Sometimes Higher Heart Rate Variability Is Not Better Heart Rate Variability: Results of Graphical and Nonlinear Analyses

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Higher HRV Not Always Better HRV. **Objective:** To determine the prevalence and effect on traditional heart rate variability (HRV) indices of abnormal HRV patterns in the elderly.

**Methods:** Hourly Poincaré plots and plots of spectral HRV from normal-to-normal interbeat intervals and hourly nonlinear HRV values were examined in a subset of 290 consecutive participants in the Cardiovascular Health Study. Only subjects in normal sinus rhythm with ≥18 hours of usable data were included. Eligible subjects were 71 ± 5 years. During 7 years of follow-up, 21.7% had died. Hours were scored as normal (0), borderline (0.5), or abnormal (1) from a combination of plot appearance and HRV. Summed scores were normalized to 100% to create an abnormality score (ABN). Short-term HRV versus each 5th percentile of ABN was plotted and a cutpoint for markedly increased HRV identified. The t-tests compared HRV for subjects above and below this cutpoint. Cox regression evaluated the association of ABN and mortality.

**Results:** Of 5,815 eligible hourly plots, 64.4% were normal, 14.5% borderline, and 21.1% abnormal. HR, SDNN, SDNNIDX, In VLF and LF power, and power law slope did not differ by the cutpoint for increased short-term HRV, while SDANN and ln ULF power were significantly lower for those above the cutpoint. However, many HRV indices including LF/HF ratio and normalized LF and HF power were significantly different between groups (P < 0.001). Increased ABN was significantly associated with mortality (P = 0.019). Despite similar values for many HRV indices, being in the group above the cutpoint was significantly associated with mortality (P = 0.04).

**Conclusions:** Abnormal HR patterns that elevate many HRV indices are prevalent among the elderly and associated with higher risk of mortality. Consideration of abnormal HRV may improve HRV-based risk stratification. (J Cardiovasc Electrophysiol, Vol. 16, pp. 954-959, September 2005)

heart rate variability, risk factor, population study, elderly

Introduction

Heart rate variability (HRV) quantifies changes in intervals between sinus heart beats that reflect cardiac autonomic functioning. Increased HRV, measured in the time or frequency domain, has been associated with increased mortality in numerous clinical studies. At the same time, recent results suggest that abnormal values for nonlinear HRV measures, associated with increased randomness of the heart rate, that is, a high degree of sinus arrhythmia of nonrespiratory origin, are even more strongly associated with risk of mortality. This indicates that the global concept of HRV may encompass two aspects: one reflecting normal cardiac autonomic control (normal sinus rhythm) and one reflecting random variations due to underlying abnormalities in cardiac control or function (erratic rhythm) that may be associated with worse outcomes. Standard time and frequency domain measures do not distinguish between these two forms of HRV. This suggests that there could be patients with increased HRV associated with higher, rather than lower, risk, potentially diluting the predictive value of some time and frequency domain HRV indices. At the same time, identification of patients with a high degree of erratic rhythm could prove useful for risk stratification.

Both Poincaré plots (scatterplots of each interbeat interval against the prior one) and plots of the HRV power spectrum (fast Fourier transform [FFT] patterns) offer graphical methods to examine heart rate patterns. Indeed, Mäkikallio et al. have shown that increased abnormality of heart rate patterns, seen on Poincaré plots from the hour before, was associated with the onset of ventricular tachycardia (VT) in postmyocardial infarction (MI) patients.

In the current exploration of the prevalence of abnormal HR patterns and their effect on HRV measures, we examined hourly Poincaré plot and FFT patterns from normal-to-normal (N-N) interbeat intervals, in conjunction with hourly values for nonlinear HRV, from 24-hour Holter recordings in a subset of consecutive subjects from the Cardiovascular Health Study (CHS). The CHS is a large NIH-funded population study of risk factors for cardiovascular disease and stroke in older adults. We hypothesized that a higher prevalence of abnormal hourly heart rate patterns would be associated with increased HRV. We further hypothesized that a higher

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prevalence of abnormal heart rate patterns might be associated with mortality after adjustment for age and gender, factors known to be associated with mortality in the elderly.

Methods

The CHS is a prospective population-based study of 5,201 participants aged >65 years. The overall design, objectives and recruitment strategy of the CHS and characteristics of the cohort have been described in detail elsewhere.\textsuperscript{10,11} ID codes in the CHS began with 3, 4, 5, and 6. For the current exploration, we choose all 289 subjects who had baseline Holter recordings and ID codes beginning with the number 3 (Forsyth county field center).

