Substrate Imaging to Guide Primary Prevention Implantable Cardioverter-Defibrillator in Ischemic Cardiomyopathy: Fanciful or Realistic Aim?

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Sudden cardiac death (SCD) is one of the leading causes of death among patients with heart failure and reduced left ventricular ejection fraction (LVEF) with an estimated cumulative incidence of 8.8% over 3 years (1). Current American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines provide a Class I recommendation for implantable cardioverter-defibrillator (ICD) for primary prevention of SCD in patients with reduced LVEF based on large randomized controlled trials (RCTs) (2). However, only 21% of such patients received appropriate ICD shocks over 5 years in the Sudden Cardiac Death in Heart Failure Trial (3). There are 2 likely mechanisms for this phenomenon: 1) presence of risk-gradient with a subgroup of patients at low risk of SCD despite reduced LVEF; and 2) subgroup of patients whose competing risk of mortality from non-arrhythmic causes especially pump failure is much higher than the risk of arrhythmic death (4). Thus, a large number of these patients would not derive benefit from ICD implantation while subjected to a significant risk of device related complications. Inappropriate ICD shocks account for one-third of all ICD shocks and are associated with increased risk of all-cause mortality (5). Therefore, risk stratification beyond LVEF is needed to identify individuals who may benefit from primary prevention ICD. This would also improve cost-effectiveness of primary prevention ICD.

**SUBSTRATE IMAGING FOR RISK STRATIFICATION OF SCD**

SCD risk stratification is based on elucidating substrate for ventricular arrhythmias (VAs) and identification of arrhythmia triggers. Risk markers include surface electrocardiographic markers of autonomic modulation, abnormal impulse conduction or abnormal repolarization, invasive electrophysiological testing, genetic biomarkers, and molecular biomarkers of oxidative stress, inflammation, myocardial stress, and neurohormonal activation (6,7). However, clinical utility of these markers is limited by their poor sensitivity and specificity for prediction of arrhythmic mortality (7). Advanced imaging using cardiac magnetic resonance (CMR), single-photon emission computed tomography, or positron-emission tomography (PET) provides direct visualization and quantification of arrhythmic substrate in the form of myocardial scar, ischemia, and denervation.

Despite numerous studies spanning over the past 2 decades evaluating the role of substrate imaging for enriching SCD risk stratification, the association of chronic myocardial ischemia with VAs and arrhythmic SCD remains inconclusive. Several small studies found association of hyperemic myocardial blood flow, impaired coronary flow reserve, or peri-infarct ischemia with inducible VAs or clinical arrhythmic events in patients with LVEF ≤35% (8-10). However, these studies were limited by small sample sizes with no or limited risk-adjustment, wide confidence intervals, and non-uniform characterization of ischemia. In a larger study of 439 consecutive...
TABLE 1 Substrate Imaging for Risk Stratification of Arrhythmic Sudden Cardiac Death

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CMR — cardiac magnetic resonance; ICD — implantable cardioverter-defibrillator; LVEF — left ventricular ejection fraction; RCT — randomized controlled trial.

patients with LVEF ≤35% and rest/stress cardiac PET scan, none of the markers of comprehensively assessed myocardial ischemia including global or peri-infarct ischemia, coronary flow reserve, or resting and hyperemic myocardial blood flows were associated with clinical events of SCD or appropriate ICD shocks over a median follow-up of 3.2 years in either univariable or multivariable analyses (11). These findings were robust in patients with ischemic cardiomyopathy after accounting for post-PET revascularization. Furthermore, myocardial ischemia has been shown to be an infrequent cause of VAs in patients with prior myocardial infarction (12). Thus, the potential for ischemia imaging to improve risk-stratification of SCD in stable patients with reduced LVEF is limited at best.

Unlike chronic ischemia, the studies linking myocardial scar with VAs and SCD have yielded relatively more consistent results (11,13-15). Myocardial scar is characterized on CMR as late gadolinium enhancement (LGE) and on cardiac PET scans as severe fixed perfusion defect with >50% reduction in counts during perfusion imaging or lack of metabolic activity on F-18 fluordeoxyglucose imaging. LGE is associated with inducible VAs, ICD shocks, and SCD (13). In a large prospective study of 217 patients referred for cardiac resynchronization therapy with pre-procedure CMR, none of the patients without LGE experienced ICD therapy or SCD over a median follow-up of 3 years (14). However, LGE was present in 91% of patients with ischemic cardiomyopathy limiting its utility as a binary marker of risk stratification in this population. Among patients with LGE, scar mass and border zone (areas of mixed scar and viable tissue) mass was associated with higher hazard of VA events (14).

