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Heart Rate Chaos as a Mortality Predictor in Mild to Moderate Heart Failure

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Abstract—**Linear and nonlinear indices of heart rate variability (HRV) have been shown to predict mortality in congestive heart failure (CHF). However, most nonlinear indices describe only the fractality or complexity of HRV but not the intrinsic chaotic properties. In the present study, we performed linear (time- and frequency-domain), complexity (sample entropy), fractal (detrended fluctuation analysis) and chaos (numerical titration) analyses on the HRV of 50 CHF patients from the United Kingdom heart failure evaluation and assessment of risk trial database. Receiver operating characteristic and survival analysis yielded the chaos level to be the best predictor of mortality (followed by low/high frequency power ratio, LF/HF), such that these indices were significant in both univariate and multivariate models. These results indicate the power of heart rate chaos analysis as a potential prognostic tool for CHF.**

I. Introduction

HEART rate variability (HRV) analysis in the congestive heart failure (CHF) population has become of interest over the past decade as a mortality predictor. Linear and nonlinear analysis of HRV provides a non-invasive, inexpensive method to detect autonomic changes and aid the physician's treatment of the condition. Results of previous studies rely heavily on the advancement of the disease in the subject group as well as the number of subjects included in the study such that studies often present contradictory results. In mild to severe CHF subjects, time-domain indices of total HRV (standard deviation of all normal-to-normal (NN) intervals) and the short-term component of HRV (percentage of NN intervals larger than 50 ms) have been shown to be significant univariate predictors of mortality [1-3, 5-7]. The significance of frequency-domain components such as very-low-, low-, and high-frequency, is not as well-established, since the significant univariate HRV indices vary with different studies; however, studies with significant absolute frequency-domain predictors included severe CHF subjects in the population [1, 3, 5, 8].

Nonlinear indices, though not as widely studied, have proven to be significant in various studies. Brouwer determined Poincare plots to be a significant predictor of mortality when time- and frequency-domain indices were not [9]. Other univariate predictors include the 1/f slope [1], detrended fluctuation analysis index [8], and short-term fractal exponent [10], whereas Ho found approximate entropy to not be a predictor of mortality [8].

Though many studies identified HRV indices as univariate predictors of mortality, many were not significant predictors in a multivariate model with chemical and other physiological data [1-4]. In this study, time- and frequency-domain, complexity, fractal, and chaos analysis were performed on the RR series of mild to moderate heart failure subjects in order to determine the predictors of death in univariate and multivariate models. We hypothesized that the combination traditional linear indices with a variety of other HRV indices yield a more accurate HRV multivariate model for mortality prediction.

II. Methodology

A. Data Acquisition

The data for the study consisted of RR intervals of 50 randomly chosen patients from the United Kingdom heart failure evaluation and assessment of risk trial (UK-HEART) study [2, 11-14]. The data were gathered in 8 hospitals across the United Kingdom, where 18-85 year-old outpatients with symptoms of CHF for at least three months were recruited between April 1993 and December 1995. Patients were in New York Heart Association (NYHA) functional class I-III and had evidence of cardiac dysfunction at rest such as pulmonary venous congestion, pulmonary edema or cardiothoracic ratio > 0.55 on at least one chest radiograph, or a documented radionuclide or echocardiographic ejection fraction < 45%. A twenty-four hour ambulatory electrocardiogram was recorded (Tracker, Reynolds Medical Ltd) during normal activity. These recordings were analyzed with a Pathfinder system by a technical staff to identify and exclude patients with arrhythmias, whose presence could affect the outcome of CHF, and to extract the normal-to-normal RR intervals.

Of the 50 patients chosen for the study, 28 survived the 5-

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year follow-up period. None of the patients in the study were treated with beta-blockers.

