Heart Rate Variability is Confounded by the Presence of Erratic Sinus Rhythm

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Abstract

Decreased heart rate variability (HRV) predicts adverse outcomes. HRV can be elevated by episodes of significant non-respiratory sinus arrhythmia (i.e., a highly erratic sinus rhythm with normal p-waves, ESR). This elevated HRV could confound risk stratification by increasing HRV in high-risk patients. HRV was determined from tapes recorded at baseline in the Cardiovascular Health Study, a population study of older adults. Twenty-four hour time, frequency and non-linear domain HRV was compared between ESR+ and ESR- subjects, with (CVD+) and without (CVD-) cardiovascular disease. ESR+ was associated with higher HRV in the time and frequency domains and with decreased short-term fractal scaling exponent and increased ratios of the dimensions of the Poincaré plot fitted ellipse. (ESR+ and CVD+) subjects with had the highest HRV for virtually all indices, while (ESR- and CVD+) had the lowest HRV. Since decreased HRV is associated with adverse outcomes, ESR is likely to dilute the predictive power of HRV.

1. Introduction

Analysis of heart rate variability (HRV), which is based on the fluctuations of intervals between normal heart beats, provides a window onto autonomic nervous system function [1]. HRV can be analyzed in the time domain, the frequency domain, and using recently-developed non-linear techniques. The predictive power of decreased HRV for mortality in adults was first realized among post-MI patients [2]. The finding that decreased HRV, in the time or frequency domain, measured shortly after MI is associated with increased risk of mortality independent of other risk factors, has been replicated in numerous studies [3,4,5,6]. Recently, the predictive power of non-linear HRV for mortality post-MI has been shown to be equal to or perhaps greater than standard HRV indices [7]. The predictive value of decreased HRV has also been observed in population studies [8,9,10].

It has generally been assumed that decreased HRV reflects abnormal cardiac autonomic modulation and that, conversely, higher values of HRV reflect more normal cardiac autonomic modulation. However, investigators from the Zutphen study reported that a *higher* HRV that did not appear to reflect respiratory modulation of heart rate, was also associated with increased mortality [11]. We, too, have observed that there is a form of higher HRV that is associated with a somewhat erratic sinus rhythm and abnormal power spectral plots. We speculated that this increased HRV, which does not appear to reflect a more normal cardiac autonomic modulation, might confound the relationship between HRV and cardiac health.

The Cardiovascular Health Study (CHS), an NIH-sponsored longitudinal study of coronary heart disease and stroke in 5,201 men and women aged 65 years and older is the largest population-based 24-hour Holter study to date. At baseline, 1421 subjects volunteered to have Holter recordings. Each participant underwent extensive testing at baseline to identify the presence and severity of cardiovascular risk factors and the presence of overt disease. About 34% of the Holter cohort proved to have no clinical or subclinical cardiovascular disease and 30% had clinical cardiovascular disease. The purpose of the current study was to investigate the effect of erratic sinus HR patterns on the relationship between HRV and clinical cardiovascular disease for broad range of 24-hour HRV time domain, frequency domain and non-linear HRV indices.

2. Methods

2.1. Tape analysis

Tapes in the CHS were processed by research Holter technicians at the Washington University School of Medicine Heart Rate Variability Laboratory, using a GE Marquette MARS 8000 Holter analyzer (GE-Marquette, Milwaukee, WI). All Holter analyses were reviewed in detail by one of us (PKS). After editing, the labeled QRS data stream was transferred to a Sun workstation (Sun Microsystems, Palto Alto, CA) for HRV analysis. Excluded from the HRV analysis were: subjects with atrial fibrillation or pacemakers and subjects with either

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a wandering atrial pacemaker or a cardiac rhythm too irregular to accurately classify normal and supraventricular beats. Of the remaining subjects, N=457 who had no evidence of cardiovascular disease and N=369 who had documented cardiovascular disease were included in the current analysis. These were further divided into four groups: CVD- and ESR-, CVD- and ESR+, CVD+ and ESR-, CVD+and ESR+.

2.2. HRV indices

The following 24-hour time domain measures of HRV were calculated from N-N (normal-to-normal) intervals: average N-N in ms; SDNN (in ms), the standard deviation of N-Ns; SDNNIDX (in ms), the average of the standard deviations of N-Ns for each 5-min segment; rMSSD (in ms), the root mean square of differences between successive N-Ns; and the coefficient of variance (CV), the average of SDNN/average N-N for each 5-minute segment.

The following standard frequency domain components of HRV, measured in milliseconds squared, were computed: total power (TP) from 1.15 x 10-5 to 0.50 Hz; ultra-low-frequency (ULF) power, 1.15 x 10^{-5}-0.0033 Hz; very-low-frequency (VLF) power, 0.0033- 0.04 Hz; low-frequency (LF) power, 0.04- 0.15 Hz; high-frequency (HF) power, 0.15- 0.40 Hz and the LF/HF ratio. Also, normalized LF power (NLF) and normalize HF power (NHF) were determined.