Analysis of Holter Tapes

Tapes in the CHS were recorded on Del Mar Avionics recorders and processed by research technicians at the Washington University School of Medicine Heart Rate Variability Laboratory, using a GE Marquette MARS 8000 Holter analyzer (GE Medical System, Milwaukee, WI, USA). Data were reviewed and edited by the technicians using standard Holter analysis procedures. All analyses were reviewed in detail by one of us (PKS) with special attention paid to ensuring that only N-N beats with uniformly detected onsets were included in the HRV analysis. After editing, the labeled QRS data stream was transferred to a Sun Enterprise 450 server (Sun Microsystems, Palo Alto, CA, USA) for 24-hour time domain, frequency domain, and nonlinear HRV analysis. In addition, 2-minute-averaged hourly power spectral plots and hourly Poincaré plots were printed, and hourly values for the HRV indices described below calculated. For an hour to be included, 80% of the data had to consist of N-N intervals. In virtually every case, the reason for an hour to be excluded was an inadequate electrocardiogram (ECG) signal or too many beats excluded because of nonuniform beat detection, rather than a high degree of ectopy.

HRV Variables Reflecting Randomness in HR Patterns

1. DFA1 and DFA2. Detrended fluctuation analysis (DFA) quantifies the fractal scaling properties of the short-term RR interval time series. Higher values reflect a more correlated time series, while markedly decreased values reflect a highly random time series. The details of this method have been described elsewhere.\textsuperscript{12,13} Fractal scaling exponents were determined/1,000 beats and averaged, on an hourly basis, for short-term (≤11 beats, DFA1) and longer-term (12–20 beats, DFA2) RR interval data.\textsuperscript{9} Only N-N intervals were used for this calculation.

2. Interbeat Correlation Coefficient (ICC). The Pearson’s correlation between N-N interbeat intervals was calculated/1,000 beats for each hour and averaged. Increased irregularity in the heart rate time series results in a decreased ICC.\textsuperscript{14}

Characterization of Hourly Power Spectral Plots

Frequency domain HRV partitions the variance of the heart rate into its underlying frequency components using the FFT. The variance at each underlying frequency can be displayed in a plot of the results. In each plot, the y-axis is the variance at each frequency, and the x-axis is the underlying frequency in Hz. Hourly plots were generated from an average of the plots for each 2-minute segment. Figure 1a,b provide examples of normal-appearing hourly FFT plots from the nighttime period. Normal FFTs can be characterized as “organized looking” with little power (area under the curve) above the high-frequency band (0.4 Hz). Nighttime and naptime plots tend also to show distinct peaks in the high-frequency band, associated with higher respiration-associated vagal modulation of heart rate during sleep. This is generally absent during the daytime awake periods. Additionally, as seen in Figure 1a, at night or during naps, a peak is sometimes seen in the very low frequency (VLF) band (0.004–0.04 Hz), associated with cyclic variation of heart rate due to sleep-disordered breathing.\textsuperscript{15} The detailed characterization of subjects with heart-rate-based evidence for sleep-disordered breathing is a matter for another study, and for the purpose of this study of excess randomness in HRV, a strong VLF peak, due to cyclic variation of heart rate, was not classified as abnormal.

Figure 1c,d shows FFTs for hours coded as abnormal. In contrast to 1a and 1b, these plots are often irregular and disorganized with significant power beyond the HF band. Highly abnormal FFTs, like those in Figure 1c,d, are readily identifiable by any observer.

Characterization of Poincaré Plots

Normal Poincaré plots for the same subjects and times as in Figure 1a,b are seen in Figure 2a,b. Normal-looking 1-hour Poincaré plots were ellipsoidal or mildly comet-shaped, with few data points outside the main figure. Abnormal Poincaré plots for the hours seen in Figure 1c,d are shown in Figure 2c,d. Points on these plots are clearly more scattered than in normal ones. We observed, however, that when the degree of abnormality was mild, Poincaré plots were more sensitive to abnormal rhythms than their corresponding power spectral plots.

