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Heart Rate Variability and Autonomic Nerve Activities in Ambulatory Dogs

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Abstract—**Analysis of heart rate variability is a valuable method to investigate the sympathetic and parasympathetic function of the autonomic nervous system. Although such analyses can provide quantitative estimates of autonomic neural activity, simultaneous recording of neural activities and ECG will allow more direct investigation of neural modulation of heart rate. We developed a method that allows direct and long-term recording of neural activities and ECG using wireless device implanted in ambulatory dogs. The aim of this study was to investigate the relationship between autonomic neural firing and heart rate variability. In this study, HRV and neural activities were assessed for 5 continuous days. HRV was evaluated by calculating the mean and the standard deviation of inter-beat intervals in 24 hours. Neural activities were obtained by the sum of the filtered rectified neural signals after 200 Hz high-pass filtering to remove ECG interference. The plots showing HRV as a function of both the sympathetic and vagal activities will offer significant insights into neural modulation of heart rate in normal and diseased hearts.**

I. Introduction

Analysis of Heart Rate Variability (HRV), the analysis of variations in the instantaneous heart rate time series using the beat-to-beat RR-intervals, has been shown as a reliable technique to assess autonomic activity in patients with cardiovascular disease[1]. HRV is a valuable tool to investigate the sympathetic and parasympathetic function of the autonomic nervous system. It provides information about the sympathetic-parasympathetic autonomic balance and thus about the risk for sudden cardiac death, cardiac arrhythmias or heart attack. Task Force of the European Society of Cardiology the North America Society of Pacing Electrophysiology[1] gave a detailed review of the physiology of heart rate variability and summarized the standards of measurement and clinical use of this technology. It has been suggested that assessment of the variability of heart rate could provide a noninvasive measure of cardiac sympathetic and vagal nervous system function, and the risks of cardiac and sudden death in patients with advanced cardiac disease [2]. A reliable noninvasive measure of cardiac sympathetic activity would also likely have prognostic implications, such as in the prediction of increased mortality in chronic heart failure [3].

Heart rate variability can provide quantitative indirect estimates of autonomic neural activities. However, so far, simultaneous recording and analysis over a 24-hour period of neural activities (including sympathetic and vagal nerve activities) and ECG have not been available. Recently, Jung et al.[4] recorded continuously stellate ganglion nerve activity in ambulatory dogs. The authors showed a circadian variation in sympathetic outflow from canine stellate ganglia, and circadian variation of SGNA is an important cause of circadian variations of cardiac sympathetic tone. It is important to develop methods for analyzing HRV and autonomic nerve activities from long-term recordings, as the methods can be used to study disease processes. The primary aim of this study was to develop a method for continuous recording and measurement of sympathetic and vagal nerve activities and ECG simultaneously in free-moving dogs. After successful neural activity and ECG recordings, quantitative analyses of recording were performed to demonstrate the relationship of the neural activities and HRV over 24-hour in dogs.

II. Methods

Surgical preparation and electrical recording

Sterile surgery on the dogs was performed under isoflurane general anesthesia. A Data Sciences International (DSI, St Paul, MN) transmitter with three channels was implanted for continuous recording of left stellate ganglion nerve activity (SGNA), cardiothoracic branch vagal nerve activity (VNA) and subcutaneous electrocardiogram (ECG) simultaneously. The recording electrodes of DSI were implanted under the fascia of the left stellate ganglion. A second pair was laid over the superior cardiac branch of the left thoracic vagal nerve. One pair of widely spaced bipolar electrodes was implanted to the subcutaneous tissues to record surface ECG. The hole then was then surgically closed and baseline recording was started.

Four receiver panels were installed on the dog cage to receive the radiofrequency signal (0-500 Hz) coming from the implanted transmitter. The receiver panels were connected to a signal box that sent the recorded and digitized signals to a remote computer through an Internet connection. Using this method, we could obtain continuous neural and ECG recording for up to 8 weeks.