Measurement of ULF and VLF power was based on *en bloc* analysis of the entire 24-hour recording. Other power spectral HRV indices reported here (LF, HF, LF/HF) reflect the average of 5-minute segments in which >80% of the beats are normal. Frequency domain indices of HRV were ln transformed.

Non-linear HRV indices included: power law slope , short-term fractal scaling exponent for short-term (<12 beats, DFA1), and SD12, the average of the ratio of the lengths of the axes of an imaginary ellipse fitted around the Poincaré plot for each 1000 beats. Changes of >30% in adjacent interbeat intervals fell outside the ellipse and were excluded from the calculation

2.3. Identification of erratic sinus rhythm

The presence of significant erratic sinus rhythm (ESR) was determined by examination of the 24-hour averaged and hourly 2-min averaged power spectral plots for each subject. Subjects with ESR, i.e., an abnormal distribution of power in the various HRV bands, were identified based on either clearly abnormal 24-hour
averaged plots, or in borderline cases, fewer than 3 normal-appearing hourly plots during the nighttime. Figure 1 shows examples of normal and abnormal hourly HRV power spectral plots from different time periods. Arrows point to normal nighttime high frequency peaks. Similar patterns were seen in normal and abnormal 24-hour plots.

2.4. Statistics

ANOVA and chi-square analyses compared age and gender between groups. The SPSS UNIANOVA procedure compared age-, and gender-adjusted values for

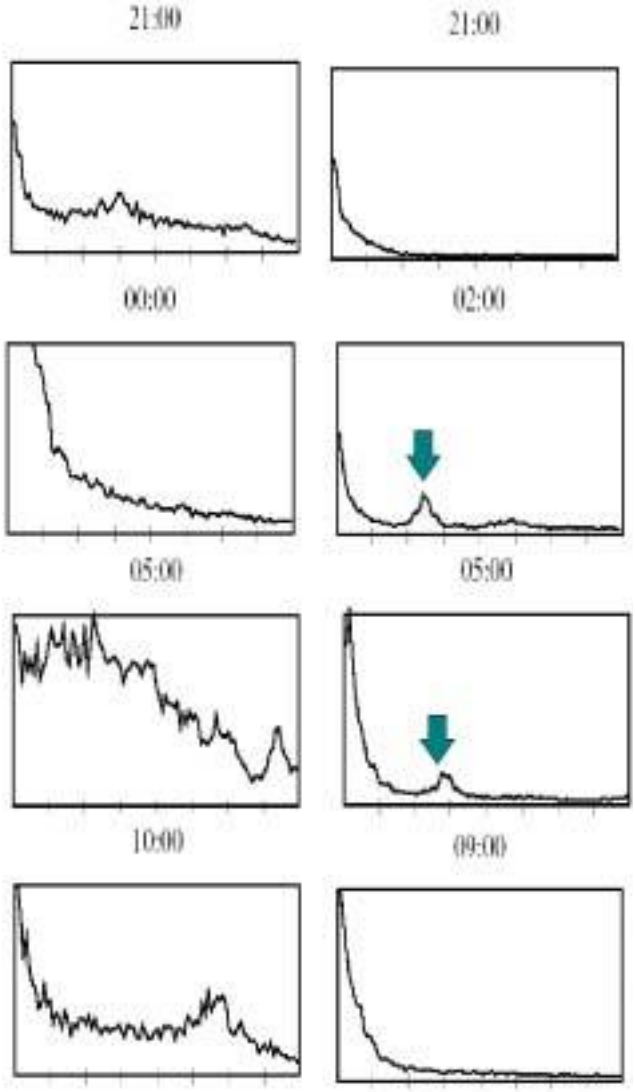

Figure 1. Comparison of hourly power spectral plots for subjects with (left hand side) and without (right hand side) erratic sinus rhythm. Arrows point to high frequency peaks in normal plots.

each HRV index by presence or absence of ESR, by

presence or absence of CVD, and identified interactions between ESR and CVD.

3. Results

3.1. Comparison of subjects with and without ESR

As can be seen from Table 1, mean age increased in association with both the presence of CVD and the presence of ESR. On *post hoc* testing, all age differences were statistically significant except between subjects with ESR and no CVD and subjects with CVD and no ESR. Also, as can be seen from the table the proportion of males was higher in both CVD+ groups.

Table 1. Comparison of Age and Gender Across Groups

	CVD- ESR- N=400 Mean (SD)	CVD- ESR+ N=57 Mean (SD)	CVD+ ESR- N=312 Mean (SD)	CVD+ ESR+ N=57 Mean (SD)
Age years	70.2 (3.9)	71.6 (4.3)	72.3 (5.2)	73.6 (5.2)
% male	35.3	24.6	53.2	66.7

3.2. Association of ESR and HRV

The association between ESR and increased age- and gender-adjusted HRV is clearly shown on Table 2. Only SDANN and ln ULF, which reflect primarily circadian HRV, and power law slope which reflects the fractal scaling properties of HRV over a period of minutes to hours, were not different between groups. DFA1 was decreased in subjects with ESR.