B. HRV Analysis

1) Numerical Titration

Numerical titration provides sufficient proof of chaotic dynamics in a short, noise-contaminated series [15]. Acting similar to a chemical titration, the chaos level (acid) is quantified by neutralization with white noise (base). For a nonlinear signal, white noise is added at 1% of the signal power in each step before being again scrutinized for nonlinearity. A significantly better fit of the nonlinear Volterra series to a linear model, as measured by the f-test and the Akaike information criterion, determines nonlinearity. The output of titration, the noise limit (NL) measures the chaos level as the percentage of added white noise before nonlinearity is no longer detected. Thus, for a chaotic signal NL>0, whereas for a linear or random signal, NL=0.

The noise limit was calculated for 12-minute non-overlapping segments of the entire recording. The other output of titration, the nonlinearity detection rate (DR), is the percentage of nonlinear segments in the given time window. The NL and DR were then averaged over the day (8am-8pm), night (8pm-8am), and 24 hours to yield three indices of NL and DR for each subject.

2) Sample Entropy

Entropy measures quantify the regularity of a series, such that the entropy of a series decreases with increasing predictability of the series' fluctuations. Approximate entropy (ApEn), developed by Pincus [16], reflects the logarithmic likelihood that two sequences that are similar (within a tolerance r) for m points remain similar on incremental comparisons. Though the algorithm has been widely implemented, accuracy depends heavily on the length of the data and the algorithm counts self matches in order to avoid singularities. Sample entropy (SampEn), developed by Richman [17], reduces the bias of ApEn and improves on its inconsistencies. Sample entropy was calculated for every 12-minute segment with $m = 2$ and $r =$ 20% of the standard deviation of each segment. The SampEn values were then averaged over the day (8am-8pm), night (8pm-8am), and 24 hours to yield three indices of SampEn.

3) Detrended Fluctuation Analysis

Detrended fluctuation analysis (DFA) quantifies long-range power law correlations as well as mono-fractal scaling properties in a signal [18, 19] by means of a modified root mean square analysis of a random walk [20]. The scaling exponents are calculated such that the input signal is not limited to noise-free and stationary series, since apparent correlations due to non-stationarity are not detected, but the series must be of extensive length. Thus, the short-range (α_s) and long-range (α_l) correlations were computed for the entire RR series.

4) Time-domain Analysis

The analysis included several traditional time-domain measures [21]: the standard deviation of all NN intervals (SDNN), the standard deviation of the averages of NN intervals for 5-minute segments in the complete recording (SDANN), the square root of the mean of the sum of squares of differences between adjacent NN intervals (RMSSD), and the percentage of adjacent intervals that differ by more than 50 ms (pNN50). SDNN yields a measure of overall HRV while SDANN characterizes the long-term component and both RMSSD and pNN50 characterize the short-term oscillations. All time-domain indices were calculated for the entire recording.

5) Frequency-domain Analysis

The total power (TP), low frequency (LF), and high frequency (HF) were measured by frequency-domain analysis. The RR series was divided into 12-minute segments for analysis, a duration that is long-enough time to capture the LF component [21] while eliminating the nonstationary characteristic of the heart rate. Cubic spline interpolation at 4 Hz was performed on the data in each 12-minute segment to achieve even sampling of the series. The power spectral density (PSD) was calculated by means of the widely-applied Welch's method [22, 23] of averaged modified periodograms. The TP (0 Hz – 0.4 Hz), LF (0.04 Hz - 0.15 Hz), and HF (0.15 Hz - 0.4 Hz) were averaged over the day (8am-8pm), night (8pm-8am), and 24 hours.

C. Statistical Analysis

Receiver operating characteristic (ROC) curve analysis was performed to determine the best HRV indices for distinguishing those who died from the survivors. The area under the ROC curve (AUC), sensitivity (Se), and specificity (Sp) were calculated for all indices.

Survival functions were estimated by the Kaplan-Meier method. The Cox proportional hazards model established associations between the HRV indices and the time of death. Univariate analysis was performed on all the HRV indices, whereas multivariate analysis only included the indices which had been significant (p value<0.05) as independent predictors of mortality.

III. Results

The 24-hour mean values and standard error of noise limit and LF/HF are plotted in Fig. 1. The survivor group's circadian rhythm in Fig. 1 illustrates the necessity for evaluation of the HRV indices during day (8am-8pm) and night (8pm-8am).

