Myocardial Iron and Arrhythmia Risk: Magnetic “Shades of Gray”? 

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Although the past several decades have brought improvements in acute coronary syndrome care with decreased post-myocardial infarction (MI) mortality, the percentage of cardiovascular mortality from sudden cardiac arrest (SCA) has not experienced the same decline. Current methods to stratify risk of SCA mortality are limited to decreased left ventricular function and occasionally surrogate markers of electric instability (eg, microvolt T-wave alternans). Given the limited sensitivity of many of these indices to discriminate SCA risk across the spectrum of patients with ischemic heart disease, efforts to define functional and structural biomarkers of malignant arrhythmia susceptibility that transcend left ventricular ejection fraction have been a focus of intense investigation.

Cardiac magnetic resonance (CMR) provides a multiparametric imaging biomarker of myocardial structure, function, and tissue architecture post MI. Since the advent of late gadolinium enhancement (LGE), CMR quantification of myocardial fibrosis—long considered important loci of malignant arrhythmia—has been investigated into the prognostic importance of LGE alongside traditional markers of cardiac function has grown. Various groups have demonstrated the association of LGE with SCA or appropriate defibrillator therapy in a variety of myocardial diseases, including dilated cardiomyopathy, post-MI, and hypertrophic cardiomyopathy. Furthermore, CMR methods to phenotype heterogeneity within scar that is thought to form a nidus for arrhythmia (the peri-infarct zone) have emerged, with several reports suggesting a potential link between the gray zone within an infarct and subsequent clinical risk. Although prospective investigation into the prognostic role of these markers continues, the collective balance of data in the field of cardiovascular imaging suggests that the presence and extent of myocardial fibrosis by LGE is strongly associated with arrhythmia, heart failure, and cardiac mortality.

Nevertheless, the search for alternative, independent imaging-based parameters of SCA risk has recently undergone a renaissance, with a focus on methods that target tissue-based structural changes in the heart, preferably without recourse to contrast agents with potential nephrogenic effects. In this context, a growing body of evidence has linked intramyocardial hemorrhage during the index MI with future adverse left ventricular remodeling, poorer cardiac prognosis, and arrhythmic risk. Interestingly, in a canine model of MI using T2* imaging CMR, these investigators have established that hemorrhage during the index MI is associated with late iron deposition and subsequent macrophage infiltration in the infarct zone, as well as important changes in surrogate markers of arrhythmic risk, including late potentials and QT dispersion. However, validation of the association between infarct zone iron deposition with SCA risk in a population of patients with chronic MI has heretofore been lacking. The data presented by Cokic et al in this issue of Circulation: Cardiovascular Imaging address this gap.

Building on previous work by their group, Cokic et al performed a retrospective analysis of 94 individuals referred for predefibrillator CMR. Patients with an ischemic cardiomyopathy (left ventricular ejection fraction, <0.35) on heart failure therapy for >3 months were included. LGE imaging (with a 5-SD cutoff) and peri-infarct zone assessment (with a 2/3-SD cutoff) were performed. The investigators used balanced steady-state free precession imaging, with its inherent mixed T2/T1 weighting, coregistered with LGE imaging to identify areas of scar. Hypointense core regions (HIC; classified as present or absent) were defined by visual determination of pixel signal intensity within areas of LGE. All individuals had defibrillator placement with conventional programming and predetermined device interrogation follow-up.

A composite primary end point of appropriate defibrillator therapy, SCA or sudden death occurred in 19 individuals, 18 of whom had a hypointense core. Accordingly, the presence of a HIC was associated with a significant increase in hazard of arrhythmia, with significant incremental discrimination for the primary end point on addition of HIC status to left ventricular ejection fraction and LGE size. The authors elegantly use T2* quantification within the infarct zone (using similar techniques as in their previous work) to validate HIC regions as areas of iron deposition within infarction. In addition, they demonstrate a relationship of greater peri-infarct zone volume with greater total iron deposition (by T2*) and the presence of a HIC, suggesting a potential link between these distinct CMR-determined imaging surrogates of arrhythmic risk. Collectively, the investigators conclude that steady-state free precession imaging may capture areas of hypointense core that are fundamentally related to iron deposition, infarct zone heterogeneity, and arrhythmic risk.

Although the study presents some provocative uses of standard CMR sequences to assess tissue-based phenotypes,
there remain several open questions. The population investigated here was relatively small with limited follow-up and a small number of events (leading to wide confidence limits), with the subsequent potential for overstating the incremental prognostic and discriminatory significance of HIC beyond more traditional markers (eg, LGE). Among patients not meeting the primary end point, ≈40% were HIC positive, which could reflect either the limited follow-up or a less than optimal specificity of this novel marker. However, the study provides ample evidence to justify application of these methods in larger, population-based studies with longer follow-up dedicated to the detection of SCA events to provide validation. The restriction of the study to patients with depressed left ventricular function limits the generalizability of these techniques to the large population of individuals with modestly depressed myocardial function who remain at high risk post MI (eg, LV ejection fraction, 0.35–0.50). Finally, imaging-based limitations (eg, with off-resonance artifacts at higher field strengths, presence of fat or calcification within infarct) may also influence image interpretation (and generalizability) in chronic MI.

Despite these caveats, the authors are to be congratulated for their innovative application of CMR techniques to this growing field. The authors provide convincing animal model evidence for the association between complementary CMR phenotypes that have been implicated in arrhythmic risk (eg, peri-infarct zone and iron deposition) with HIC. The study provides much needed clinical translation to their previous work using T2* CMR to a more widely available technique—steady-state free precession cine function imaging—available in all CMR systems, and sets the stage for larger investigations using these techniques in emerging populations (eg, preserved left ventricular ejection fraction and epidemiological SCA cohorts). Ultimately, the elegant line of translational imaging investigation provides firm evidence that iron deposition can be detected using advanced (T2*) and standard (steady-state free precession) CMR techniques and is associated with arrhythmic risk. Indeed, CMR may cast light on the shades of gray involved in arrhythmia post MI.

Disclosures
None.

References

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