3.3. Interactions between ESR and CVD

Highly significant interactions were noted between CVD and ESR for *all* time domain HRV indices ($p<0.009$, except $p=0.033$ for SDANN). In every case, the highest values of HRV were found in subjects with ESR and CVD. Among subjects without ESR, HRV was either decreased (SDNN, SDANN, CV) or not different (SDNNIDX, rMSSD) in those with CVD compared to those without CVD.

Similar results were observed in the frequency domain where ln TP, ln ULF, ln VLF and ln LF were *lowest* among CVD without ESR and *highest* among CVD with ESR. Ln HF was not different between those with and without CVD in subjects without ESR, but in those with ESR, ln HF was higher among subjects with CVD. There were no interactions for the LF/HF ratio or normalized LF power which were consistently higher for healthy subjects, independent of ESR status. Consistent with this, normalized HF power was lower for both groups of healthy subjects.

Among the non-linear HRV indices, DFA1 remained significantly lower for both ESR groups, but did not differ by clinical status. SD12, however, remained higher for CAD patients in both ESR categories. There was a significant interaction for power law slope which was more negative for CAD patients without ESR compared to normals and more positive for CAD patients with ESR compared to normals with ESR.

Table 2. Age- and gender-adjusted HRV for subjects with and without ESR [Mean (SE)].

	ESR-	ESR+	p-value
SDNN	116 (2)	130 (4)	<0.001
SDANN	106 (2)	113 (4)	0.098
SDNNIDX	40.3 (0.8)	57.4 (1.6)	<0.001
rMSSD	21.8 (0.7)	54.5 (1.5)	<0.001
CV%	4.8 (0.1)	6.3 (0.2)	<0.001
ln TP	9.41 (0.03)	9.58 (0.07)	0.031
ln ULF	9.28 (0.03)	9.38 (0.07)	0.284
ln VLF	6.78 (0.04)	7.04 (0.08)	0
ln LF	5.61 (0.04)	6.28 (0.09)	<0.001
ln HF	4.46 (0.05)	6.01(0.10)	<0.001
LF/HF	4.54 (0.11)	2.11(0.24)	<0.001
NLF	46.4 (0.44)	38.2 (0.95)	<0.001
NHF	17.8 (0.35)	29.1 (0.76)	<0.001
DFA1	1.07 (0.01)	0.79 (0.02)	<0.001
SD12	0.25 (0.01)	0.44 (0.01)	<0.001
Power law slope	-1.34(0.01)	-1.31 (0.02)	0.143

4. Discussion

Results clearly suggest that the presence of significant ESR, which was noted in 12% of those older adults without and in 18% of older adults with cardiovascular disease, has the potential to significantly confound risk stratification using HRV. ESR was associated with *increased* HRV for virtually *all* indices, although the increase for SDANN and ln ULF which reflect HR changes on a scale of >5 minutes per cycle was not statistically significant. Also, the increase for power law slope, which reflects fractal scaling of heart rate over a period of minutes to hours did not reach statistical significance.

The significant interactions between ESR and presence of cardiovascular disease resulted in the *highest* values for HRV being found in those who had *both ESR and*

cardiovascular disease. Although increased HRV has been shown to be associated with decreased risk of mortality, this highest HRV group is not likely to be the lowest risk group in this population. Indeed, in the current study, mortality at 9-year follow up was 12% for those with neither ESR nor CVD, 17.5% for those with ESR an d no CVD, 32% for those without ESR but with CVD, and 49% for those with ESR and CVD.

It is interesting to note that DFA1is the only HRV index among those that have been reported to be predictors of mortality in populations studies or post-MI that was not elevated by ESR, i.e., ESR was associated with lower DFA1, and lower DFA1 is associated with worse survival [9]. Indeed, there is evidence that DFA1 is a better predictor of outcome than standard HRV indices [9]. Results also suggest that increased SD12, which is elevated by both ESR and CVD may be potentially useful as a predictor of outcome.

Limitations of this study must be noted. All tapes had been carefully scanned to accurately identify supraventricular and ventricular ectopic beats. As previously mentioned, those tapes where supraventricular beats could not be accurately labeled were excluded from the analysis. Identification of ESR was by visual inspection of HRV power spectral plots. Only those that were *clearly* abnormal, as shown in Figure 1, were classified as erratic. It is clear from examination of heart rate tachograms that ESR is not an all or nothing phenomenon and that short epochs of ESR that might not be sufficient to markedly affect the hourly averaged power spectral plot, yet would be expected to elevate HRV to some degree, are common in the CHS and in post-MI populations. Thus, a mathematical algorithm to systematically identify and quantify ESR would be useful and exclusion of ESR epochs might well improve the ability of HRV to identify subjects at risk for mortality.

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