A. ROC Analysis

The five HRV indices with the highest goodness of test as measured by the area under the ROC curve were: day LF/HF (.778), α_s (0.747), 24-hour LF/HF (0.742), day DR (0.731), and 24-hour DR (0.726).

The HRV indices with highest accuracy, as measured by the best detection point on the ROC curve, along with the AUC, sensitivity, specificity, and critical value at which the Se and Sp were achieved are listed in Table I. The HRV indices which were higher in the nonsurvivor group are identified by an asterisk. In addition to the HRV indices

listed in Table I, ROC analysis showed higher values of night DR, 24-hour DR, day DR, day HF, 24-hour HF, and night HF in the nonsurvivor group. The SDANN, SDNN, night SampEn, day VLF, day LF, night LF, 24-hour LF, pNN50, 24-hour TP, night TP, and day TP were higher in the survivor group. The AUC of RMSSD was 0.5, such that detection with this parameter equals that of a random test.

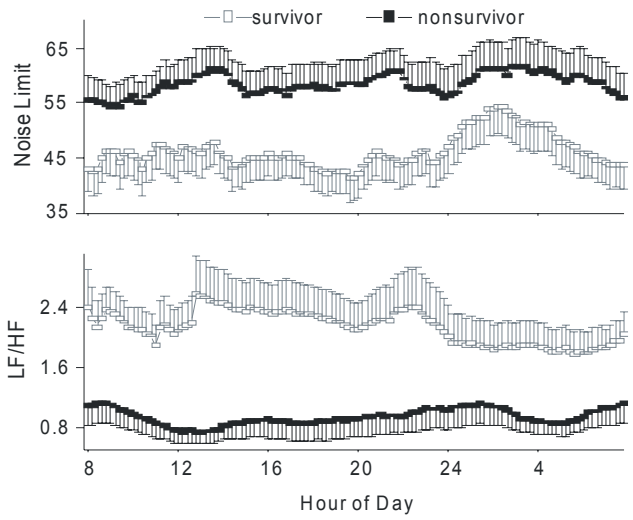

Fig. 1. Average noise limit and LF/HF for survivor and non-survivor group. The error bars show the standard error for each segment. The values for each 12-minute segment were averaged over 3-hours to yield smooth curves.

TABLE I. INDICES WITH HIGHEST ACCURACY IN ROC ANALYSIS

Index	AUC	Se (%)	Sp (%)	Critical Value
NL (day) *	0.70	77.27	75.00	50.90
LF/HF (day)	0.78	71.43	77.27	1.20
LF/HF (24 h)	0.74	67.86	72.72	1.06
LF/HF (night)	0.72	67.86	72.72	0.99
NL (24 h) *	0.69	72.72	67.86	53.59
α_l	0.64	85.71	59.09	0.89
NL (night) *	0.66	77.27	60.71	47.49
α_s	0.75	92.86	54.55	0.49
SampEn (24 h)	0.68	78.57	59.09	0.87
SampEn (day)	0.67	85.71	54.55	0.79

* Has higher value for the nonsurvivor group.

B. *Survival Analysis*

In Cox univariate analysis, most HRV indices were significantly associated with mortality. Where significance was defined as p value<0.05, survivors exhibited higher short-range correlation, LF/HF ratio (24 h, day, and night), VLF (24 h, night), SampEn (24 h, day, and night), SDANN, and SDNN. The significant HRV indices in the univariate model which were positively correlated with death corresponded to chaos analysis: detection rate (24 h and day) and noise limit (24 h and day). The Kaplan-Meier survival curves for different ranges of NL, LF/HF, and DR during the day are plotted in Fig. 2. The difference between the NL curves (p value = 0.0141), the DR curves (p value = 0.0110), and the LF/HF curves (p value = 0.0168) were all significant.