Characterization of Poincaré and FFT Plots in Conjunction with HRV Values

For each subject, each hour was coded as normal (0), borderline (0.5), or abnormal (1) based on hourly plots and HRV values. We a priori defined “possibly abnormal” values as: DFA1 < 0.85, DFA2 < 1.00, ICC < 0.85 based on prior calculations with ROC curves in a subset of the data. Hours with all values above these thresholds were coded as normal.
Figure 2. Normal and abnormal Poincaré plots from the same periods and subjects seen in Figure 1.

if both plots appeared to be normal. An hour coded as abnormal had at least one abnormal-looking plot and values for at least one of the HRV indices below the possibly abnormal cutpoint. Any discrepancy between the appearance of one or both plots and the HRV values resulted in that hour being coded as borderline. Often, borderline plots were observed at the boundary between clearly normal hours and hours with abnormal plots. Similarly, if the plot was normal, but ≥2 HRV values were abnormal, that hour was coded as borderline. A very few plots had normal-looking patterns with extremely low values for only one HRV index. Those normal-looking plots with highly abnormal DFA1 or ICC (<0.70) were labeled as borderline, but, because we had previously observed low values for DFA2 during normal stage 2 sleep, DFA2 < 0.85 that occurred during the nighttime or during naps was considered normal.

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Calculation of the Abnormality Score

After each hour had been characterized, scores (0, 0.5, or 1 for each hour) were added. To permit comparisons, a percentage (sum/number of hours available) was calculated and denoted as the “abnormality score” (0–100%).

Cutpoints for Increased HRV

Short-term, beat-to-beat HRV should be the most affected by a high degree of nonrespiratory sinus arrhythmia. Therefore, short-term HRV by abnormality score was plotted and a cutpoint for the abnormality score associated with markedly increased short-term HRV identified.

Statistical Analyses

To determine which HRV indices are affected by abnormal HR patterns, 24-hour HRV indices were compared, using t-tests, for abnormality scores above and below the cutpoint for increased short-term HRV. Age, gender, and clinical variables were compared between those above and below this cutpoint by t-test and chi-square analysis. The univariate and multivariate relationship between the abnormality score and mortality was tested by Cox regression analysis. Statistical significance was set at P < 0.05. Software was SPSS 11.0 (SPSS, Chicago, IL, USA).

Results

Subjects were aged 70.7 ± 4.5 years (range: 65–86), 154 males, 135 females. At the end of 7 years of follow-up, 63 (21.7%) had died. Of 289 subjects, 7 were excluded: 5 with atrial fibrillation or a pacemaker and 2 with a rhythm too irregular for reliable HRV analysis. Clinical cardiovascular disease defined as atrial fibrillation, pacemaker, history of intermittent claudication, peripheral vascular surgery, history of congestive heart failure, history of stroke, transient ischemic attack, carotid surgery, history of coronary artery bypass grafting or percutaneous transluminal coronary angioplasty, history of angina, use of nitroglycerin, or history of myocardial infarction was present in 27% of subjects. This included 8.3% of subjects who were post-MI and 22.4% with coronary heart disease. Only 2% had congestive heart failure, while 14.5% reported having angina, 14.5% had chronic obstructive pulmonary disease (COPD) and 12.8% were diabetic. Beta-blocker use was reported in 12.1% of subjects and 14.5% were on an angiotensin-converting enzyme (ACE) inhibitor.

Eligible subjects had a total of 5,815 out of a possible 6,816 analyzable hourly data segments (85%). Of the eligible hourly plots, 64.4% were coded as normal, 14.5% as borderline, and 21.1% as abnormal. Among plots coded as abnormal, there was a broad degree of abnormality. Figure 3 shows the broad distribution of the abnormality scores in the population.

HRV and Abnormality Scores

Figure 4 shows representative bar plots of short-term HRV by each 5th percentile of abnormality scores (percentile group). As can be seen from the plots, there is a large increase in short-term HRV for mean abnormality scores at the 16th group and above (increased short-term HRV cutpoint). Table 1 compares 24-hour time domain HRV for subjects with abnormality scores above and below this cutpoint. As can be seen from the table, AVNN and SDNN were not significantly different between groups. SDANN, an HRV index that is based on 5-minute-averaged heart rates and should, therefore, be insensitive to nonrespiratory sinus arrhythmia, was significantly lower in the group with more abnormal plots, suggesting that SDNN may be mildly exaggerated by
erratic rhythm. Consistent with the criteria for selecting the cutpoint, all short-term HRV indices (pNN50, rMSSD, and pNN625%) were elevated in the group with higher abnormality scores. SDNNIDX that reflects the average standard deviation of HRV for each 5 minutes, also tended to be higher in this group.

