Subcutaneous nerve activity is more accurate than heart rate variability in estimating cardiac sympathetic tone in ambulatory dogs with myocardial infarction

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BACKGROUND We recently reported that subcutaneous nerve activity (SCNA) can be used to estimate sympathetic tone.

OBJECTIVE The purpose of this study was to test the hypothesis that left thoracic SCNA is more accurate than heart rate variability (HRV) in estimating cardiac sympathetic tone in ambulatory dogs with myocardial infarction (MI).

METHODS We used an implanted radiotransmitter to study left stellate ganglion nerve activity (SGNA), vagal nerve activity (VNA), and thoracic SCNA in 9 dogs at baseline and up to 8 weeks after MI. HRV was determined based on time–domain, frequency–domain, and nonlinear analyses.

RESULTS The correlation coefficients between integrated SGNA and SCNA averaged 0.74 (95% confidence interval [CI] 0.41–1.06) at baseline and 0.82 (95% CI, 0.63-1.01) after MI ($P < .05$ for both). The absolute values of the correlation coefficients were significantly larger than that between SGNA and HRV analysis based on time–domain, frequency–domain, and nonlinear analyses, respectively, at baseline ($P < .05$ for all) and after MI ($P < .05$ for all). There was a clear increment of SGNA and SCNA at 2, 4, 6, and 8 weeks after MI, whereas HRV parameters showed no significant changes. Significant circadian variations were noted in SCNA, SGNA, and all HRV parameters at baseline and after MI, respectively. Atrial tachycardia (AT) episodes were invariably preceded by SCNA and SGNA, which were progressively increased from 120th, 90th, 60th, to 30th seconds before AT onset. No such changes of HRV parameters were observed before AT onset.

CONCLUSION SCNA is more accurate than HRV in estimating cardiac sympathetic tone in ambulatory dogs with MI.

KEYWORDS Heart rate variability; Autonomic nervous system; Subcutaneous nerve activity; Myocardial infarction; Atrial arrhythmia

ABBREVIATIONS **AT** = atrial tachycardia; **CI** = confidence interval; **DC** = deceleration capacity; **ECG** = electrocardiogram; **HF** = high frequency; **HF_{nu}** = high-frequency normalized unit; **HRV** = heart rate variability; **LF** = low frequency; **LF_{nu}** = low-frequency normalized unit; **MI** = myocardial infarction; **pNN_{50}** = proportion of NN_{50} divided by total number of NNs; **PRSA** = phase-rectified signal average; **SCNA** = subcutaneous nerve activity; **SDNN** = standard deviation of normal to normal beat intervals; **SGNA** = stellate ganglion nerve activity; **TP** = total power; **VLF** = very low frequency; **VNA** = vagal nerve activity; **VT** = ventricular tachycardia

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Introduction

Heart rate variability (HRV) is a method frequently used to estimate autonomic tone.[1] Depressed HRV is a powerful predictor of sudden cardiac death and arrhythmic complications

in patients after acute myocardial infarction (MI) independent of left ventricular ejection fraction. Its importance is also supported by the fact that 11,980 articles in the PubMed database contain the exact phrase "heart rate variability" as of January 2014. The most commonly used HRV methods include either time–domain or frequency–domain analyses.[1] In addition, recent studies showed that nonlinear analysis of HRV may detect abnormal patterns of R-R fluctuations more efficiently than standard HRV measurements.[2] Among these new methods is phase-rectified signal averaging (PRSA),[3] which is used to quantify the quasi-periodic accelerations and decelerations in short-term heart rate. The latter is normally masked by nonstationarities (such as ectopic beats and changes in activity), noise, and artifacts. PRSA characterizes how the heart behaves around points of deceleration (deceleration capacity [DC]) and acceleration (acceleration capacity) under a given recording condition. Bauer et al found that a low DC was a stronger predictor of mortality after MI than traditional HRV techniques.[4,5] Recently, we demonstrated that left thoracic subcutaneous nerve activity (SCNA) could be used to accurately estimate left stellate ganglion nerve activity (SGNA) in normal ambulatory dogs and to predict susceptibility to ventricular tachycardia (VT) and ventricular fibrillation in a canine model of ventricular arrhythmia and sudden cardiac death.[6,7] However, whether SCNA can be used as a marker of cardiac sympathetic tone in ambulatory dogs with MI remained unknown. In a previous study from our laboratory, Han et al[8] simultaneously recorded left SGNA, left thoracic vagal nerve activity (VNA), and the subcutaneous electrocardiogram (ECG) in 9 ambulatory dogs at baseline and after MI. That dataset gave us an excellent opportunity to study the relationship between HRV, SGNA, and SCNA in dogs with MI without the need to use additional animals for experiments. The purpose of the present study was to perform further analyses of that dataset to test the hypothesis that SCNA is better than HRV in estimating cardiac sympathetic tone in ambulatory dogs with MI.

