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Heart Rate Turbulence Parameters Correlate with Post-PVC Changes in Muscle Sympathetic Activity

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Abstract

Background—Heart rate turbulence (HRT) has been shown to be vagally-mediated with a strong correlation to baroreflex indices. However, the relationship between HRT and peripheral sympathetic nerve activity (SNA) following a premature ventricular contraction (PVC) remains unclear.

Objective—We sought to evaluate the relationship between HRT and the changes in peripheral SNA following PVCs.

Methods—We recorded post-ganglionic muscle SNA during ECG monitoring in 8 patients with spontaneous PVCs. Fifty-two PVCs were observed and analyzed for turbulence onset (TO) and slope (TS). SNA was quantified during 1) the dominant burst following the PVC (Dominant-Burst Area), and 2) the 10 seconds following the dominant burst (Post-Burst SNA).

Results—The mean TO was $0.1 \pm 4.6\%$ and the mean TS was 6.1 ± 6.6 . The Dominant-Burst Area negatively correlated with TO ($r = -0.50$, $p = 0.0002$). The Post-Burst SNA showed a significant positive correlation with TO ($r = 0.44$, $p = 0.001$) and a negative correlation with TS ($r = -0.42$, $p = 0.002$). These correlations remained significant after controlling for either the PVC coupling interval or the left ventricular ejection fraction.

Conclusions—Our findings highlight the relationship between perturbations in HRT and pathology in the sympathetic limb of the autonomic nervous system. Future studies are needed to evaluate the prognostic role of baroreflex control of sympathetic activity in patients with structural heart disease.

Keywords

heart rate turbulence; sympathetic nervous system; baroreflex; premature ventricular contraction

Introduction

Following a premature ventricular contraction (PVC), there is a compensatory sinus pause, followed by sinus acceleration that typically overshoots the baseline heart rate before gradually decelerating back to baseline. This sequence of cycle length changes has been labeled 'Heart Rate Turbulence' (HRT)¹. Perturbations in HRT have been identified as physiologic markers

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of increased risk for sudden cardiac death and mortality in heart disease²⁻⁶. Specifically, blunted post-PVC sinus acceleration (less negative Turbulence Onset (TO)) and reduced subsequent deceleration (lower Turbulence Slope (TS)) have been shown to correlate with higher mortality in patients with structural heart disease.

The phenomenon of HRT is attributed to the arterial baroreflex. The decrease in blood pressure that accompanies a premature beat causes reflex inhibition of the vagus nerve and a delayed sympathetically mediated rise in blood pressure. The former accelerates the sinus rate, and the latter restores vagal flow, leading to deceleration of the sinus rate, again via the baroreflex⁷. The contribution of the sympathetic arm of the autonomic nervous system to HRT has not been quantified before, although there are several reasons to suggest the presence of a quantitative relationship. For one, post-extrasystolic potentiation and the delayed blood pressure overshoot are highly dependent on sympathetic nervous system activation⁸. For another, TO and TS have been found to correlate with the PVC coupling interval⁹⁻¹¹, which in turn is known to correlate strongly with sympathetic activity¹².

In the present study, we sought to explore the relation between muscle sympathetic nervous activity (SNA) and HRT in human subjects referred for electrophysiologic evaluation. We hypothesized that 1) the early post-PVC sympathoexcitation, measured by the amplitude of the post-PVC burst, would correlate with the magnitude of sinus acceleration (i.e. negatively correlate with TO), and that 2) the late sympathoinhibition associated with the post-extrasystolic potentiation and increase in blood pressure would positively correlate with the magnitude of subsequent sinus deceleration (i.e. positively correlate with TS).

Methods

Study Design

The study was performed at the University of Utah Hospital and the Dallas Veterans Affairs Medical Center, and was approved by the local institutional review boards. Patients were approached for enrollment if referred for invasive electrophysiologic study, either for the workup of cardiac syncope, ablation of known arrhythmias, or risk stratification. Exclusion criteria included the absence of sinus rhythm or ventricular ectopy during monitoring, and the inability to record SNA. After informed consent was obtained, HR measurements using ECG monitoring and direct muscle SNA recordings were obtained. Blood pressure was recorded via a femoral arterial catheter. Clinical data, including echocardiographic left ventricular ejection fractions (LVEF) were ascertained from medical records. Spontaneous PVCs were identified by ECG inspection and cycle length data were calculated and analyzed for TO and TS. These HRT parameters were then assessed for correlation with direct measures of SNA.

