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EDITORIAL COMMENT

Estimating Cardiac Sympathetic Activity From Subcutaneous Nerve Recordings

More Than Skin Deep?*

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Cardiac arrhythmias remain a major cause of morbidity and mortality in developed nations (1). Given the strong relationship between the autonomic nervous system (ANS) and arrhythmogenesis (2), understanding ANS function in health and disease states to harness its benefits for therapeutic purposes is under intense study. Approaches generally include examining cardiac responses to activation and blockade of sympathetic and parasympathetic function, as well as recording from various ganglia, superficial nerves (e.g., peroneal), and sites within the central nervous system, to understand patterns of neuronal firing and outflow to organs in response to stimuli or disease states (3).

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Recordings of neural activity date back approximately 50 years (4) and are performed routinely in animal models and in humans; they generally involve direct sampling of activity from muscle, the peroneal nerve, renal nerve, vagus nerve, and the sympathetic chain/ganglia, to name a few (3). In this issue of *JACC: Clinical Electrophysiology*, Shelton et al. (5) report on the use of subcutaneous nerve activity (SCNA) to estimate sympathetic activity and outflow. The main purpose of the study was to validate SCNA, a new method recently described by the group, as a means to estimate cardiac sympathetic activity in a canine model of pacing-induced heart failure (HF). The authors evaluated the temporal relationship between SCNA and simultaneously recorded left stellate ganglion nerve activity (SGNA), as well as the association of both factors with atrial arrhythmia onset. Vagus nerve activity was also recorded, although parasympathetic activity was not a major focus of the study. The impact of cryoablation of bilateral stellate ganglia (BSG) on SCNA and atrial arrhythmogenesis was also examined. The authors report a correlation coefficient of 0.64 (95% confidence interval: 0.58 to 0.70) between SGNA and SCNA, and they suggest that SCNA can be accurately used to estimate cardiac sympathetic tone in dogs with HF. The authors observed interestingly that a rise in SCNA invariably predicted atrial arrhythmogenesis and that cryoablation of BSG significantly reduced SCNA and eliminated all atrial arrhythmias.

First, noninvasive or minimally invasive approaches to estimating sympathetic tone are of immense value given the strong relationship between sympathoexcitation and both atrial and ventricular arrhythmogenesis, and cardiac dysfunction in general (2). Approaches that accurately estimate sympathetic outflow can be used in numerous ways for identifying, preventing, and treating a variety of cardiovascular problems, and this value extends to almost every organ or tissue bed (6-8). In addition to improving our understanding of the neural basis of cardiac pathology in humans, identification of pathological increases in sympathetic outflow can be incorporated into systems that alert patients to evoke

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a self-initiated intervention. They can be integrated into implanted cardiac electrical devices or implanted neuromodulation-based devices to provide closed-loop real-time interventions to prevent and/or treat arrhythmias. It should be highlighted that such an approach is an advocated strategy for neuromodulation, given the tremendous plasticity within the ANS, which in large part may underlie multiple failed neuromodulation studies.

The value in the present study (5) is in its push toward realizing this goal. If SCNA can indeed be used to estimate cardiac sympathetic outflow, it opens new doors toward realizing the potential of the ANS in the diagnosis and treatment of cardiac diseases. However, several important considerations must be taken into account in the interpretation of the implications of this study. Technically, the approach used in the present study deviates from typical approaches for superficial nerves. The electrodes had an impedance of 0.7 to 0.8 Ω, and recordings were amplified 10,000 times and sampled at 1,000 Hz. Typical impedances for superficial nerves range from 50 kΩ to 10 MΩ and generally fall in the 1 to 2 MΩ range (3), orders of magnitude higher than that used in the study by Shelton et al., and are likely to have tremendously influenced the authors' recordings. Band-pass filtering can also range from 300 to 3,000 Hz and typically fall in the 700 to 2,000 Hz range. In the present study, high-pass filtering was performed at 150 Hz for SGNA, SCNA, and vagus nerve activity, which may have also influenced the recordings made, as this filter setting is typically used for nerve bundle recordings. These factors raise the concern that the recording and filtering characteristics introduced similar signals into the recordings and may account for the correlation seen. A first-of-its-kind guideline for recording sympathetic nerve activity was recently published and provides more details on requirements for recording and quantification (3).

In addition, SCNA, as with skin sympathetic nerve activity, likely reflects a mixed population of vasoconstrictor, vasodilator, piloerector, and sudomotor nerves, which confound interpretation, and mechanistic dissection of results (2). These recordings will be more sensitive to perturbations than recordings within stellate ganglia, having already been shown to be dissociated from muscle sympathetic nerve activity (9). This action likely accounts for the profound variability seen in the correlation coefficients, especially for the control group that did not undergo cryoablation (0.21 to 0.61) before pacing. Furthermore, it is unclear what value a correlation coefficient of 0.21, despite a highly significant p value (<0.005), means for cardiac neurophysiology. Although correlation coefficients were higher (0.56 to 0.84) in the cryoablation group, one should be cautious in interpreting these coefficients because the cryoablation is likely to have introduced a complex set of reflex changes.

It is interesting that all episodes of atrial tachycardia observed in this canine HF model were preceded by SCNA activity (5). Furthermore, the authors suggest that all episodes of atrial tachycardia were eliminated by BSG cryoablation, even in the presence of pacing-induced HF. This finding suggests that in this model, atrial arrhythmogenesis is completely related to sympathetic function, which is perhaps surprising, as it is generally accepted that sympathetic activity contributes to arrhythmogenesis, rather than being the sole cause (1,2). In addition, there seemed to be a reduction in episodes of atrial tachycardia after pacing-induced HF was instituted (243 vs. 117 episodes). This finding is somewhat unexpected and indicates a complex set of processes governing neural and myocardial remodeling.

In summary, noninvasive or minimally invasive approaches to estimate cardiac sympathetic outflow are very valuable. Such approaches will profoundly affect our understanding of neural control of cardiac function in health and disease, and will accelerate the development of successful techniques for clinically useful neuromodulation-based therapies. Whether SCNA or skin sympathetic nerve activity can accurately reflect cardiac sympathetic outflow remains unclear; however, the present study by Shelton et al. (5) is a step in that direction.

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