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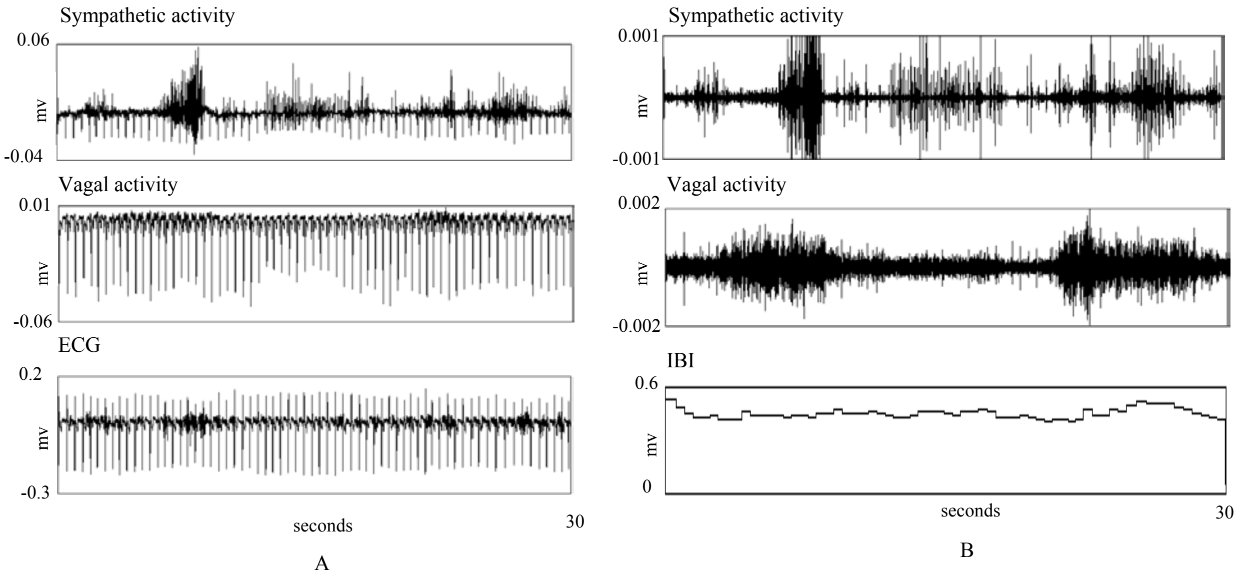

Figure 1. Raw traces and filtered traces for nerve activities and ECG. **A**: Raw continuous traces for sympathetic activity, vagal activity and ECG; **B**: Continuous traces of the signals after being filtered or processed of the same 30 seconds of data for sympathetic activity, vagal activity and R-R intervals (IBI).

Data analysis

Heart rate variability was assessed in the time domain by calculating the mean normal-to-normal (NN) intervals and the standard deviation of the NN interval (SDNN) in 5-minute time segments and on a 24-hour basis over 5 continuous days. The DSI system produced a large amount of segmented data files that made the analysis very time-consuming. In order to effectively analyze long-term trend of the large data files, a custom-designed program was developed using Labview^{TM} software to automatically import, filter and analyze the data obtained from the DSI transmitter to correlate the autonomic nerve activity with the heart rate variability.

Since determination of the QRS complex and more specifically, reliable detection of the R wave peak plays a central role in the computer-based ECG signal analysis, the Hilbert Transform algorithm was used to facilitate the measurement of RR interval. The Hilbert Transform is an analytical technique for transforming the filtered ECG signal into its instantaneous amplitudes and frequencies [5]. The Hilbert transform approach requires that the signal be evenly sampled and restricted to a limited frequency range. Therefore, the ECG signals were bandpass-filtered to 8-20 Hz. In addition, the sympathetic and vagal nerve signals were also digitally filtered with a 200 Hz high-pass filter in the software. Four groups of data with a duration time of 5 minutes were obtained based on the recordings including two group of data for two neural activities obtained by the sum of filtered and rectified nerve signal, mean of NN and SDNN. For the neural activities and HRV measurement, a relationship was demonstrated by plotting two neural activities, mean and standard deviation of NN on a 24-hour basis for 5 continuous days from midnight to the following midnight. Each group of neural activity data for was normalized to its corresponding range, and this value was multiplied by 100; and then the mean of NN intervals and SDNN were plotted against two neural activities with neural activity 1 (sympathetic nerve activity) as x-axis and neural activity 2 (vagal nerve activity) as y-axis.

