Editorial

Life out of balance: The sympathetic nervous system and cardiac arrhythmias

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See article by Sosunov et al. [1] (pages 659–669) in this issue.

That the sympathetic nervous system has profound and recurrent effects on cardiac electrical activity has been an article of faith (ampley supported by fact) for decades. However, our understanding of the role of sympathetic activity in the development of cardiac arrhythmias remains fragmented. In this issue of the journal, Sosunov and co-workers contribute an important piece to this puzzle [1]. They present a conceptually straightforward and technically demanding series of experiments that asks the question ‘what are the electrophysiological consequences of right stellatectomy in the dog?’. In the process of answering that question, they have uncovered several interesting consequences of this type of denervation. However, they have also, as one might hope with any worthwhile study, raised more questions than they have answered.

One of the more intriguing unanswered questions relates to potential roles for the sympathetic nervous system in the development of ventricular arrhythmias in patients afflicted with the long QT syndrome (LQTS). In a recent editorial, Peter Schwartz revisited, with some circumspection, the now all but abandoned terrain of the ‘sympathetic imbalance’ hypothesis for that syndrome [2]. In his review of the theory, he emphasized the generally acknowledged triggering role of the sympathetic nervous system. Perhaps more importantly, he presented a cogent argument and brief outline of evidence for a role of sympathetic stimulation as a modifier of the arrhythmogenic substrate in patients with LQTS.

Sosunov et al. [1] provide additional support for a contribution of sympathetic innervation to the development of a permissive substrate for ventricular arrhythmias. In particular, they cite experimental evidence for a trophic effect of sympathetic neurotransmitters on the expression of certain cardiac ion channels, including repolarizing K+ current channels, and suggest that the absence of such effects in sympathetically denervated myocardium may account for some of their observations. Not only have such effects been demonstrated in normal myocardium [3], but there is evidence that the trophic effects of sympathetic neurotransmitters may alter the electrophysiological substrate in diseased hearts as well [4–6].

Given the documented effects of sympathetic neurotransmitters on the expression of certain ion channels, perhaps a revisiting of the ‘sympathetic imbalance’ hypothesis is in order. The studies cited above would seem to suggest at least two additional ‘modifier’ roles for the sympathetic nervous system. Either may help to explain the routine clinical finding that groups of patients with a common genotype frequently exhibit a spectrum of phenotypes [7].

The first possibility is that an imbalance of sympathetic innervation (defined broadly to encompass different densities of sympathetic nerves, receptors, components of second messenger cascades, etc.) may result in non-uniform expression of errant genes in patients with LQTS. Consequently, the density of an abnormal ionic current might vary across different regions of the heart, in association with variation in the density of sympathetic innervation. The consequences arising from such heterogeneity of expression could include increased QT interval and QT dispersion, which could, in turn, increase susceptibility to the development of triggered activity, conduction block and reentrant excitation.

The second possibility is that sympathetic imbalance may alter ‘compensatory’ mechanisms set in motion by the presence of a mutant ion channel, particularly with respect to increased or decreased expression of complimentary or competing plateau currents. The possibility that a cardiac myocyte might monitor the currents being expressed at any given time and adjust its spectrum of ionic currents to satisfy an optimal setpoint with respect to the balance of currents, and that such a process might be modulated by the sympathetic nervous system, seems less like ‘science-
faction’ than it might have even a few years ago, in light of the current fascination with ionic remodeling [8–10]. Such a mechanism might even help to explain the observation that in the present study right stellectomy initially was associated with prolongation of the QT interval, but that with time the QT prolongation abated.

The German shepherd model of inherited ventricular arrhythmias and sudden cardiac death [11], which motivated the experiments by Sosunov et al. [1], could provide a proving ground for tests of the hypothesis that sympathetic imbalance confers non-uniform gene expression. In these animals, sympathetic innervation of the left ventricle is significantly attenuated, compared to the right ventricle [12], and cellular electrophysiological abnormalities are largely restricted to denervated regions of tissue [5,13,14]. The German shepherds offer the additional advantage of exhibiting a naturally evolving syndrome complete with ventricular arrhythmias and sudden death [11], features not reproduced by right stellectomy alone, as reported by Sosunov et al. [1]. Perhaps the initial investigation could focus on the distribution of the transient outward current ($I_{to}$) and its channel proteins (primarily Kv 4.3 and its associated beta subunit [15,16]), recognizing that even in normally innervated canine ventricles distribution of $I_{to}$ is not uniform [17].

A caveat regarding $I_{to}$, however: despite the numerous studies demonstrating an association between various forms of cardiac disease and a reduction of $I_{to}$ density (e.g. see Refs. [5,18–21]), it still is unclear (at least to this observer) whether $I_{to}$ is a canary in the mineshaft, in that its disappearance is a reliable harbinger of impending cardiac disease, or a red herring – an easily identified distraction whose disappearance merely reflects the fact that it is of so little importance to cell function that it is jettisoned at the first sign of trouble.

That issue aside, studies of $I_{to}$ and other repolarizing currents may provide important clues to the relationship between sympathetic innervation and ion channel gene expression. Investigations of that type promise to build on the observations of Sosunov et al., hopefully to the point where we have a sufficiently clear understanding of the role of sympathetic activity in the genesis of cardiac arrhythmias to more effectively manage patients at risk for such arrhythmias.

References