Similarly, in the frequency domain, shown in Table 2, total power, the frequency domain analog to SDNN was not different between groups while ultra low frequency power that reflects all variability with a period >5 minutes was significantly lower in the group with more abnormal plots. Not surprisingly, VLF power that reflects heart rate changes with periods between 20 seconds and 5 minutes, was not different between groups. Low-frequency power that reflects changes in heart rate with cycle lengths between 3 and 8 times/min was also not significantly different between groups, but the remaining frequency domain indices: the LF/HF ratio (lower), normalized low frequency power (lower), normalized high-frequency power (higher), and high-frequency power (higher) were significantly affected (P < 0.001) by the high degree of nonrespiratory sinus arrhythmia in the group with higher abnormality scores. All of these have been used as surrogates for cardiac autonomic modulation in various studies.

Consistent with the criteria used to classify the hourly plots, the nonlinear indices DFA1 and DFA2 were markedly lower in the group with higher abnormality scores, but the longer-term nonlinear index power law slope, reflecting properties of the heart rate time series on a scale of minutes to hours, was not different.

**TABLE 1**

Comparison of 24-Hour Time Domain HRV Indices for Subjects Above (N = 67) and Below (N = 203) the Cutpoint for Markedly Increased Short-Term HRV

<table>
<thead>
<tr>
<th></th>
<th>Above</th>
<th>Below</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVNN (msec)</td>
<td>840 ± 129</td>
<td>819 ± 97</td>
<td>0.156</td>
</tr>
<tr>
<td>SDNN (msec)</td>
<td>118 ± 42</td>
<td>125 ± 33</td>
<td>0.121</td>
</tr>
<tr>
<td>SDANN (msec)</td>
<td>104 ± 36</td>
<td>115 ± 32</td>
<td>0.016</td>
</tr>
<tr>
<td>SDNNIDX (msec)</td>
<td>48 ± 20</td>
<td>43 ± 13</td>
<td>0.052</td>
</tr>
<tr>
<td>pNN50 (%)</td>
<td>12.6 ± 10.9</td>
<td>3.7 ± 3.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>rMSSD (msec)</td>
<td>42 ± 25</td>
<td>22 ± 19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>pNN625 (%)</td>
<td>11.3 ± 9.4</td>
<td>3.1 ± 3.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

AVNN = average of normal-to-normal (N-N) intervals; SDNN = standard deviation of all N-Ns; SDANN = standard deviation of 5-minute averages of N-Ns; SDNNIDX = average of standard deviations of N-Ns over 5 minutes; pNN50 = percentage of N-Ns more than 50 msec different from prior N-N; rMSSD = root mean square of successive differences of N-Ns; pNN625 = percentage of N-Ns more than 6.25% of local 5-minute average different from prior interval.

**Association Between Abnormality Score, Age, Gender, Clinical Variables, and All-Cause Mortality**

Subjects within the higher group of abnormality scores were not different in age (71 ± 5 years higher vs 71 ± 4 years for lower), nor were they more likely to be female (20% males, 22% females). Subjects in the higher group of abnormality scores were more likely to have clinical cardiovascular disease at the time of the recording (34.2% vs 18.3%, P = 0.005). However, there was no significant relationship between post-MI status, presence of coronary heart disease, angina, COPD, diabetes, beta blocker or ACE inhibitor use, and being in the higher or lower group of abnormality scores.

The association of abnormality score and mortality was significant, with higher abnormality scores associated with
increased risk of death (Hazard Ratio = 1.009 [95% CI: 1.001–1.017], P = 0.019). Similarly, being in the higher group of abnormality scores was also associated with increased risk of mortality (P = 0.04).

We explored the cutpoint in abnormality score associated with the greatest separation of survivors and nonsurvivors. A cutpoint of 59% (N = 57 above, N = 214 below) marginally improved the prediction of mortality, with P value for the Cox regression falling to P = 0.015. Mortality upon 7-year follow-up was 18% for abnormality scores ≤ 59% and 33% for abnormality scores > 59%. This association remained significant (P = 0.047) after adjustment for both age and gender; however, because of the significant relationship between the presence of clinical cardiovascular disease and mortality, this relationship was no longer significant after adjustment for clinical cardiovascular disease status (P = 0.11).

