Multiscale Complexity Analysis of Heart Rate Dynamics in Heart Failure: Preliminary Findings from the MUSIC Study

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Abstract

Recently, a new complexity measure, multiscale entropy (MSE), has been developed based on the quantification of heart rate fluctuations over a range of time scales. Here, we use the MSE algorithm to analyze the cardiac interbeat interval time series from patients with congestive heart failure (CHF) enrolled in the MUSIC study. Our hypothesis is that the heart rate time series from the patients who survived have more dynamical complexity that those from patients who did not survive.

MUSIC (Muerte Subita en Insufficiencia Cardiaca) is a prospective multicenter longitudinal study designed to assess risk predictors of death in patients with heart failure. The MSE algorithm was used to quantify the degree of complexity of the interbeat interval time series derived from 24-hour Holter recordings. The analysis was performed up to scale 20 that corresponds to approximately 20 seconds.

For all measured time scales, the mean MSE values were significantly ($p < 0.01$) higher for the entire RR time series from the group of patients who survived than for the time series from the group of non-survivors. Similar results were obtained from the analysis of the time series of consecutive sinus (NN) beats. These findings indicate that the heart rate dynamics of survivors are more complex than those of non-survivors, and suggest that MSE analysis may be useful in risk stratification of patients with mild-moderate symptoms of CHF.

1. Introduction

The development of new markers of mortality risk in congestive heart failure (CHF), including sudden cardiac death, is a major challenge in contemporary cardiology. The primary objectives of this paper are: 1) to discuss briefly the relevance of measures of complexity to physiology, 2) to compare the complexity of heartbeat time series from CHF patients enrolled in the MUSIC study who survived and who did not survive, and 3) to compare the complexity of heartbeat time series from patients who died from sudden cardiac death (SCD) with those who died due to CHF progression or acute myocardial infarction

2. Methods: subjects

MUSIC (MUerte Subita e Insuficiencia Cardiaca = Sudden Death in Heart Failure) is a prospective multicenter longitudinal study designed to assess risk predictors of all cause mortality and sudden death in heart failure patients. The study population consists of consecutive CHF patients in New York Heart Association (NYHA) class II-III referred to heart failure units and enrolled in 9 centers in Spain as previously described [1, 2, 3]. Patients were followed-up of at least 2 years; the primary endpoint was total mortality and the secondary endpoints were sudden and non-sudden death. Briefly, the study group included those with systolic and/or diastolic dysfunction from ischemic or non-ischemic etiologies.

Specific enrollment criteria for the MUSIC Study included CHF symptoms more than 3 months after last hospitalization due to heart failure decompensation and at least one of the following echocardiographic criteria: left ventricle ejection fraction less than 40%, left ventricular diastolic diameter over 60 mm, left ventricular hypertrophy (septum or posterior wall thickness over 14 mm), or abnormal relaxation patterns characteristic for diastolic dysfunction. The exclusion criteria were as follows: heart

failure secondary to an acute reversible cause in patients with no prior history of heart failure (e.g. hyperthyroidism); heart failure secondary to valvular heart disease amenable to surgical repair; right ventricular heart failure associated with chronic cor pulmonale or concomitant terminal disease. The study protocol was approved by institutional Investigation Committees and all patients signed informed consent.

The following data were collected: demographic and clinical data, echocardiography, chest X-ray, blood tests, including N-terminal prohormone B-type natiuretic hormone levels, 12-lead electrocardiogram (ECG) and 24-hour Holter monitoring. Here we present preliminary findings from complexity analysis of interbeat interval time series. The sub-study population that we analyzed consisted of 576 patients with underlying sinus rhythm, including 418 males and 158 females, mean age 62 ± 12 years. The total mortality rate was 10% (n=46) and the sudden cardiac death rate was 5% (n=28) (see Table 1).

3. Methods: complexity analysis

Healthy systems have intact multiscale control mechanisms. In contrast, pathology is associated with degraded and/or decoupled regulatory networks and generates less complex outputs [4, 5, 6]. Therefore, we hypothesize that dynamical complexity decreases with disease and that the complexity of heartbeat time series from CHF patients who survived is higher than those who did not survive.

Complexity of an output signal is related to the presence of the structurally rich patterns in the data [7]. Of note, complexity is different from randomness. Complex physiologic signals typically exhibit multiscale variability, long-range correlations, time-irreversibility, non-linearity and non-stationarity [8].

