Distinguishing Normal and Abnormal Heart Rate Variability Using Graphical and Non-Linear Analyses

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Abstract

Abnormal HRV could confound risk stratification. Method: Hourly Poincaré and FFT plots examined in 270 tapes from the Cardiovascular Health Study. After 8 years, 63 subjects had died. Hourly short and longer-term detrended fractal scaling exponent and interbeat correlations were calculated. Hourly HRV was scored as normal (0), borderline (0.5) or abnormal (1) from plot appearance and HRV values. Scores were summed by subject and normalized to create an abnormality score (ABN,0-100%). Cox regression determined the relationship of ABN and mortality. Results: Increased ABN was associated with mortality, p=0.005. After adjustment for age (p=0.001) and gender (p=0.005), ABN remained associated with mortality (p=0.015). When ABN was dichotomized at 57%, HR and SDNN were not different, but higher ABN (N=67) had significantly increased short and intermediate-term HRV and mortality. Conclusion: Even with a relatively crude quantification method, abnormal rhythms were associated with both mortality and increased HRV.

1. Introduction

Heart rate variability (HRV), based on the fluctuations of intervals between normal heart beats, reflects autonomic nervous system function [1]. HRV is analyzed in the time and frequency domain, and using non-linear techniques. Decreased time or frequency domain heart rate variability (HRV) is independently associated with increased mortality in clinical [2] and population [3,4] studies. In cardiac patients, non-linear HRV, reflecting increased randomness of heart rate, has been strongly associated with mortality [5]. Thus, HRV includes two components: normal variation associated with better and abnormal, more random variation associated with worse outcomes. Increased randomness can elevate time and frequency domain HRV, so that higher HRV can be associated with higher risk in some patients, diluting the predictive value of traditional HRV measures.

In this study, we applied a semi-quantitative method, using both graphical and non-linear analyses, to quantify, on an hourly basis, the degree to which HRV for each subject was normal or increased by abnormal patterns of non-respiratory sinus arrhythmia. This was expressed as an "abnormality score" (ABN). The relationship of ABN and subsequent mortality in a subset of 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 was determined. In addition, we compared time and frequency domain HRV for those with ABN above and below the point at which short-term HRV was markedly elevated.

2.1 Subjects

The baseline Holter cohort with usable tapes consisted of 1384 participants. ID codes in the CHS began with 3,4,5 and 6. For the current intensive study, we choose all 290 subjects who had baseline recordings and ID codes beginning with the number 3.

2.2 Analysis of Holter recordings

Tapes were processed at the Washington University School of Medicine Heart Rate Variability Laboratory, using a GE Marquette MARS 8000 Holter analyzer (GE Medical System, Milwaukee, WI). All analyses were reviewed in detail by one of us (PKS) with special attention to ensuring that only normal-to-normal (NN) beats with uniformly detected onsets, within each recording, were included in the analysis. The longest and shortest true NN intervals were identified for each tape, and intervals outside of these limits, as well as all ectopic beats, excluded from all calculations and plots. After editing, the labeled QRS data stream was transferred to a Sun workstation (Sun Microsystems, Palo Alto, CA) for 24-hour time domain, frequency domain and non-linear HRV analysis. Hourly power spectral and Poincaré plots were created, and hourly values for the HRV indices described below calculated. For an hour to be acceptable for analysis, 80% of the data had to be NN intervals.

2.3. Hourly HRV indices

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HRV variables examined included: the short-term fractal scaling exponent (DFA1), the longer-term fractal scaling exponent (DFA2) and the interbeat correlation coefficient (ICC).

1) *DFA1 and DFA2.* Detrended fluctration analysis (DFA) quantifies the fractal scaling properties of the short-term R-R interval time series. Higher values for DFA reflect a more correlated time series, while decreased values reflect a highly random time series [6,7]. The details of this method have been described elsewhere [6,7]. Hourly DFA was determined/1000 beats and averaged, on a hourly basis, for short-term (≤11 beats, DFA1) and longer-term (12-20 beats, DFA2) NN interval data.