Sympathetic Nerve Recordings

Efferent, postganglionic muscle SNA was recorded from the left peroneal nerve as previously described¹³. Briefly, a sterile microelectrode was inserted into a fascicle of the peroneal nerve near the fibular head. Muscle sympathetic nerve bursts during sinus rhythm were identified by their temporal relationship to the sinus cardiac cycle, their increasing frequency during Valsalva maneuvers, the occurrence of large bursts accompanying PVCs and the failure to respond to arousal stimuli or stroking of the skin in the region of innervation.

The SNA was quantified as the total area under the curve of filtered nerve recordings during bursts. Custom software was used to identify possible bursts where the SNA signal exceeded 5% above the corrected baseline (relative to the range of values seen in the filtered signal), and to locate onsets and offsets using a 2nd derivative filter. User input was required to confirm onsets and offsets, and to reject obvious artifact. SNA was quantified during: 1) the dominant

burst following the PVC (Dominant-Burst Area), and 2) the 10 seconds following the dominant burst (Post-Burst SNA). The Dominant-Burst Area represents the solitary area of a single burst, and is not time-adjusted i.e. the onset/offset of this quantification were not fixed but depended on the burst width itself. The Post-Burst SNA is time adjusted, therefore representing the aggregate level of sympathetic activity. As inter-individual changes in filtering and signal quality can affect nerve signal amplitudes, absolute comparisons of burst areas between patients are unreliable. For this reason, the SNA values were normalized, as a ratio, to the baseline SNA (the 15 seconds of SNA recorded prior to the PVC), and are expressed in arbitrary units (AU).

The Dominant-Burst Area represents the early increase in sympathetic activity following an extrasystolic beat. Since the Post-Burst SNA calculation excludes the dominant burst, it represents the late sympathoinhibition commonly seen following the post-extrasystolic potentiation of contractility.

Heart Rate Turbulence

Standard 3-lead telemetry ECG recordings were made during sympathetic nerve recordings. Resting recordings were made for 5-15 minutes and spontaneous PVCs were catalogued. A custom software program was used for cycle length analysis. For beat detection, a lead with a clear, solitary intrinsic negative QRS deflection was chosen. The recording from this lead was further processed with smoothing and first derivative filters, providing reliable high amplitude deflections for identifying distinct ventricular complexes. After QRS detection, the root mean square signal was calculated for each patient using raw recordings from all leads. Baseline correction was performed on all beats by subtraction, zeroing the TP or PR segments. QRS peaks were identified using a parabolic, least-mean-squared error estimate of the root mean square ECG, which reduced the sensitivity of peak identification to high frequency noise. Cycle lengths (CL) were defined as the time between subsequent QRS peaks. To facilitate side-by-side analysis of HRT and SNA recordings, the CL data was plotted versus time (rather than beat number). TO was calculated as the percentage difference in CL from the mean of the two beats following the PVC relative to the two beats preceding the compensatory pause. Therefore, a negative TO value indicates sinus acceleration after PVC, thus reflecting normal physiology. TS was calculated as the maximum of all slopes determined by linear fit of each 5-beat sequence starting with the beat following the compensatory pause and ending with the 20th beat thereafter¹⁴. Though CL data is displayed versus time, the slope calculation used beat number as the denominator, as is standard.

Statistical Methods

Since there were large variations in both HRT and SNA parameters between different episodes in individual patients, each episode was treated in this analysis as a statistically independent event. Although tachograms are usually signal-averaged by patient in standard HRT assessment, the limits imposed on observation time by the logistics of SNA recording greatly reduce the total number of PVCs observed and thereby preclude meaningful signal-averaging. As most SNA and HRT measures were nonnormally distributed, correlations between these variables were assessed with Spearman's rank correlation to avoid excessive effect of outlying values on correlations. A simple linear regression model was used to assess interaction between PVC coupling interval and post-PVC dominant-burst area in predicting HRT parameters, as residuals were normally distributed in this model. Similarly, linear regression was used to assess the effect of LVEF on correlation between PVC prematurity and HRT parameters. As the normality of residuals assumption was not met in the multivariable models with LVEF and SNA predicting HRT parameters, TO and TS were converted to binary variables (normal versus abnormal, with cutoffs of TO=0% and TS=2.5ms/RR) and logistic regression was used.