III. RESULTS AND DISCUSSIONS

The recordings of 5 continuous days were used to analyze the nerve activities and heart rate variability. Figure 1 shows the samples of the raw traces of 30 seconds of data with and without filtering. Figure 1A demonstrates the raw recordings for sympathetic activity, vagal activity and ECG, respectively. There are ECG interfaces for sympathetic activity and vagal activity (shown in Figure 1A); therefore, high-pass filtering was used to minimize these ECG interfaces in order to measure the nerve activities more accurately (shown in Figure 1B). Figure 1B shows the traces after filtering for corresponding sympathetic and vagal activities. The filter setting for sympathetic and vagal activities are 200 Hz high-pass. We also measured the inter-beat interval (IBI) based on the Hilbert transform algorithm described above. The IBI is plotted as the bottom panel in Figure 1B.

Data describing the relationships of sympathetic nerve activity, vagal nerve activity both using 200 Hz high-pass filters, Mean of NN, and SDNN and time are depicted in Figure 2. All data sets were obtained in 5-minute segments. The analyses are on a 24-hour basis, from midnight to the following midnight. Figure 2 (A) describes the sympathetic activity over time, in which we can see the high sympathetic activity during daytime. The exact nature of this circadian

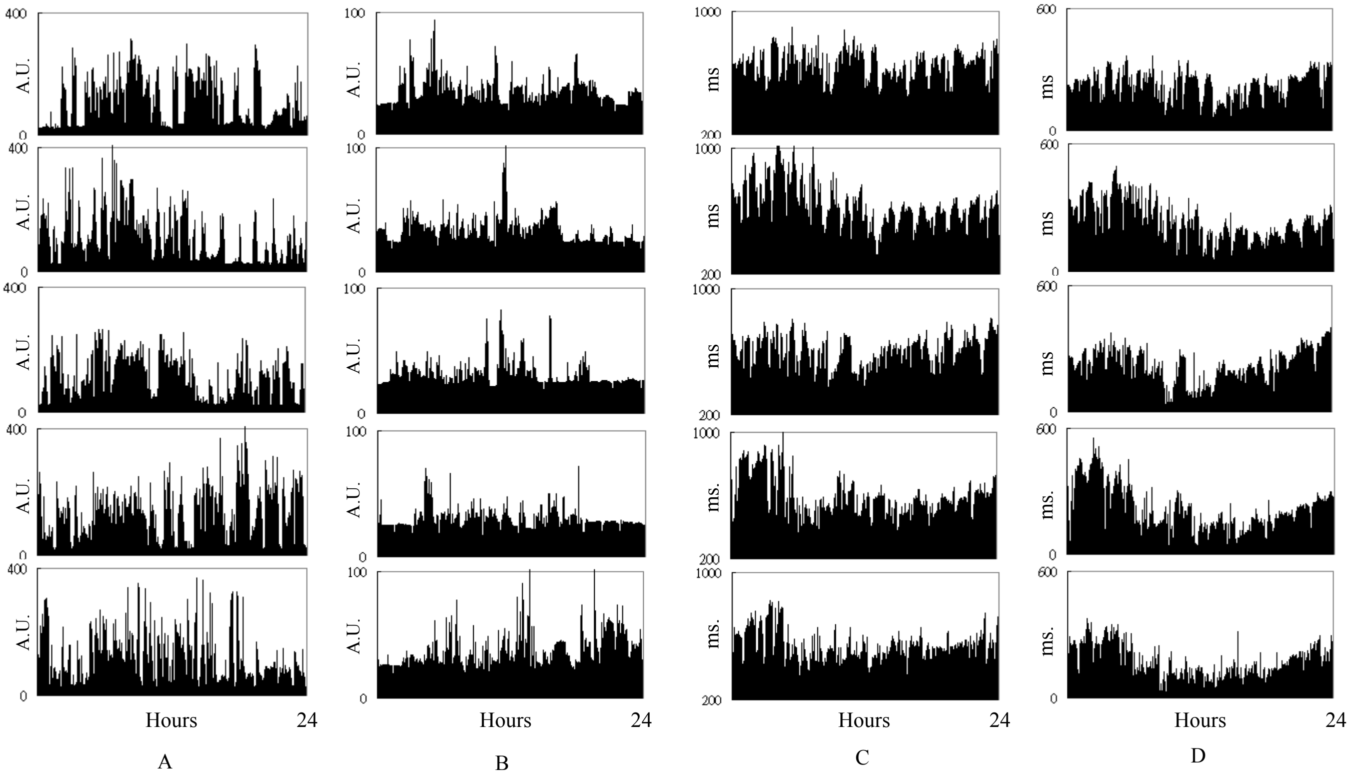

Figure 2 Neural activities and HRV on 1-day period beginning from midnight. A: Sympathetic nerve activity. B: Vagal verve activity. C: Mean of NN. D: Standard deviation of NN

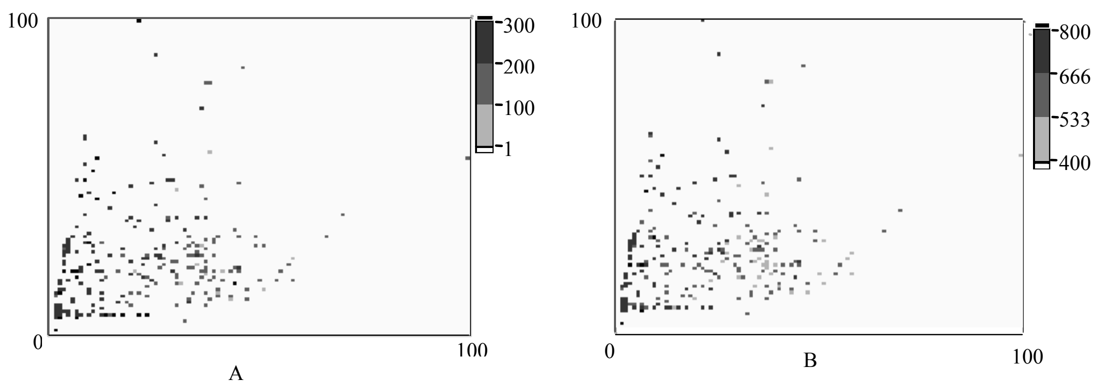

