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

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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.[1, 2] Despite therapeutic advances in the treatment of coronary heart disease and heart failure (HF) and emphasis on SCD primary prevention with prophylactic implantable cardioverter defibrillators (ICDs), SCD accounts for 2.04 million or 40–50% of the potential years of life lost due to all premature cardiac death.[2] SCD exceeds all non-cardiac causes of death except overall cancer and accidents.[2] However, it is well-recognized that our current approach to SCD risk stratification that relies on a left ventricular ejection fraction (LVEF) below 30–35% to identify primary prevention ICD candidates has limited overall societal impact. Particularly among patients with non-ischemic cardiomyopathy (NICM) with low LVEF, absolute SCD rates are declining in conjunction with comprehensive HF medical therapy and cardiac resynchronization therapy, as evidenced by the recently published DANISH trial.[3, 4] In contrast, individuals with LVEF above 35% account for the highest absolute number of SCDs, comprising 70–80% of those who experience SCD.[5, 6]

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

Myocardial fibrosis is a major pathophysiologic determinant of arrhythmic propensity in both ischemic cardiomyopathy (ICM) 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 electrophysiologic derangements that increase propensity for ventricular arrhythmias and SCD due to scar-related re-entry. It is increasingly recognized that scar heterogeneity within the myocardium is especially arrhythmogenic. The intermingling of

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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 re-entrant 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 1105 total ICM and NICM patients.[9] 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.[9] 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 (RR) of SCD (RR 4.33, 95% CI 2.98–6.29) compared to 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.[10] Compared to 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 regarding how best to incorporate CMR into clinical decision-making for SCD.

The work by Pontone et al[11] in this issue of *Circulation: Cardiovascular Imaging* seeks to clarify some of this ambiguity. The authors imaged by standard 2D transthoracic echocardiography (TTE) and CMR-LGE, 409 consecutive ICM and NICM patients with chronic HF referred for evaluation of potential primary prevention ICD implantation between January 2011 and December 2013. Patients were followed clinically and with 24 hour Holter monitoring at 6 months and then yearly thereafter until study completion. The primary combined endpoint consisted of long runs of non-sustained ventricular tachycardia (NSVT) ≥10 consecutive beats above 120 beats per minute or sustained VT; 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%. 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 LV volumes (r=0.82–0.85) and modest correlation for LVEF (r=0.66, $p<0.01$). Compared to CMR, TTE underestimated LV volumes by 34–43 ml/m^2 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 non-contrast 2D TTE.[12, 13] Other studies have generally noted an

overestimation of LVEF by CMR rather than TTE but also reported similar wide limits of agreement between LVEF determined by 2D TTE and CMR approaching 10–15%.[13] These results highlight several important points about LVEF measurement which can significantly impact therapeutic decision-making. Firstly, 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. Secondly, 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 below 35%, CMR LVEF below 35%, and LGE presence were all highly associated with arrhythmic outcome. The combination of LVEF below 35% and LGE presence had the highest AUC of 67.3 though the AUC of 63.8 for LGE presence alone was in fact, not statistically different in this sample. Compared to TTE LVEF below 35%, adding CMR LVEF below 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 above 35% and no LGE, while those with LVEF above 35% but were LGE positive had a high rate of events of approximately 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. While 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 PVCs 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 U.S. Non-contrast TTEs were performed. Use of contrast-enhanced 2D TTE as well as 3D approaches has been shown to improve accuracy and reproducibility of LV volume and LVEF assessments.[12, 13] Of the 103 arrhythmic events, the majority (61%) comprised runs of NSVT ≥ 10 consecutive beats, which is not equivalent to SCD. Median follow-up time was relatively short at 545 days/1.5 years. Dichotomous presence vs. 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 below 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 very low risk subgroup (<1% per year) for SCD outcomes among those with LV dysfunction,[9, 14] which could better target ICD devices to those truly at high risk.

The work by Pontone et al.[11] 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 utility 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. (ref 15) We suggest a prospective randomized study of ICM and NICM patients not currently meeting clinical guidelines for ICD with LVEF between 35–50%, 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.

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