Ventricular arrhythmias and autonomic nervous system: evolving role of radionuclide imaging

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Autonomic nervous system exerts a strong influence on arrhythmogenesis.^{1,2} Focus in the recent years has changed from affirming this concept, to translating it, into clinically useful information. Risk stratification of patients beyond left ventricular ejection fraction (LVEF) has been the focus of most studies.^{3–6} They have almost exclusively studied the sympathetic innervation of the ventricular myocardium, which is easier to evaluate, with currently available radionuclide tracers than parasympathetic innervation. The principle question these studies have tried to address is: Does sympathetic denervation as assessed by nuclear imaging help in better risk stratification of heart failure (HF) patients by identifying those at increased risk of ventricular arrhythmia (VA)?

CARDIAC SYMPATHETIC INNERVATION AND ITS ROLE IN ARRHYTHMOGENESIS

Sympathetic neurons, which supply the atrial and ventricular myocardium, are postganglionic fibers, whose cell bodies are located in the cervical and thoracic sympathetic ganglia. This is in contrast with the parasympathetic neurons which are preganglionic fibers arising from the Vagus nerve and synapse with ganglia located in the epicardial fat pad.^{7,8} Sympathetic stimulation results in release of norepinephrine (NE), stored in vesicles, in the pre-synaptic nerve terminal to the synaptic cleft, where it exerts its influence on myocytes

via the β adrenergic receptors. Beta receptor stimulation is known to increase inward calcium current through L-type Calcium channels and also outward potassium current through IKs. Net effect of these ionic changes in normal ventricles is shortening of action potential duration (APD), as the outward current is more than the inward and decrease in dispersion of refractoriness.^{9–11} However, in disease states either acquired or congenital, which cause heterogeneous distribution of these nerve fibers, their stimulation can lead to increased dispersion of refractoriness. Patients with ischemic cardiomyopathy can have areas of increased sympathetic nerve sprouting adjacent to areas with denervation.¹² This heterogeneity in distribution can lead to changes in refractoriness and electrical properties of myocardium thus creating an ideal environment for re-entrant arrhythmias.

IMAGING THE CARDIAC SYMPATHETIC NERVOUS SYSTEM

The major neurotransmitter released at sympathetic neuromuscular junction is NE, its radiolabelled analogs provide an opportunity for nuclear imaging of cardiac sympathetic neurons. Guanethidine is a false neurotransmitter analog of NE, which by chemical modification produces a molecule, metaiodobenzylguanidine (mIBG) that can be labeled with radioactive iodine and therefore imaged. It is not metabolized by MAO unlike NE and thus concentrated in the nerve terminals. I^{123} emits predominantly gamma photons of 159 KeV and can thus be easily imaged with SPECT camera.^{13,14} There are other analogs of NE, which can be used for PET imaging. C^{11} -labeled hydroxyephedrine (HED) is most commonly studied. It has higher selectivity for neuronal NE uptake mechanism and more homogenous uptake. These properties may allow better differentiation of denervated myocardium from normal innervation.¹⁵ Other agents are being evaluated to study different properties of the sympathetic nervous system,

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independent of the NE uptake, like vesicular storage function and adrenergic receptors density. Imaging, using combination of these agents may provide a more complete understanding of the sympathetic nervous system in an individual patient. Analysis of cardiac mIBG images currently consists of global tracer uptake assessment on planar images, tracer washout between early and delayed planar images and regional uptake on tomographic images. Global mIBG uptake is usually represented as early and late heart to mediastinum uptake ratio (HMR), which is derived by comparing the pixel activity over a region of interest in the heart, with that in the upper mediastinum. A ratio of 2.2 ± 0.3 is considered normal and a ratio of <1.6 (two standard deviation below normal) is considered abnormal and correlates with increases risk.^{16,17} Planar imaging however cannot discern regional differences in sympathetic innervation of myocardium which tomographic imaging can do. SPECT mIBG scans has also been used in conjunction with perfusion imaging to identify areas of denervated but perfused myocardium.³ These tend to be the infarct border zones with viable but denervated myocardium and have been associated in small studies with inducibility of VA.¹⁸ SPECT mIBG imaging however does not account for the global down regulation of MIBG storage in some patients with heart failure, limiting accurate quantification of defects.⁶ Also use of a scoring system similar to perfusion imaging may be of limited value, as segment with very low or very high score (thus signifying complete denervation and normal innervation, respectively) are unlikely to be arrhythmogenic and a summed score incorporating these segments can be erroneous.