2) *Interbeat Correlation Coefficient* (ICC). The Pearson's correlation between NN intervals was calculated/1000 beats and averaged/hr. Increased irregularity in the heart rate time series results in decreased values for the ICC[8].

2.4. Characterization of hourly power spectral plots

Figure 1 shows normal-appearing hourly FFT plots from day and nighttime periods. Normal FFTs can be characterized as "organized-looking" with a distinct 1/f distribution of spectral power in the region between 10^{-2} and 10^{-4} Hz and relatively little power (area under the curve) above the high frequency (HF) band (0.4 Hz). Night and naptime plots tend also to have a distinct peak in the high frequency (HF) band, associated with higher, respiration-associated vagal modulation of heart rate during sleep (Figures 1a,c). This peak 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 [9]. For this study, a "sleep apnea" peak was not considered abnormal.

Figure 2 shows abnormal FFTs. In contrast to those in Figure 1, plots are irregular and disorganized and, in some, the distinct 1/f distribution of spectral power described above is not seen. Significant power is often seen beyond the HF band (>0.04 Hz). Highly abnormal FFTs, especially those in Figure 2c-f, are readily and unambiguously identifiable by any observer.

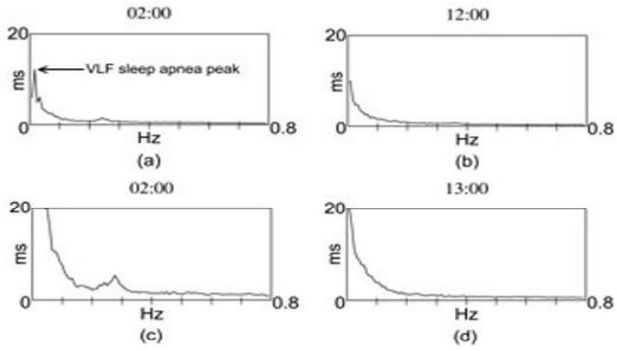

Figure 1. Examples of normal FFTs

2.5. Characterization of Poincaré plots

Normal Poincaré plots for the same subjects and time periods as in Figure 1 are in Figure 3. Poincaré plots are a graphical representative of the change in heart period from one beat to the next. Normal-looking 1-hour Poincaré plots of NN intervals were ellipsoid or sometimes mildly comet-shaped, with few data points outside the main figure.

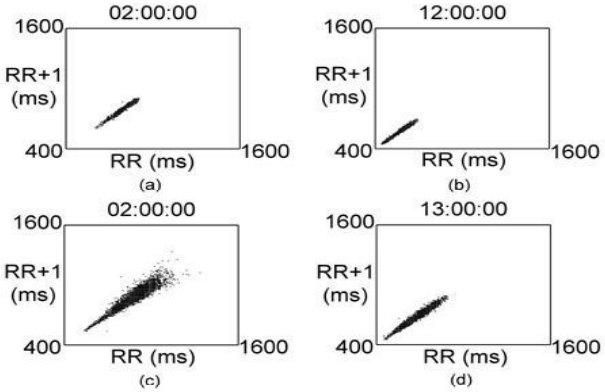

Figure 2. Normal Poincaré plots for the same subjects seen in Figure 1.

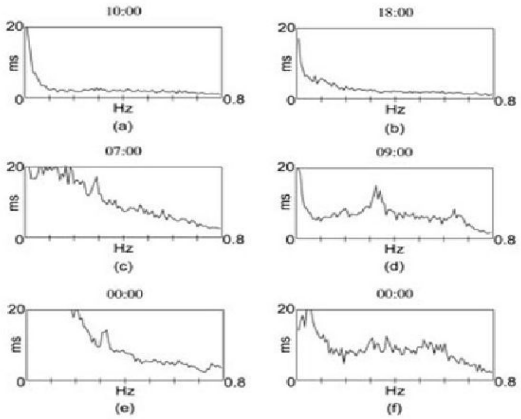

Figure 3. Examples of borderline (2a,b) and clearly abdominal (2c,d,e,f) FFTs

Highly abnormal Poincaré plots for the hours seen in Figure 2 are shown in Figure 4. Points on these plots are far more scattered than in normal plots with patterns ranging from a clearly visible ellipsoid pattern with many points outside it (Figure 4a) to plots with a nearly random-looking distribution of points (Figure 4f).