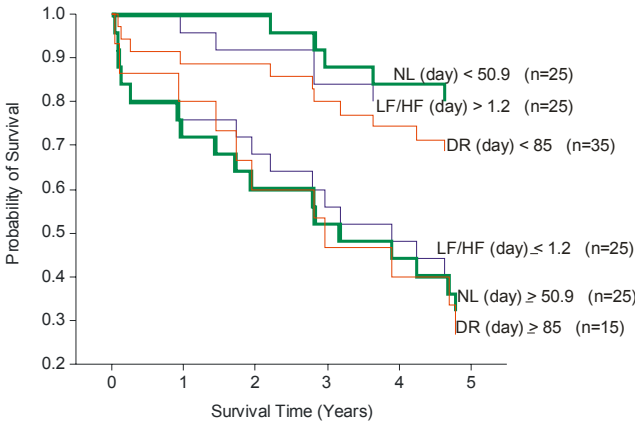

Fig. 2. Survival curves. The Kaplan-Meier survival curves for NL (black line), LF/HF (dotted line) and DR (gray line) during the day. The critical values were determined from ROC analysis.

In multivariate analysis (Table II), the sample entropy, time-domain indices, and short-range correlation were no longer significantly associated with mortality.

TABLE II. COX PROPORTIONAL HAZARDS ANALYSIS

Index	Univariate χ^2	Multivariate χ^2	Multivariate P value
NL (24 h)	4.20	5.71	0.0268
NL (day)	5.76	5.58	0.0182
LF/HF (night)	5.21	5.33	0.0209
LF/HF (day)	7.42	5.25	0.0219
LF/HF (24 h)	6.71	5.20	0.0226
DR (day)	7.11	4.91	0.0267
DR (24 h)	6.08	3.85	0.0499
SampEn (night)	6.32	2.85	0.0916
SDNN	6.34	2.34	0.1262
SampEn (24 h)	5.82	2.25	0.1338
SDANN	5.60	1.45	0.2286
SampEn (day)	4.38	1.43	0.2324
α_s	8.29	0.09	0.7682

IV. DISCUSSION

ROC analysis and survival analysis yielded similar results for the best predictive variables, suggesting these indices, particularly the noise limit and LF/HF, predict mortality in both individual and group settings. In addition, the sensitivity and specificity values of the NL and LF/HF during the day are higher than those of the previously developed low/high risk index for the UK-HEART dataset [12]. The survival curves plotted in Fig. 2 illustrate the ability of the NL, LF/HF, and DR in predicting mortality, where the best prediction was achieved by NL.

Time-domain analysis was in agreement with published results, such that SDNN and SDANN were predictors in the univariate model. For frequency-domain indices, the detection accuracy of the LF/HF at all times can be attributed to the survivor group having a slightly lower HF and slightly higher LF than the nonsurvivors. Though the LF and HF indices were not significant predictors, the difference in the groups was magnified by taking the ratio.

The significance of the entropy predictors was not in agreement with Ho's [8] results, since all entropy measures were univariate predictors of mortality. However, the different results could be due to differences in the subject populations as well as the use of approximate entropy versus sample entropy. The short-range and long-range correlation in DFA did not result in accurate detection indices in the ROC analysis, though better detection was achieved than with the absolute frequency indices. As in Makikallio's study [10], the short-range exponent proved significant as a univariate predictor.

The significance of detection rate and noise limit as univariate and multivariate predictors of mortality results from the chaotic nature of the heart rate and the variations of the chaotic properties with pathologies [24]. The time limitation of prediction properties of NL and DR, which are not significant predictors at night, is a consequence of the circadian rhythms of these variables. Both the NL and DR are higher in the nonsurvivors, but the stronger circadian rhythm of the survivors eliminates the significance of the indices in distinguishing both groups.

V. Conclusion

ROC and survival analysis yielded the noise limit, a measure of HRV chaoticity, to be the best predictor of mortality. Death in CHF was also associated with other variables such as increased nonlinearity detection rate and decreased LF/HF, SDNN, SDANN, and SampEn. These indices present a potential non-invasive prognostic tool for congestive heart failure.

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