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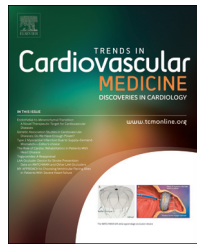

Recording sympathetic nerve activity from the skin

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ABSTRACT

Sympathetic tone is important in cardiac arrhythmogenesis; however, methods to estimate sympathetic tone are either invasive or require proper sinus node function that may be abnormal in disease states. Because of the direct and extensive connections among various nerve structures, it is possible for the sympathetic nerves in the various structures to activate simultaneously. Therefore, we hypothesized that nerve activity can be recorded from the skin and it can be used to estimate the cardiac sympathetic tone. Preclinical studies in canines demonstrated that nerve activity is detectable using conventional ECG electrodes and can be used to estimate cardiac sympathetic tone. Subsequent clinical studies further supported this concept. In addition to studying the autonomic mechanisms of cardiac arrhythmia, these new methods may have broad application in studying both cardiac and non-cardiac diseases.

Key words: Sympathetic nerve activity, Autonomic nervous system, Arrhythmia.

Introduction

Since the invention of the electrocardiogram (ECG) by Einthoven [1], the ECG has been an important part of clinical practice. A primary reason for the popularity of the ECG is that it is non-invasive and can be performed in any patient by placing electrodes on the skin. The present methods of ECG recording focus on detecting electrical signals from the heart. However, we hypothesized that the application of the ECG could be expanded to also record sympathetic nerve activity (SNA). Sympathetic tone is important in cardiac arrhythmogenesis [2,3], and a commonly used method to estimate cardiac autonomic nerve activity is to calculate heart rate variability, or sympathetic nerve activity can be directly measured by microneurography [4,5]. However, these methods are either too invasive and cannot be done in ambulatory subjects or require proper sinus node response to autonomic stimulation that may be abnormal in disease states [6,7], and may not reflect the sympathetic tone in those conditions [8].

Cardiac sympathetic innervation comes from the paravertebral cervical and thoracic ganglia [9]. Among them, the stellate (cervicothoracic) ganglion is a major source of sympathetic innervation. It connects constantly with phrenic nerves and almost as often to the vagal nerves [9]. The paravertebral ganglia also directly connect with spinal nerves [10], which connect with the intercostal nerves [11]. These intercostal nerves split into ramus cutaneous lateralis and a deep branch to the musculus rectus abdominis [12].

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Histological studies of human skin biopsy confirmed the presence of abundant sympathetic nerves in arteriovenous anastomoses, arrector pilorum muscles, and arterioles [13]. Using horseradish peroxidase as tracer, Baron et al [14] and Taniguchi et al [15] found that all skin sensory and sympathetic neurons are located ipsilaterally. The sympathetic somata are located in the middle cervical and stellate ganglia as well as in the thoracic ganglia. Because of the direct and extensive connections among various nerve structures, it is possible for the sympathetic nerves in the various structures to activate simultaneously. Therefore, we hypothesized that SNA recorded from the upper thorax can be used to estimate the cardiac sympathetic tone and that this nerve activity could be recorded from the skin.

To preserve the signal from the ECG and to eliminate noise, the American Heart Association (AHA) standard recommendation for low-pass filtering of the ECG is 150 Hz for adolescents and adults, and 250 Hz for children [16]. Higher frequency signals, although known to be clinically important [17], are routinely eliminated by this low-pass filtering. Because there is no need to record high-frequency signals, the conventional ECG and Holter monitoring devices do not have a wide bandwidth and high sampling rate. The high-frequency signals that are eliminated may contain both muscle and nerve activities. McAuley et al [18] reported that the electromyography (EMG) usually has a frequency of $<$100 Hz. At most, small amounts of muscle activity could reach 400 Hz [19]. The standard high-pass setting for observing nerve activity during a microneurography study is 700 Hz [20]. Using equipment with a wide bandwidth (2 kHz) and high sampling rates (4–10 K/s) we hypothesized that nerve activity could be simultaneously recorded along with the ECG. Signals recorded from electrodes on the skin are band passed between 0.5 and 150 Hz to display ECG signal. The same signals can then be high-pass filtered to reveal nerve activity. Data Supplement Fig. S1 illustrates the above concept. It shows fast Fourier transform (FFT) analyses of the signals recorded from the skin. High-pass filtering at 150 Hz eliminated the ECG signals. High-pass filtering at 500 or 700 Hz increased the specificity but reduced the sensitivity of any nerve recordings. The signal-to-noise ratio is reduced. However, the basic patterns of nerve discharges remain.