SYMPATHETIC NERVOUS SYSTEM IMAGING AND VENTRICULAR ARRHYTHMIA

Sympathetic denervation has been studied to risk stratify HF patients and to localize arrhythmogenic sites in the myocardium. Any test used to risk stratify patients should have a very high negative predictive value (NPV) for physicians to feel confident in withholding treatment. In ADMIRE-HF, (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) which was a large scale prospective study using mIBG imaging in patients with NYHA class II/III heart failure and $LVEF \leq 35\%$ ¹⁹ NPV for H/M ratio >1.8 for fatal or potentially fatal arrhythmic event was 100%. These patients however composed only 5% of the study population.^{19,20} Highest frequency of arrhythmic events occurred in patients with H/M ratio between 1.3 and 1.39. Patients with lower H/M ratio did have higher mortality, suggesting the higher

prevalence of non-arrhythmic causes of death, like pump failure and non-cardiac causes. PARAPET (Prediction of Arrhythmic Events with Positron Emission Tomography) trial studied a strictly arrhythmic end point of sudden cardiac arrest (SCA) defined as arrhythmic death or an ICD discharge for VA >240 beats per minute.²¹ This study divided the subjects into tertiles of increasing volume of denervated myocardium assessed by PET imaging using HED. Patients in the highest tertile had a significantly higher SCA event rate suggesting linear relationship. The mean defect size was 27% for denervated myocardium as compared to ADMIRE-HF where more than 75% of patients had at least 50% of their myocardium involved. This may explain the linear effect observed, however, it is difficult to compare studies using different imaging modalities and tracers. Another prospective study using mIBG SPECT score, showed significantly higher incidence of ventricular arrhythmia in patients with summed SPECT score >26 as compared to those with summed SPECT score <26 .⁴

The present study by Travin et al focuses on the mIBG SPECT imaging cohort of the ADMIRE-HF study. Secondary analysis in the ADMIRE-HF study did not show an association between SPECT scores and events.¹⁹ The authors point out that blinding of readers to demographic data and to perfusion imaging may have played a part in these results and that a standardized assessment of the MIBG SPECT images taking these factors into consideration may allow for better characterization of relationship of SPECT innervation defects with arrhythmic events. The data revealed a statistically significant hazard ratio of <1 for increasing summed MIBG score. Further analysis showed that this is likely due to clustering of arrhythmic events in patients with intermediate MIBG defect scores. The authors then repeated the analysis using binary categorization of segments as normal or abnormal to rule out the possibility that overall high summed stress score may have distorted the results. Even after simple binary classifications patients with intermediate number of abnormal segments had highest arrhythmic event. These findings suggest the relationship between denervation defect size and arrhythmic risk may not be linear and patients with intermediate defects may be at higher arrhythmic risk. There are some obvious shortcomings of the trial like a large number of patients in the ADMIRE-HF study were not included in the current analysis because of absent or inadequate imaging, very few patients with low scores were included and also the patient population may have been different from prior studies^{3,4} in terms of higher defect scores thus representing a sicker heart failure populations.

CURRENT KNOWLEDGE AND FUTURE DIRECTION

No definite conclusion can be drawn from the current study by Travis et al, however it does raise an interesting question: Are patients with intermediate size denervation defects at higher risk of VA as compared to those with very large defects? This needs to be addressed in future studies, but, rather than correlating quantity of denervation defect with VA risk it may be more prudent to study heterogeneity of innervation. Increasing heterogeneity provides for higher probability of initiating and sustaining arrhythmias. Global innervation imaging parameters, like H/M ratio, can be used to broadly classify patients at low and high risk. In order to sub-stratify them, identifying arrhythmogenic substrate and sites initiating arrhythmias a more regional assessment of extent, severity, and heterogeneity of innervation by SPECT or PET imaging would be more helpful. It has to be kept in mind, most studies have looked at patients with ischemic cardiomyopathy and very little data are available for patients with dilated cardiomyopathy. Similarly role of other components of autonomic nervous system in arrhythmogenesis like adrenergic receptor density, vesicular storage function, and parasympathetic nervous system remains to be addressed.

Disclosure

The authors have indicated that they have no financial conflict of interest.

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