Entropy-based algorithms, as for example, approximate entropy [9, 10] and sample entropy [11] have been used for the analysis of physiologic signals. These algorithms quantify the degree of irregularity of a time series on the shortest time scale but fail to quantify its information content on longer time scales. Meaningful complexity measures, however, should account for the multiple time scales inherent in physiologic signals [12, 13].

We developed the multiscale entropy (MSE) algorithm [6, 14] to quantify the degree of irregularity over a range of time scales. Briefly, the method comprises three steps: i) construction of coarse-grained time series, ii) quantification of the entropy of each coarse-grained time series, and iii) summation of the values entropy values over a range of scales.

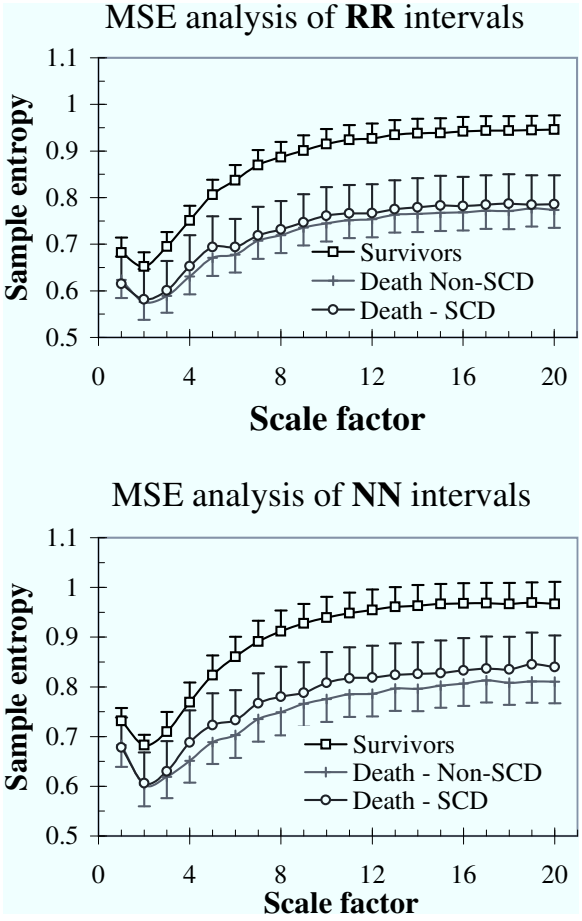

Figure 1. MSE analysis of the interbeat interval time series. Top panel shows the MSE results for the RR interval time series. All physiologic intervals are included in these time series. Bottom panel shows the MSE results for the normal-to-normal (NN) interval time series. The major difference between the RR and the NN time series is that the former includes ventricular premature beats. Symbols and error bars represent mean values for each group and standard errors, respectively. The value of the parameters used for the computation of the sample entropy were: $N = 4 \times 10^4$, $m = 2$ and $r = 0.15$. SCD, sudden cardiac death.

4. Results

In Fig. 1 we present the results of applying the MSE method to the analysis of the interbeat interval time series from the MUSIC Study patients. Qualitative similar results are obtained from both the analysis of the RR and the NN (normal-to-normal) interval time series. For all scales the entropy values were significantly higher (t-test, $p < 0.01$) for the group of patients who survived compared with the group of those who did not survive, which includes both the patients who died suddenly and from heart failure pro-

gression. Although the entropy values were slightly higher for the group of patients who died suddenly than for the group of patients who died from heart failure progression, the differences were not statistically significant.

Standard heart rate variability time and frequency domain analyses and heart rate turbulence for this study are being presented elsewhere [1, 2, 3].

5. Conclusions

Non-survivors in sinus rhythm from the MUSIC had significantly lower heart rate complexity than survivors as measured with the MSE method.

6. Future directions and questions

Our preliminary analysis raises a number of questions that require further analysis:

- Does MSE add independent value to total mortality and sudden cardiac death predictors in concert with other HRV/ECG/clinical measures?
- Does MSE differ in CHF subsets: diastolic versus systolic; diabetics vs non-diabetics; ischemic vs non-ischemic?
- What are the mechanisms of loss of heart rate complexity in CHF?
- Can complexity analysis be used to assess the efficacy of therapeutic interventions?

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