Figure 3. The relationship of neural activities and HRV. A: the relationship between Mean of NN and two neural activities with sympathetic activity as x-axis and parasympathetic activity as y-axis; B: the relationship between standard deviation of NN and two neural activities with sympathetic activity as x-axis and parasympathetic activity as y-axis

sympathetic tone was unclear [4]; the possible mechanism of regulating sympathetic tone is serum catecholamine concentration, which is higher during the day than at night [6]. Figure 2B gives the parasympathetic activity over time for 5 continuous days. Figure 2C and Figure 2D describe the mean of NN and the standard deviation of NN over 24 hours.

As a new means of assessing autonomic nervous system function, the relationship of heart rate variability and two neural activities was depicted in Figure 3. Two neural activities are normalized to 0-1, and then the normalized values multiplied by 100; X-axis indicates sympathetic activity and y-axis is the vagal activity. The grayscale of the dots indicates the relationship of mean (Figure 3A) or standard deviation (Figure 3B) of NN against two neural activities. From Figure 3, we can observe that the mean and SDNN are associated with two neural activities and the mean and SDNN tend to be smaller when sympathetic activity becomes stronger. These methods will be extended to trace disease processes, such as heart failure or long-term drug effects.

IV. Summary

HRV has been an indirect method to estimate autonomic function. We demonstrate results from an ambulatory animal model that allows direct measurement of neural activities and HRV. Specifically, the plots showing HRV as a function of both the sympathetic and vagal activities will offer significant insights into neural modulation of heart rate in normal and diseased hearts.

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