Decision Making for Implantable Cardioverter Defibrillator Implantation: Is There a Role for Neurohumoral Imaging?

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Risk prediction for sudden cardiac death (SCD) remains one of the most challenging tasks in medicine. The dire consequence of not identifying an individual who is otherwise doing well clinically but will succumb to a sudden arrhythmic death that is potentially either preventable or treatable has driven the search for a strategy that will identify these individuals. It has also been recognized that risk stratification is needed in patients who are currently classified into a high-risk group based on a depressed left ventricular ejection fraction, but who may never have an arrhythmic event. Although multiple implantable cardioverter defibrillator (ICD) trials have demonstrated a benefit to ICD therapy when patients were enrolled based primarily on having a depressed left ventricular ejection fraction, the optimal utilization of ICDs remains unclear. Undoubtedly there are a substantial subgroup of these patients that benefit from ICD implantation, but there are also cohorts that will likely not benefit and some may even be harmed by the ICD. To date, no risk stratifiers have been identified that resolve these issues. The challenges and potential approaches to improve risk stratification have been extensively discussed. In this issue of Circulation: Cardiovascular Imaging, Hachamovitch et al have taken on these challenges directly with their study designed to evaluate whether $^{123}$I-$m$IBG imaging has a role as a gatekeeper for ICD use.

See Article by Hachamovitch et al

During the past several decades, many noninvasive risk stratification techniques have been proposed and evaluated, including predominantly left ventricular functional assessment and ECG-based techniques. The advanced ECG analyses have included heart rate variability, signal averaged ECG, T-wave alternans, among others. The development of these techniques was based on strong pathophysiologic links to lethal ventricular tachyarrhythmias, namely altered autonomic inputs, abnormally delayed depolarization, and altered repolarization patterns. In many studies, these techniques have demonstrated a statistically significant ability to further assess risk, but their role in individual prognostication has nevertheless been disappointing.

Cardiac sympathetic imaging with $^{123}$I-$m$IBG represents a potentially important effort to advance risk stratification for arrhythmic sudden death based on the known role of disturbed autonomic function and adrenergic activation in the development of sudden death. The Adreview Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF) trial demonstrated that the heart/mediastinal (H/M) ratio derived from planar imaging was an independent predictor of the combined end point of heart failure progression, potentially life-threatening arrhythmic event, or cardiac death. Secondary analysis showed that arrhythmic events were more common in patients with an H/M ratio <1.6. Other clinical trials have demonstrated that various parameters related to $^{123}$I-$m$IBG imaging have value in predicting arrhythmic events. In a study of 106 patients with heart failure (left ventricular ejection fraction <40%), Tamaki et al revealed that $^{123}$I-$m$IBG myocardial washout predicted SCD events and did so better than H/M ratios. Boogers et al focused on the potential value of $^{123}$I-$m$IBG imaging in 116 patients who studied before ICD implantation and showed that late single-photon emission computed tomography (SPECT) $^{123}$I-$m$IBG defects were independently predictive of subsequent ICD therapy, as well as a combined end point of ICD treatment and cardiovascular death. Of note, large defects on SPECT imaging were far more predictive of these end points than small $^{123}$I-$m$IBG defects. The H/M ratio was not a significant predictor of appropriate ICD therapy. Interestingly, the present study of 777 patients, representing 81% of the original ADMIRE-HF cohort, also failed to support the value of planar H/M ratios for predicting who benefits from an ICD.

In the current report, Hachamovitch et al have undertaken an extensive modeling analysis in patients without an ICD at the time of enrollment in ADMIRE-HF to determine whether the $^{123}$I-$m$IBG scan result can identify which patients might have improved survival with ICD placement. On the basis of their analysis, the authors conclude that $^{123}$I-$m$IBG heart:mediastinal ratios inversely relate to mortality, but do not identify which patients benefit from ICD. Notably, this trial did not evaluate the predictive value of regional denervation beyond H/M ratios. The authors have done an excellent job delineating the limitations of their analysis, and the reader is referred to the primary article to appreciate the extent of these limitations. Nevertheless, it is useful to ponder the implications of the results of this analysis which will be the focus of the remainder of this editorial.
It is well appreciated that adrenergic activation is involved in the pathogenesis of arrhythmic sudden death, at least in a substantial portion of victims. Sympathetic activation alters conduction velocities and refractory periods in the ventricle. Differential responses in different regions of the myopathic heart can create electrophysiologically heterogeneous zones, which form the basis for arrhythmogenesis. This electrophysiologic heterogeneity has been well demonstrated in the setting of myocardial infarction, where sites that are apical to the infarct experience denervation and demonstrate denervation supersensitivity to catecholamine infusion.\textsuperscript{11} The role of denervated myocardium for predicting major arrhythmic events was demonstrated in the Prediction of Arrhythmic Events with Positron Emission Tomography (PARAPET) study.\textsuperscript{12} A substantial amount of denervated myocardium (37.5\%) was required for high-risk classification. After multivariable adjustment, the hazard ratio for sudden cardiac arrest was 3.57 for increased percent of denervated myocardium.