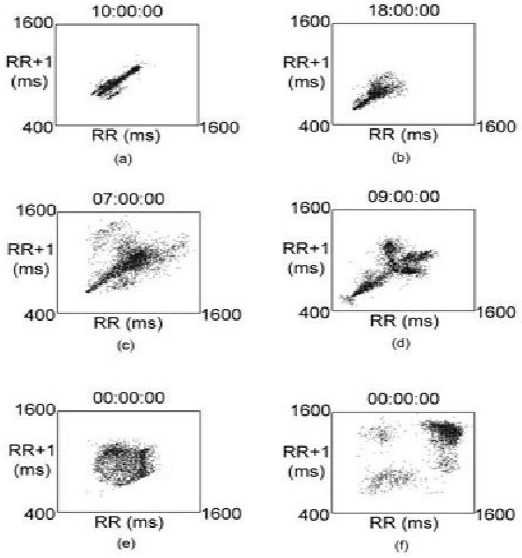

Figure 4. Abnormal Poincaré for the same subjects and periods as Figure 2.

2.6. Categorization of hourly plots

For each subject, both hourly plots and HRV values were examined and coded as normal (0), borderline (0.5) or abnormal (1). Based on ROC curves in a subset of the data, we *a priori* defined "possibly-abnormal" values as: DFA1 <0.85, DFA2<1.00, and ICC<0.85. Hours with all values above these values were coded as normal if plots appeared to be normal. An hour coded abnormal had abnormal-looking plots and values for at least one index below the possibly-abnormal cutpoint. If there was a discrepancy between the plots and HRV values, *i.e.* numbers all within normal limits, but the plot had some abnormal features, that hour was coded as borderline. Often, such plots were at the boundary between hours with clearly abnormal and hours with normal plots. Similarly, if the plot appeared normal, but ∃2 HRV values were abnormal, that hour was coded as borderline.

Most hours could clearly be categorized, but there were exceptions. A very few plots had normal-looking patterns with very low values for one HRV index. Those normal-looking plots with DFA1 or ICC (<0.70) were labeled as borderline, but, because we had previously observed low DFA2 during normal stage 2 sleep, values for DFA2 <0.85 during the nighttime or during naps were considered normal.

2.7. Calculation of abnormality scores

After each hour had been characterized, the scores were added. The abnormality score (ABN, 0-100%) was the percentage (sum/number of hours available).

2.8. Abnormality score cutpoint for increased HRV

Short-term, beat-to-beat HRV would be the most affected by increased non-respiratory sinus arrhythmia. Therefore, short-term HRV by 5th %ile of ABN was plotted, and a cutpoint for ABN associated with markedly increased short-term HRV identified.

2.9. Statistical analyses

To determine which HRV indices are affected by increased ABN, time and frequency domain and non-linear HRV were compared, using t-tests, for ABN ∃ and < the cutpoint for increased short-term HRV. Age and gender were compared by group using Chi-Square analysis. Univariate and multivariate relationship between ABN and mortality was tested by Cox Regression analysis. Statistical significance was set at $p<0.05$. Software was SPSS 11.0 (SPSS, Chicago, IL).

3. Results

Subjects were 70.7 ± 4.5 yrs (range 65-86), 155 M, 135 F. Of 290 subjects, 7 were excluded: 5 with atrial fibrillation or a pacemaker and 2 with a rhythm too irregular for reliable HRV analysis. N=13 subjects with <18 eligible hours of data and were also excluded. After 7 years, 63 eligible subjects had died. Subjects had 5815 out of a possible 6816 analyzable hours (85%). Of these, 64.4% were coded normal, 14.5% borderline and 21.1% abnormal.