Discussion

We have found, in a community-based study of older adults that a significant degree of nonrespiratory sinus arrhythmia (erratic rhythm) on Holter was not exceptional. Many time and frequency domain HRV indices presumed to reflect better autonomic function were elevated in association with higher abnormality scores. Moreover, higher abnormality scores were associated with an increased prevalence of clinical cardiovascular disease. Thus, in some populations, higher HRV may not always reflect better cardiac autonomic function. While longer-term HRV, like SDNN that is predominantly influenced by circadian rhythms, was not strongly affected by erratic rhythm, results help explain why values for short-term HRV, for example, pNN50 and high-frequency power, presumed to reflect vagal modulation of heart rate, often do not differ between healthy and cardiac patients or between survivors and nonsurvivors in post-MI studies, despite the clear experimental association of decreased vagal tone and risk of arrhythmic events. \(^{16}\) In addition, this helps explain why nonlinear HRV, which is more abnormal in the presence of erratic rhythm, has proven, at times, superior to traditional HRV for risk stratification. While the methodology used in this exploratory study was crude, and not designed to provide a novel method for risk stratification, results support the development of more sophisticated tools to account for abnormal heart rate patterns and potentially enhance the ability of traditional HRV to risk stratify.

Etiology of Erratic Rhythms

The exact nature of erratic rhythm that we observed is unknown. It is possible that it represents a very subtle form of supraventricular ectopy, but if so, it cannot readily be seen on Holter scanning. We tested, in a subset of the data, whether intensive filtering of the N-N interval signal might eliminate abnormal plots. Filtering so that no interval changed by > 20% had no effect on the appearance of the Poincaré plots. Filtering at 10% reduced, but did not eliminate, the abnormal appearance of the plots. Other evidence suggests that erratic rhythm might be a consequence of high sympathetic activation. In a study of normal volunteers, increasing doses of norepinephrine resulted in a similar RR interval behavior, such as abrupt prolongations in RR intervals that were not related to respiration and that resulted in decreased DFA1.\(^{17}\) This is consistent with the finding that CHF patients with “complex” Poincaré plots had a significantly higher serum norepinephrine level than patients with “torpedo-shaped” plots.\(^{18}\) Importantly, consistent with our results, SDNN was not different between groups with complex and torpedo-shaped plots.

We were concerned that the subtle erratic rhythm seen in some patients, that is, very low values for DFA1 in association with normally shaped plots, might be caused by uneven detection of the onsets of N-N beats, despite our explicit attention to excluding abnormally detected beats. Accordingly, we reanalyzed four tapes with this phenomenon. Beat detection proved to be uniform and reanalysis did not change the results.

Identification of Erratic Rhythm Using a Single Nonlinear HRV Index

We hoped that a single hourly nonlinear HRV index from among those currently in use could reliably identify abnormal patterns without the tedious task of visual inspection. However, it appears that the different hourly HRV indices captured different aspects of abnormal patterns, and the correlation
between them was relatively weak ($r = 0.58$–$0.69$). Mildly abnormal-looking plots were seen with all values within normal limits, but this was never the case for extremely abnormal ones, suggesting that a small degree of erratic rhythm is insufficient to affect hourly HRV measures. Also, we considered the use of SD12, a measure of the relative dimensions of the Poincaré plot; however, DFA1, DFA2, and the ICC proved to be more sensitive and specific than SD12 and the measure was dropped.

**Clinical Significance of Abnormal Heart Rate Patterns**

Prior studies have supported the clinical importance of abnormal heart rate patterns.19-21 These studies, based on Poincaré plots generated from 24-hour RR interval data, have demonstrated an association between abnormal heart rate patterns and mortality among CHF patients. Abnormal heart rate patterns have also been associated with the risk of VT9 and, in another study from the same group, postcoronary artery bypass surgery (CABG) patients also demonstrated increased randomness of the heart period time series, compared to the same patients before surgery. Moreover, a more random heart rate pattern, predicted ischemic events in these post-CABG patients.22

**Limitations**

Limitations of the current exploration of the prevalence of erratic rhythm among the elderly include the simple, qualitative categorization of abnormal plots, independent of the degree of abnormality present. Moreover, 1-hour blocks of time may not be optimal, although 1-hour plots clearly provide information obscured by a single 24-hour plot. Additional mathematical techniques for quantifying erratic rhythm and/or for filtering it out of the recording might improve risk stratification. Results support the importance of considering this other source of HRV when considering the use of HRV as a surrogate for cardiac autonomic modulation, both to permit more accurate evaluation of vagal modulation of heart rate and also to improve the ability of HRV to identify those at higher risk of mortality.

**References**

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