myocardial injury leads to extensive structural and functional cardiac remodeling with resultant myocardial

loss, with or without compensatory myocyte hypertrophy, and replacement of the extracellular matrix with fibrosis. 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 because of scar-related reentry. It is increasingly recognized that scar heterogeneity within the myocardium is especially arrhythmogenic. The intermingling of 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. Hence, identifying and characterizing the underlying arrhythmogenic substrate of myocardial scar have great potential to improve SCD risk stratification.

Cardiac magnetic resonance imaging with late gadolinium enhancement (CMR-LGE) has unparalleled ability to characterize myocardial tissue composition. It has been increasingly used to advance our understanding of the pathophysiology, diagnosis, and treatment of ventricular arrhythmias. A 2013 meta-analysis assessing the accuracy of CMR-LGE for SCD risk stratification identified 11 published studies with a total of 1105 ischemic cardiomyopathy and NICM patients.<sup>9</sup> Overall mean/median follow-up was 8.5/41 months with 207 ventricular arrhythmic events defined as SCD, resuscitated cardiac arrest, ventricular arrhythmias, or appropriate ICD therapy.<sup>9</sup> Patients with a greater extent of CMR scar (defined as the CMR index most strongly associated with risk in each study) had a markedly increased overall relative risk of SCD (relative risk, 4.33; 95% confidence interval, 2.98–6.29) compared with those with a lower extent. A subsequent 2014 meta-analysis focusing only on NICM studies analyzed 7 studies with 1194 patients and reported on SCD, aborted SCD, or appropriate ICD therapy for ventricular arrhythmias during follow-up.<sup>10</sup> Compared with LGE absence, LGE presence was associated with an odds ratio of 5.32 for the combined outcome. Most published studies enrolled patients with current clinical indications for ICD with few including those with more preserved LVEF. To date, the restricted range of LVEF in the published literature limits assessment of the incremental value of CMR over and above LVEF and contributes to current ambiguity on how best to incorporate CMR into clinical decision making for SCD.

The work by Pontone et al<sup>11</sup> in this issue of *Circulation: Cardiovascular Imaging* seeks to clarify some of this ambiguity. The authors imaged, by standard 2-dimensional transthoracic echocardiography (TTE) and CMR-LGE, 409 consecutive ischemic cardiomyopathy and NICM patients with chronic heart failure referred for evaluation of potential

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primary prevention ICD implantation between January 2011 and December 2013. Patients were followed up clinically and with 24-hour Holter monitoring at 6 months and then yearly thereafter until study completion. The primary combined end point consisted of long runs of nonsustained ventricular tachycardia  $\geq 10$  consecutive beats  $>120$  bpm or sustained ventricular tachycardia, ventricular arrhythmia aborted by an appropriate ICD shock, or SCD. During median follow-up duration of 545 days/1.5 years, 103 patients (25%) had an event. ICD implantation occurred during follow-up in 34% of patients. Strengths of the study are its relatively wide range of LVEFs and the systematic imaging by both TTE and CMR within days of one another.

CMR and TTE were positively correlated with high correlation coefficients for left ventricular (LV) volumes ( $r=0.82-0.85$ ) and modest correlation for LVEF ( $r=0.66$ ;  $P<0.01$ ). Compared with CMR, TTE underestimated LV volumes by 34 to 43 mL/m<sup>2</sup> and overestimated LVEF by 4%. Intra- and interobserver variabilities in LV measurements were significantly lower with CMR, as previously reported. The observed underestimation in LV volumes is similar to that reported in other studies for noncontrast 2-dimensional TTE.<sup>12,13</sup> Other studies have generally noted an overestimation of LVEF by CMR rather than by TTE and also reported similar wide limits of agreement between LVEF determined by 2-dimensional TTE and CMR approaching 10% to 15%.<sup>13</sup> These results highlight several important points about LVEF measurement, which can significantly affect therapeutic decision making. First, imaging methods and thresholds are not interchangeable. Normal values, and hence abnormal thresholds, can differ inherently by the imaging method. Hence, cutoff values should be individualized for the imaging modality. Second, when precision in LVEF is required, particularly when LVEF is in the intermediate range, CMR is preferable to TTE.