Recently, methods have been developed to record autonomic nerve activity in ambulatory dogs, and through this process, it has been documented that sympathetic nerve activity immediately precedes the onset of atrial and ventricular arrhythmias as well as sudden cardiac death [21–24]. These methods have included to directly record sympathetic nerve activity from either subcutaneous tissues or on the surface of the skin in canine models. We found that both subcutaneous nerve activity (SCNA) and superficial skin sympathetic nerve activity (SKNA) closely correlate with stellate ganglia nerve activity (SGNA) in ambulatory canine models [25–27]. From these results, we hypothesized that with high-frequency sampling and high-pass filtering, we can also record SNA from the skin or subcutaneously just underneath the skin in the clinical setting.

Preclinical studies in ambulatory dogs

In an initial series of experiments, a radiotransmitter (D70-EEE, Data Sciences International, St. Paul, MN) was implanted in dogs to record SGNA and vagal nerve activity (VNA) [23,24,28,29]. A third pair of bipolar electrodes was placed in the subcutaneous space, with one electrode each inserted under the subcutaneous tissue of left thorax and left abdomen. After 2 weeks of recovery, the radiotransmitter was turned on to continuously record from all 3 electrodes at a sampling rate of 1000 Hz. To optimize nerve signals and to filter out any residual ECG signals, data from the left stellate ganglion, the left thoracic vagus nerve, and the subcutaneous tissue were high-pass filtered at 150 Hz and simultaneously

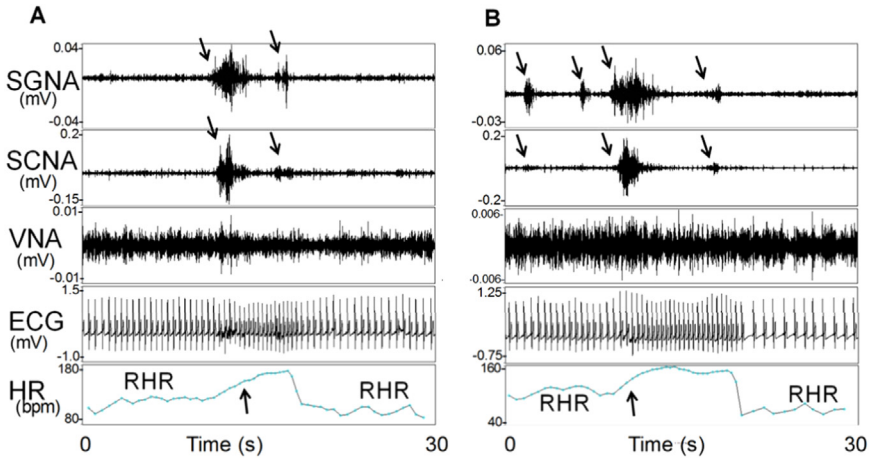

Fig. 1 – SCNA and SGNA are associated with heart rate elevation in an ambulatory dog. The first portion of (A) Rhythmic heart rate (HR) variations consistent with respiratory heart rate responses (RHR). SGNA and SCNA (downward arrows) then activated simultaneously, resulting in heart rate acceleration (upward arrow). There were no obvious changes of VNA in this recording. Simultaneous cessation of the SGNA and SCNA was associated with a reduction of the heart rate and the resumption of RHR. (B) Simultaneous activation of SGNA, SCNA (downward arrows) in the same dog 25 s after (A). Downward arrows point to simultaneous nerve activities in SGNA and SCNA. Upward arrow indicates the onset of tachycardia. ECG, electrocardiogram. (Adapted with permission from Robinson et al. [33])