To assess for relationships between hemodynamic perturbations and sympathetic activity, the diastolic pressure was determined on the beat immediately preceding and following the PVC. Systolic peaks for post-extrasystolic beats 3-10 were also identified, and the systolic trend was characterized using a linear estimate of each 3-beat sequence (e.g. beats 3-5, beats 4-6, etc.). Data distributions are described as mean $\pm$ standard deviation unless otherwise stated. Statistical significance was defined by a probability of type I error < 0.05 . All statistical calculations were performed using Intercooled Stata, v9.0 for Macintosh.

Results

Patient Characteristics

Successful SNA recordings were obtained in 8 subjects who met the above inclusion criteria. There were 6 men and 2 women with a mean age of 53 ± 8 years. The racial distribution was 7 Caucasian and 1 African American. Five had a normal and 3 had a depressed left ventricular ejection fraction with an overall mean of $47 \pm 13\%$. All patients had spontaneous PVCs with a mean of 6.5 ± 7.0 episodes per patient, during an average of ~ 15 minutes of observation. There were a total of 52 spontaneous PVCs during adequate SNA recording. HRT and SNA analysis were performed on all these PVCs. An example recording is shown in Figure 1.

Heart rate turbulence

The mean TO was $0.1 \pm 4.6\%$ and the mean TS was 6.1 ± 6.6 . On average, the maximum turbulence slope began 5.6 ± 3.5 beats after the PVC. Both of these parameters varied widely between different episodes for individual patients. While the distribution of TO was relatively symmetric about its mean, the distribution of TS exhibited a significant rightward skew (see Figure 2). Nonetheless, the range of values for TO and TS in this population was similar to that reported in previous studies¹. Also consistent with previous reports, TO and TS were negatively correlated ($r = -0.31$, $p = 0.03$).

Sympathetic Nerve Activity

SNA was successfully recorded in all 8 patients. A clear post-PVC burst was identifiable following each of the 52 extrasystoles (see Figure 1). The mean latency between the onset of the premature QRS and the peak of the post-PVC burst was 1280 ± 623 ms. Sympathoinhibition followed the dominant burst in most (77%), but not all episodes. On average, the ratio of the post-PVC Dominant-Burst Area to baseline SNA was 3.4 ± 2.1 . As expected, there was a negative correlation between the Dominant-Burst Area and the Post-Burst SNA ($r = -0.31$, $p = 0.03$). The Dominant-Burst Area exhibited a negative correlation with TO ($r = -0.50$, $p = 0.0002$), where greater sinus acceleration was associated with increased early SNA response (see Figure 3A). No significant correlation was found between the Dominant-Burst Area and TS (see Figure 3B). The Post-Burst SNA correlated positively with TO ($r = 0.44$, $p = 0.001$) and negatively with TS ($r = -0.42$, $p = 0.002$) (see Figure 4). To ensure these correlations were not unduly influenced by the two extreme Post-Burst SNA values (seen in Figure 4), we repeated these calculations excluding these values, and the findings did not change significantly. As sympathoinhibition is expected after PVCs, we also assessed the correlation between TO and the Post-Burst SNA after excluding episodes with post-PVC sympathoexcitation, revealing an even stronger correlation ($r = 0.59$, $p = 0.0001$).

Surprisingly, the magnitude of the PVC-induced diastolic pressure drop did not correlate with the Dominant-Burst Area ($r = 0.15$, $p = 0.51$). The mean rate of systolic pressure recovery was greatest in beats 3-5 (1.1 mmHg/beat), and slowed progressively (beats 4-6: 0.85 mmHg/beat, beats 5-7: 0.67 mmHg/beat, beats 6-8: 0.32 mmHg/beat, beats 7-9: -0.50 mmHg/beat, beats 8-10: -0.60 mmHg/beat). There was no correlation between the Dominant-Burst Area and early systolic pressure recovery (beats 3-5: $r = 0.02$, beats 4-6: $r = -0.04$, beats 5-7: $r = 0.01$). A stronger

correlation was present between Dominant-Burst Area and the pressure rise in beats 6-8 ($r=0.37$, $p=0.08$), although this correlation was not statistically significant. Post-Burst SNA negatively correlated with the degree of early pressure recovery in beats 3-5 ($r=-0.49$, $p=0.02$), but did not correlate well with systolic trends in subsequent beat sequences.