As individual risk factors, the authors found that TTE LVEF  $<35\%$ , CMR LVEF  $<35\%$ , and LGE presence were all highly associated with arrhythmic outcome. The combination of LVEF  $<35\%$  and LGE presence had the highest area under the curve of 67.3, although the area under the curve of 63.8 for LGE presence alone was in fact not statistically different in this sample. Compared with TTE LVEF  $<35\%$ , adding CMR LVEF  $<35\%$  to the multivariable model improved net reclassification by 47%. This was further improved by 41% when LGE presence was incrementally added. The lowest 2-year risk of arrhythmic outcome occurred in patients with LVEF  $>35\%$  and no LGE, whereas those with LVEF  $>35\%$  but were LGE positive had a high rate of events of  $\approx 20\%$  by study end. Thus, this work supports the growing literature demonstrating the value of LGE presence in predicting arrhythmic outcome and highlights the incremental diagnostic and prognostic accuracy of CMR in LVEF quantification above that of TTE.

Several limitations should be noted. There was a fair amount of heterogeneity in the referral base. Although the majority of patients (69%) were referred for low LVEF near the clinical threshold for ICD implantation, the remainder consisted of those with mild LV dysfunction with history of frequent premature ventricular contractions and/or wide complex tachycardia in 20% and unexplained syncope in 11%. Men predominated (80%). The duration of the cardiomyopathy was not reported.

This was a single-center study performed in Italy, which may limit generalizability to the United States. Noncontrast TTEs were performed. Use of contrast-enhanced 2-dimensional TTE and 3-dimensional approaches has been shown to improve accuracy and reproducibility of LV volume and LVEF assessments.<sup>12,13</sup> Of the 103 arrhythmic events, the majority (61%) comprised runs of nonsustained ventricular tachycardia  $\geq 10$  consecutive beats, which is not equivalent to SCD. Median follow-up time was relatively short at 545 days/1.5 years. Dichotomous presence versus absence of LGE, rather than quantification of LGE amount, was assessed. As seen by the Kaplan–Meier curves, event rates were high in all patients with CMR LVEF  $<35\%$  regardless of LGE presence or absence. We have shown the additional predictive value of scar quantification combined with biomarker assessment in improving risk assessment. Low amounts of myocardial scar, particularly heterogeneous gray zone scar, in combination with low high-sensitivity C-reactive protein identified a low-risk subgroup ( $<1\%$  per year) for SCD outcomes among those with LV dysfunction,<sup>9,14</sup> which could better target ICD devices to those truly at high risk.

The work by Pontone et al<sup>11</sup> further adds to the growing literature supporting improved SCD risk stratification using a detailed, nuanced approach to phenotyping of cardiac structure beyond LVEF alone. It highlights the need to move beyond the focus on a single LVEF metric and emphasizes the fact that a structurally abnormal heart could indeed have relatively preserved LVEF but is arrhythmogenic because of myocardial scar. With the growing body of evidence supporting both the pathophysiologic link and prognostic use of CMR-LGE assessment and SCD risk, it is an opportune time to reconsider a clinical trial guided by CMR-LGE to identify those at highest absolute risk for SCD.<sup>15</sup> We suggest a prospective randomized study of ischemic cardiomyopathy and NICM patients not currently meeting clinical guidelines for ICD with LVEF between 35% and 50%, all of whom undergo imaging by CMR-LGE. Consideration could also be given to including NICM patients with low LVEF, similar to those studied in DANISH, in whom there is equipoise regarding ICD benefit. Those with high-risk CMR features would then be randomized to ICD therapy or routine care with long-term follow-up for hard arrhythmic outcomes (sustained ventricular arrhythmia or SCD). Such a tailored strategy could be the first step to reducing our one-size-fits-all approach and overreliance on LVEF alone for therapeutic decision making in SCD.

## Disclosures

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