Sympathetic innervation can be imaged using 123I-meta-iodobenzylguanidine or 11C-meta-hydroxyephedrine scans (16,17). In Prediction of Arrhythmic Events With PET (PAREPET) study of 204 patients with ischemic cardiomyopathy eligible for primary prevention ICD, total denervated myocardium as well as denervated but viable myocardium (perfusion-innervation mismatch) was shown to be associated with ICD shocks or arrhythmic SCD at a median follow-up of 4.1 years (17).

The majority of these previous studies of substrate imaging were limited by a retrospective design with inherent limitation of assessing VA events, especially adjudication of SCD or appropriateness of ICD shocks. Of the prospective studies, none provided comprehensive evaluation of ischemia, scar, and denervation using both PET and CMR. Overcoming these limitations, in this issue of iJACC, Rijnierse et al. (18) prospectively investigated the utility of CMR-derived left ventricular structure, function, and scar burden, 13O-H2O PET-derived perfusion, and 11C-meta-hydroxyephedrine-PET derived innervation for prediction of VAs in patients with ischemic cardiomyopathy and
LVEF ≤35% who were eligible for primary prevention ICD. Patients underwent both CMR and PET imaging in the same hospitalization as planned ICD implantation. At baseline, uniform programming of ICDs was performed. In addition to home monitoring and event transmissions, scheduled follow-up device interrogations were performed with a minimum follow-up of 3 years for all patients. The primary outcome was appropriate ICD therapy or sustained VA >30s. The authors found that among 74 study patients, 26% experienced the primary outcome over a mean follow-up of 5.4 years. LVEF, left ventricular end-diastolic volume index, and scar border zone were associated with VAs; however, scar core size or markers of perfusion or innervation were not. The study was limited by its small sample size thus precluding meaningful multivariable analysis, interaction analysis, prediction modeling, and risk reclassification statistics. However, despite these limitations, arguably the most important finding from this extremely well-conducted investigation was the presence of significant overlap of all studied CMR and PET parameters among patients with or without VAs as seen in Figures 3 and 4 of this study (18) highlighting the limited potential for risk prediction for a given individual. A Cox regression model of LVEF and border zone mass explained only 12% of the variation of the primary outcome with a C-statistic of 0.65.

Thus, the overall results of this study are sobering with respect to advancing the concept of substrate imaging for risk prediction of ventricular arrhythmic events. Given the small sample size, these results are mostly hypothesis generating and may not be generalizable. However, in the context of prior studies, a common theme of association of scar border zone and lack of association of chronic stable ischemia with clinical ventricular arrhythmic events emerge. The lack of association of denervation with arrhythmic events is in conflict with PAREPET study of similar patient population of ischemic cardiomyopathy with LVEF ≤35% (17) and may be related to its small sample size or different definitions of denervation.

**FUTURE DIRECTIONS**

So where do we go from here? RCTs of substrate-based imaging are needed for robust evaluation of its clinical benefit for risk stratification of SCD beyond LVEF. However, there are many challenges to such investigations. For example, should patients with reduced LVEF and current eligibility for primary prevention ICD be randomized to ICD therapy versus no ICD therapy in absence of scar? Is there enough evidence for clinical equipoise in the scenario of absent scar to avoid ICD therapy? What should be the size of such a trial and how long of a follow-up should there be? The majority of patients with ischemic cardiomyopathy with persistently reduced LVEF despite revascularization and optimal medical therapy tend to have some degree of myocardial scar. In such patients, absence of scar may not be efficient for risk stratification. Would scar mass be appropriate in these patients to determine eligibility for trial? If so, would total scar mass or border zone scar mass be a better marker of trial eligibility? Is there a threshold of scar mass below which event rate is low enough for clinical equipoise? Unfortunately, current observational studies have failed to provide answers to these important questions (Table 1) and hence, RCT of substrate imaging for risk stratification of SCD in patients with severely reduced LVEF may have to wait.

Given the relatively low event rate of clinical ventricular arrhythmic events in contemporary management of patients with severely reduced LVEF, a large multicenter multinational prospective observational cohort of patients with uniform substrate imaging and long follow-up is needed (Table 1). Such a study may provide answers to relevant questions posed above. Otherwise substrate imaging for risk stratification of SCD in reduced LVEF patients may remain fanciful.

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