Effects of PVC coupling interval

Shorter PVC coupling intervals generated greater Dominant-Burst Areas, although this trend was not statistically significant ($r=-0.26$, $p=0.06$). There was a striking lack of correlation between PVC coupling interval and both TO ($r=0.00$, $p=NS$) and TS ($r=0.01$, $p=NS$). To assess whether the correlation between Dominant-Burst Area and TO was confounded by prematurity of the extrasystole, a simple linear regression model was fitted with three continuous variables: TO, Dominant-Burst Area, and PVC coupling interval, with TO as the dependent variable. In fact, this adjustment for PVC coupling interval strengthened the effect of Dominant-Burst Area ($\beta=-0.52$, $p<0.001$) compared to the unadjusted model with Dominant-Burst Area alone ($\beta=-0.48$, $p<0.001$). As expected from the univariate analysis, the PVC coupling interval was not independently associated with TO in this model.

Effects of LVEF

Patients with preserved LVEF tended to have more negative TO (-0.02 vs. 0.01 , $p=0.02$) and higher TS (7.8 vs. 3.2 ms/beat, $p=0.02$). In a logistic model that evaluated the interaction between Dominant-Burst Area and the presence of reduced LVEF in predicting TO, LVEF did not demonstrate an independent effect ($p=0.10$), and the effect of the Dominant-Burst Area remained significant ($p=0.04$).

Both LVEF reduction and Post-Burst SNA exerted independent effects in predicting TO ($p=0.03$ and $p=0.02$, respectively) and TS ($p<0.01$ and 0.03 , respectively) in logistic models. Furthermore, univariate correlation remained between Post-Burst SNA and TO after excluding patients with LVEFs below 50% ($r=0.47$, $p<0.01$).

Adjusting for LVEF did not unmask an association between the PVC coupling interval and either TO ($p=0.72$) or TS ($p=0.82$).

Discussion

The major findings of this study are: 1) The magnitude of the dominant post-PVC burst, a measure of the early post-PVC reflex sympathoexcitation, negatively correlated with turbulence onset, i.e. greater post-PVC sinus acceleration was associated with greater sympathoexcitation, and 2) post-burst SNA, a measure of the late sympathoinhibition associated with the post-extrasystolic potentiation of contractility and blood pressure, showed a positive correlation with turbulence onset and a negative correlation with turbulence slope. Although these findings do not establish causal links, to our knowledge this is the first study to show a correlation between HRT measurements and muscle SNA recordings in human subjects.

Previous studies on the role of SNA in HRT

Several studies have indicated that HRT is a baroreflex phenomenon, indirectly implicating the sympathetic nervous system. Voss et al¹⁵ reported that the changes in HR following a PVC parallel the changes in systolic blood pressure. Davies et al¹⁶ reported that TS correlates strongly with baroreflex sensitivity measured using blood pressure/heart rate correlations. Data from the ATRAMI (The Autonomic Tone and Reflexes After Myocardial Infarction) study³ showed that both TO and TS correlated with baroreflex sensitivity measured using the phenylephrine method.

A more direct role of sympathetic nervous system in HRT has only recently been reported. Wichterle et al⁷ suggested that the late systolic blood pressure dynamics following the decrease in cardiac output associated with a PVC were sympathetically mediated. In their study of 28 subjects with spontaneous PVCs, the investigators found a correlation between HRT parameters and beat-to-beat changes in peripheral vascular resistance, an indirect measure of peripheral SNA.

Present study

In the present study we directly measured post-ganglionic muscle SNA in subjects with spontaneous ectopy. We found that greater postextrasystolic sympathoexcitation, as measured by the Dominant Burst Area, correlated with more negative TO. This finding is consistent with the hypothesis that the early cardiac vagal withdrawal and the immediate post-PVC increase in muscle SNA share a common cause: the drop in blood pressure and the triggered baroreflex. Similarly, our finding that post-burst SNA, a measure of the late sympathoinhibition, was positively correlated with TO suggests that the greater the sinus acceleration immediately following a PVC, the greater the subsequent sympathoinhibition. The negative correlation between post-burst SNA and TS suggests that the greater the sympathoinhibition is, the more rapid the slowing of the sinus rate. Collectively, these findings show that perturbations in cardiac vagal innervation could very well be associated with disturbances in peripheral sympathetic activity, and therefore the latter might play a role in the increased mortality risk associated with abnormal HRT measurements.