Given the appealing pathophysiologic relationship between disturbed myocardial sympathetic function and ventricular tachyarrhythmias, why was \textsuperscript{123}I-\textit{mIBG} imaging not more informative with respect to utility of ICD therapy in the present study? There are several explanations to consider. Figure 2 in the article by Hachamovitch et al\textsuperscript{4} is striking in that across the spectrum of risk, there does not seem to be a high attributable risk to ICD treatable ventricular tachyarrhythmias, even at the lower end of the risk spectrum. Potential explanations include the 35\% rate of a nonischemic cause, impeccable guidelines-based optimum pharmacotherapy, or a selection bias. Only patients with heart failure without an ICD could be enrolled in the trial; perhaps these patients were at lower risk. It is possible that these patients may have had longstanding heart failure without events, selecting for a lower risk group. Only 25\% proceeded to receive an ICD, which is consistent with a perception of lower risk. An additional explanation may be related to the type of \textit{mIBG} imaging, as the current and most widely used approach incorporates planar imaging and calculation of the H/M ratio. This rather crude assessment of neurohumoral function does not permit geographic localization and determination of regional heterogeneities, such as permitted with tomographic imaging (SPECT or positron emission tomography).\textsuperscript{10,12} This global assessment of cardiac sympathetic function may be a marker of the extent of cardiac disease providing its well-documented overall prognostic value, but may not provide specific enough information about heterogeneity in sympathetic innervation, which may be more specifically linked to the pathogenesis of ventricular tachyarrhythmias, as suggested by Fallavollita et al.\textsuperscript{12} In addition, a threshold for a particular extent of denervation may be more valuable.\textsuperscript{10,12} It is interesting to note that in a meta-analysis of techniques for risk stratification for SCD in patients with nonischemic cardiomyopathy, none of the ECG-based autonomic markers (heart rate variability, baroreflex sensitivity, and heart rate turbulence), also correlated with neurohumoral function, were significant predictors for arrhythmic events; these global measures of autonomic function again may provide a better signal for overall cardiac mortality. Indeed, when heart rate variability was used as a risk stratifier in an ICD intervention trial in patients with recent myocardial infarction and low ejection fraction, no benefit to ICD implantation was demonstrated.\textsuperscript{13} Finally, the ADMIRE-HF study had median follow-up of only 17 months, with 23 SCDs and 26 life-threatening arrhythmias. A longer time course to allow for more arrhythmic events could also alter the conclusions.

The present study should provide us with a cautionary note as further effort is invested in the critical area of risk stratification for arrhythmic sudden death. Even if the H/M ratio were found to be a significant risk factor for arrhythmic events, the predictive value of this 1 risk factor is unlikely to be sufficient to make individual patient decisions on ICD implantation. Pepe et al\textsuperscript{14} note “a marker strongly associated with outcome (or disease) is often assumed to be effective for classifying persons according to their current or future outcome. However, for this assumption to be true, the associated odds ratio must be of a magnitude rarely seen in epidemiologic studies.” In general, this would require odds ratios exceeding 20. Traditional markers have generally demonstrated odds ratios in the 3 to 6 range,\textsuperscript{15} making them individually unsuitable for patient-level decision making. Societal and patient acceptance of risk for a SCD end point are also critical factors in the debate. As we pursue the goal of risk stratification to allow for reliable/improved individual patient decisions, it will be important to consider that the pathophysiology of arrhythmic sudden death is complex and can be characterized by the underlying substrate, triggers, and other modulating factors. It may involve abnormalities in cardiac structure and function, depolarization and repolarization abnormalities, genetic mutations, alterations in cardiac innervation, acute stressors such as ischemia or adrenergic stimulation, among others. The incorporation of a measure of sympathetic activity into a model of SCD risk prediction seems promising, as has been shown with the Seattle Heart Failure Model, where \textsuperscript{123}I-\textit{mIBG} imaging resulted in a 22.7\% net reclassification rate, beyond demographic, historical, medication, and laboratory data.\textsuperscript{16} This trial supports the concept that a single test focused on only 1 aspect of this multidimensional problem can have incremental value, but may not have adequate predictive power to provide a stand-alone risk stratifier that can accurately classify who is at risk and who is not. Given all the information that we now have on the predictive value of the tests that characterize components of the pathogenesis of sudden death, it is now time to synthesize this information and focus our efforts on developing a multidimensional or tiered approach to risk stratification that can address this problem.

**Disclosures**

Dr Goldberger is Director of the Path to Improved Risk Stratification, NFP, a not-for-profit think tank on risk stratification for prevention of sudden cardiac death, which has received unrestricted educational grants from Boston Scientific, GE Healthcare, Medtronic, and St. Jude Medical. Dr Hendel has served in the past (>2 years) as a consultant for GE Healthcare and currently is on the advisory board of Adenosine Therapeutics and a consultant and speaker for Astellas Pharma.

**References**

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