3.1. HRV and abnormality scores

Figure 5 is a plot of short-term HRV, in this case high frequency power (HF), vs. ABN. As can be seen, there is a clear increase in HF at ∃ the 16th percentile bar (ABN between 57 and 62%). Similar results were found for other short-term HRV indices: rMSSD (root mean squared successive differences), pNN50 (percent of NNs >ms different from prior NN) and pNN6.25% (percent of NNs >6.25% of local average NN >than prior NN). N=67 subjects had ABN above the cutpoint. Table 1 compares time and frequency domain HRV values for subjects ∃ vs. < the cutpoint. As can be seen, AVNN (average of NN intervals) and SDNN (standard deviation of NN intervals) were not different between groups. In the frequency domain, ln VLF (very low frequency power) was not different, but both the low (LF)/HF ratio and normalized LF power were significantly different in

the groups with higher and lower ABN.

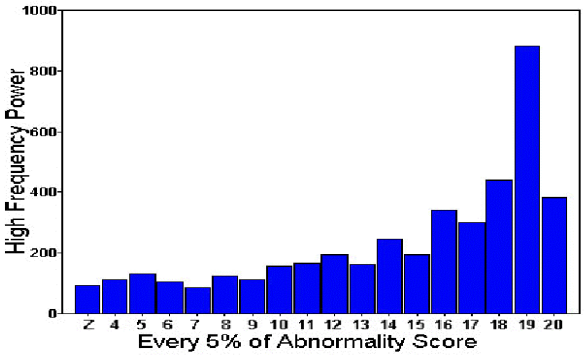

Figure 5. High frequency power for each 5% of abnormality score

Table 1. Comparison of HRV for Subjects Above and Below Cutpoint for Increased Short-Term HRV.

	Above	Below	p-value
AVNN (ms)	840 ± 129	819 ± 97	0.156
SDNN (ms)	118 ± 42	125 ± 33	0.121
pNN50 (%)	12.6± 10.9	3.7± 3.7	<0.001
Ln VLF Power	6.81 ± 0.82	6.88 ± 0.04	0.501
LF/HF ratio	2.5 ± 1.7	4.7 ± 0.2	<0.001
NormalizedLF	39.2 ± 9.1	48.0 ± 0.5	<0.001

3.2. Mortality and Abnormality

Subjects in the higher group of ABN were not different in age (71 ± 5 yrs higher *vs.* 71 ± 4 yrs), nor more likely to be female (20% females for higher, 22% females, p=0.67). The association of ABN and mortality was significant, with higher ABN associated with increased risk of death (HR=1.009 (95%CI=1.001-1.017, p=0.019). Being in the higher group of ABN was significantly associated with increased risk of mortality (p=0.04).

3.3. Discussion

Abnormal FFT and Poincaré plots are not exceptional among older adults. Increased ABN was associated with increased mortality *without* concomitant decreases in the traditional HRV, like SDNN, used for risk stratification. Increased HRV may reflect better cardiac autonomic function, among some, but not all, subjects in certain populations. Results help explain why short-term indices of HRV, such as pNN50 and HF power, often do not differ between healthy and cardiac patients or between survivors and non-survivors in post-MI studies [10]. In addition, results help explain why non-linear HRV has been superior to traditional HRV for risk stratification in some studies. While the methodology in this exploratory study was semi-quantitative and does not represent the development of a new method for risk stratification, results suggest that the development of more sophisticated tools to account for abnormal heart rate patterns would potentially improve HRV-based risk stratification.

Limitations include the categorization of abnormal plots, independent of the degree of abnormality. Also, it is not known whether one hour blocks of time are optimal. Additional techniques for quantifying abnormal HRV and/or for filtering it out of the recording might improve risk stratification.

Acknowledgements

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