The findings from the present study are consistent with the previously reported negative correlation between TO and post-extrasystolic hypotension duration¹⁷. Our findings also corroborate the study by Wichterle et al⁷ and highlight the link between cardiac vagal modulation of the sinus cycle changes following a PVC and the peripheral changes in muscle SNA. Furthermore, the suggestion of correlation between Dominant-Burst Area and systolic pressure rise in post-extrasystolic beats 6-8 helps support their assertion that early post-extrasystolic sympathoexcitation drives late blood pressure recovery.

Unlike some previous studies⁹⁻¹¹, but consistent with one induced HRT study¹⁸, we found no correlation between PVC coupling interval and HRT parameters. Although reduced LVEF has been shown to lessen this correlation⁹, controlling for LVEF did not reveal a link between coupling interval and HRT in our data. Another explanation might be the possible presence of retrograde (ventriculo-atrial) conduction, a phenomenon that was not investigated in the present study. Retrograde conduction has been shown to obliterate the correlation between PVC coupling interval and HRT parameters¹⁹.

Limitations

First, this is a small study population. As a result, these data were underpowered for a patient-by-patient analysis, and therefore assumed that PVC episodes were statistically independent events, a method vulnerable to possible confounding from the clustering of repeated measures. The complexity of these experiments makes subject enrollment difficult but provides unique observational data about human physiology, and the statistical significance of our main findings was nonetheless compelling. Secondly, the limited numbers of episodes per patient precluded the signal-averaging of tachograms, which is the standard in the calculation of HRT to minimize the impact of non-PVC-related heart rate variability. However, the correlations we report would only be weakened by not adjusting for such short-term heart rate variability phenomena. If signal-averaging were performed, the reported correlations may in fact have been stronger. Finally, our population was heterogeneous in terms of cardiac disease. Our findings may have been different if only patients with normal hearts were included, although the main findings of our study did not change after adjusting for LVEF.

Conclusion

The sympathetic and parasympathetic limbs of the autonomic nervous system are not independent, but rather rely on each other heavily for full potentiation of end-organ effect²⁰. On one hand, preserved vagal tone has been shown to be antiarrhythmic in the setting of ischemia²¹⁻²³. On the other hand, the magnitude of reflex sympathoexcitation has been shown to play a major role in determining hemodynamic stability and blood pressure recovery during induced ventricular tachycardia^{24,25}. We report here that early post-PVC reflex sympathoexcitation is negatively correlated with TO, and that late post-burst sympathoinhibition is correlated positively with TO and negatively with TS. Given the established role of vagal control in post-PVC physiology, these findings highlight the relationship between the two limbs of the autonomic nervous system and, in particular, that dysfunction in one limb is often indicative of abnormalities in the other. Future studies are needed to evaluate the prognostic role of baroreflex control of sympathetic activity in patients with structural heart disease.

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List of Abbreviations/Acronyms

HRT, Heart Rate Turbulence; SNA, Sympathetic Nerve Activity; PVC, Premature Ventricular Contraction; ECG, Electrocardiogram; TO, Turbulence Onset; TS, Turbulence Slope; LVEF, Left Ventricular Ejection Fraction; HR, Heart Rate; AU, Arbitrary Units; CL, Cycle Length.

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Figure 1.

Example recordings of ECG in Volts (V), blood pressure (BP) in mmHg, sympathetic nerve activity (SNA) in arbitrary units (AU), and the calculated cycle length (CL) trend in milliseconds from one episode. The change in diastolic blood pressure (ΔDBP) before and after the extrasystolic beat, and the slope of post-extrasystolic peaks 6 through 8 are also illustrated. In this example, there is a clear dominant burst (circled) 1.4 seconds after the premature beat, followed by the expected late sympathoinhibition.

Figure 2. Histograms of TO and TS measurements. TS exhibits a significant rightward skew in this population.

Figure 3.

A) Scatterplot of TO versus Dominant-Burst Area in arbitrary units (AU). The linear estimate is superimposed. B) Scatterplot of TS versus Dominant-Burst Area, showing no significant correlation.

Figure 4.

A) Scatterplot of TO versus Post-Burst SNA (a measure of late sympathoinhibition), in arbitrary units (AU), showing a modest but significant positive correlation. B) Scatterplot of TS versus Post-Burst SNA showing a negative correlation.