Materials and methods

We reanalyzed data on 9 ambulatory dogs with MI from a previous study.[8] The study protocols were approved by the Institutional Animal Care and Use Committee of the Indiana University School of Medicine and the Methodist Research Institute (Indianapolis, IN) and conformed to the Guide for the Care and Use of Laboratory Animals. Data Sciences International (DSI, St. Paul, MN) D70-EEE radio transmitters with 3 bipolar recording channels were implanted in 9 mongrel dogs. The first pair of bipolar electrodes was used to record from the left stellate ganglion, and the second pair was used to record from the left vagal nerve at the level 4 to 5 cm above the aortic arch. A third pair of bipolar leads was placed in the subcutaneous space of left thorax and left abdomen for ECG recording. Signals from the latter electrodes were high-pass filtered at 150 Hz to reveal nerve signals.[6] Subcutaneous interelectrode distance was not measured at the time of the study, but in similar sized dogs it is estimated at approximately 28 cm.[7] After baseline recording, acute MI was created and recording continued for an additional 8 weeks.

HRV analysis based on time–domain, frequency–domain, and PRSA methods

The R peak of QRS complex in the 5-minute window of each ECG signal was automatically detected based on the Pan Tompkins algorithm,[9] and the R-R interval tachogram was then obtained beat by beat (see Online Supplementary Figure 2). Time–domain, frequency–domain, and PRSA analyses of HRV all were performed using Matlab 2013 software (@MATLAB). The standard deviation of normal to normal beat intervals (SDNN), the square root of the mean of the squares of the successive differences between adjacent NNs, and the proportion of the number of pairs of successive NNs that differ by more than 50 ms (NN_{50}) divided by total number of NNs (pNN_{50}) calculated over 5 minutes were used to represent the HRV measures based on the time–domain method. For the frequency domain analysis, spectral power for HRV was analyzed on 5-min ECG recording segments and an autoregressive algorithm was used to analyze digitized signals from the ECG recordings (see Online Supplementary Figure 2). The total power (TP), very-low-frequency (VLF; 0.003–0.04 Hz), low-frequency (LF; 0.04–0.15 Hz), high-frequency (HF; 0.15–0.4 Hz) components, low-frequency normalized unit (LF_{nu}), high-frequency normalized unit (HF_{nu}), and LF–HF ratio were calculated based on the frequency–domain analysis. LF_{nu} was calculated as LF/(TP – VLF)*100. HF_{nu} was calculated as HF/(TP – VLF)*100.[1] PRSA was calculated according to methods published elsewhere.[4] Detailed methods are available in the Online Supplementary Material.

Statistical analysis

Unless otherwise indicated, all data are expressed as mean and 95% confidence interval (CI). Data with skewed distribution are given as median and interquartile range (25th percentile–75th percentile). For each dog, each HRV parameter was calculated from the total beats within each 5-minute window. SGNA, VNA, and SCNA were also obtained by integrating the nerve activities in the same 5-minute window. Therefore, there were a total 288 recordings per day in each dog at baseline or after MI, respectively. Shapiro-Wilk test was used to assess if the parameters in Tables 1 and 2 were in normally distributed. Paired *t* test was used to compare for normally distributed variables. Wilcoxon test was used to compare non-normally distributed variables at baseline and after MI. Pearson correlation coefficient was used to measure the correlations among all HRV parameters or SCNA vs SGNA or VNA in each dog. The significance of the consecutive values for SGNA, VNA, SCNA, SDNN, LF_{nu}, and DC in Figure 2 (baseline, and 2, 4, 6, and 8 weeks after MI) and Figure 4 (–120, –90, –60, and –30 seconds before onset of atrial tachycardia [AT]) were checked with repeated-measures 1-way analysis of variance. Cosinor tests were used to detect and quantify significant 24-hour circadian variations in the 9 dogs. Statistical analysis was performed using IBM SPSS Statistics 19 (SPSS Inc, Chicago, IL, USA). Two-sided $P < .05$ was considered significant.