Risk Stratification and Sudden Cardiac Death
Is It Time to Include Autonomic Variables?

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Sudden cardiac death (SCD) remains a major cause of mortality in patients with ischemic cardiomyopathy, and accurate risk stratification strategies can have significant public health implications by reducing mortality and healthcare costs.[1] Although effective, the population impact of implantable cardioverter-defibrillators (ICD) on cardiac mortality has been modest,[2] in part because of suboptimal risk stratification algorithms and in part because of competing causes of death in this population. In this regard, a validated risk stratification algorithm that can accurately discriminate between those patients at high risk of arrhythmic death and those more likely to die from nonarrhythmic causes is invaluable. Identification of these risk-model variables inevitably requires a thorough understanding of arrhythmogenic causes of death in high-risk populations.

See Article by Fallavollita et al

Cardiac autonomic dysfunction is known to accompany cardiovascular disease. Specifically, myocardial infarction leads to axonal injury and sympathetic denervation, not only in the scar and border-zone regions but also in areas distal to the infarct (viable but denervated myocardium).[3] Given that the majority of postganglionic cardiac neurons for sympathetic fibers lie in the stellate and middle cervical ganglia,[4–6] in the setting of peripheral nerve damage and in the presence of signals such as neural growth factor, attempts at reinnervation ensue. However, this reinnervation is incomplete and heterogeneous, and a pattern of hyperinnervation is observed in localized border-zone regions,[7] along with incomplete innervation and denervation in the rest of the scar and other border-zone areas. These localized regions of hyperinnervation, denervation, and more intact innervation in noninfarcted myocardium lead to increased heterogeneities in local ventricular repolarization time and action potential duration. Increased dispersion of repolarization has been associated with ventricular arrhythmias in patients with ischemic cardiomyopathy and in animal models of myocardial infarction.[8,9] Data from experimental infarct models and in patients with ischemic cardiomyopathy demonstrate global cardiac sympathetic remodeling after infarction, with myocardium remote from the infract exhibiting abnormal neural control.[10,11] Such regional heterogeneities in ventricular repolarization, which are increased during sympathetic activation, worsen the substrate for re-entrant ventricular arrhythmias and increases risk of SCD. Restoring normal innervation has been shown to decrease the risk of ventricular arrhythmias in experimental models.[12]

In this issue of *Circulation: Cardiovascular Imaging*, Fallavollita et al expand on their original study[13] and seek to identify specific risk factors associated with cause-specific cardiac mortality (sudden cardiac arrest versus non-SCD [NSCD]) by performing a pilot competing risks analysis of the National Institutes of Health–sponsored Prediction of Arrhythmic Events with Positron Emission Tomography trial (PARAPET).[14] In 204 patients with ischemic cardiomyopathy and reduced ejection fraction (<35%) eligible for an ICD for primary prevention, death from cardiac causes was ascertained and attributed to either sudden cardiac arrest (arrhythmic death or ICD equivalent, with an ICD discharge for ventricular fibrillation or ventricular tachycardia >240 bpm) or NSCD caused by pump failure. Positron emission tomography imaging was performed to assess myocardial sympathetic innervation, perfusion, and viability. ^{11}C-meta-hydroxyephedrine, a catecholamine analog labeled with ^{11}C that shares the same neuronal uptake mechanism as norepinephrine, was used to assess sympathetic nerve norepinephrine uptake and the extent of myocardial denervation. Chamber volumes and left ventricular ejection fraction were assessed with echocardiography.

During a 4.1-year follow-up period, 33 sudden cardiac arrests and 36 NSCDs occurred. Of note, 29 patients refused ICDs in this study. In the competing risk analysis, sudden cardiac arrest was correlated with a larger volume of denervated myocardium, greater left ventricular end-diastolic volume index, lack of angiotensin-converting enzyme inhibitor use, and elevated BNP (B-type natriuretic peptide). Meanwhile, NSCD was associated with a larger left atrial volume index and left ventricular end-diastolic volume index, older age, higher resting heart rate, and elevated creatinine. After adjustment for competing risks, left ventricular ejection fraction or New York Heart Association Class were not associated with either sudden cardiac arrest or NSCD. Similar to the original PAREPET study, infarct size did not correlate with either end point.

The results of this study offer further mechanistic insight into risk factors associated with SCD and take the outcomes of the original PAREPET trial a step further by emphasizing that the extent of myocardial denervation as assessed by positron emission tomography imaging can be independently associated with SCD, even when using a competing risk methodology. In fact, 3 of the 4 variables associated with sudden cardiac arrest in the original multivariable analysis remained unchanged

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(denervation, left ventricular end-diastolic volume index, and lack of angiotensin-converting enzyme inhibitor use; elevated BNP replaced elevated creatinine). Hence, a combination of sympathetic and myocardial remodeling seem to preferentially increase the risk of arrhythmic deaths in these patients. The extent of denervated myocardium, as assessed by positron emission tomography ^{11}C-meta-hydroxyephedrine, is most likely a marker for heterogeneous sympathetic innervation, leading to increased dispersion of ventricular repolarization.

Some of the same limitations that afflict retrospective studies apply to the current study. The studied population is small and predominantly men (90%). Certain variables, previously associated with mortality, including atrial fibrillation and chronic obstructive pulmonary disease, either were not collected or not included in the model given the population size and number of events. The limited number of patients also may potentially explain why variables such as left ventricular ejection fraction and New York Heart Association Class did not reach statistical significance for cardiac mortality, given their association with mortality in other studies.[15,16] Furthermore, retrospective adjudication of cause-specific mortality and sudden cardiac arrest may be biased. There are also limitations with the quantification of defect size, which was based on using a 75% threshold for left ventricular maximum activity, a somewhat arbitrary threshold that can lead to inaccuracies if there exists a more global reduction in innervation, which has been shown in animal models of myocardial infarction and in patients with ischemic cardiomyopathy.[10,11,17] A regional retention index calculation or more standardized quantification across patients would have been valuable.

Despite these limitations, Fallavollita et al are to be commended for their contribution, which points to the growing body of evidence supporting the inclusion of cardiac autonomic variables in assessing risk of SCD. This study, along with its predecessors, emphasize the need for incorporation of autonomic indices into risk stratification algorithms, in order to improve the prognostic ability of physicians to predict cause-specific mortality and to better allocate expensive resources and therapies, such as ICDs. Improved understanding of the mechanisms behind pathological cardiac sympathetic and parasympathetic innervation patterns also represent an important approach for future development of neuromodulatory therapies, some of which have already shown benefit in treatment of ventricular arrhythmias.[18] In this regard, future steps should include prospective validation of these autonomic variables, including sympathetic denervation, and implementation of randomized prospective studies aimed at modulating the cardiac autonomic nervous system for prevention of SCD.

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Disclosures

None.

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