Unique RR Interval Dynamics Preceding Sudden Cardiac Death

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Abstract

Sudden cardiac death (SCD) is often the first manifestation of underlying cardiac pathology, highlighting the importance of early detection using properties of the electrocardiogram (ECG). We investigated how dynamical RR interval (RRI) correlations differ between SCD and non-SCD subjects during a clinical exercise test.

We analyzed RR intervals (RRIs) extracted from Mason–Likar modified 12-lead ECG recordings obtained during a clinical exercise test (N=3406) from the FINCAVAS database. Over a follow-up period of 8.6 years (IQR 6.7—10.6), 86 subjects suffered SCD. We evaluated RRI correlations using dynamic detrended fluctuation analysis (DDFA). Eight confounding factors were assessed using a multivariable Fine–Gray subdistribution hazard model, with other deaths (N=445) treated as competing risks.

DDFA scaling exponents revealed clear differences between the alive and SCD groups. The lowest univariate hazard ratio, 0.43 (95% CI 0.34–0.54, $p = 3 \times 10^{-12}$), was observed at scale 8 and quantile heart rate (HR) 0—0.1, corresponding to a 2.4-fold increased risk of SCD with one standard deviation decrease in the scaling exponent. Similarly, the smallest multivariable hazard ratio was 0.52 (95% CI 0.40–0.69, $p = 5 \times 10^{-6}$) for the corresponding scale and HR. In conclusion, SCD patients exhibited significantly decreased scaling exponents at low HRs.

1. Introduction

Sudden cardiac death (SCD) is a critical global health issue, responsible for 2 million deaths annually [1]. It is defined as an unexpected death due to cardiac causes occurring within one hour of symptom onset, or as an unwitnessed death in a person who was symptomless 24 hours earlier [2]. SCD can strike individuals with or without known heart disease, making it a particularly challenging condition to predict and prevent. Nearly half of SCD cases occur in people with no known heart disease [3]. Detecting asymptomatic individuals at high risk for SCD, especially those with high functional capacity and no known medical conditions, is a challenging but crucial task.

With the significant increase in wearable devices collecting data in the consumer market over the past years, the potential for advanced analytics of various physiological measures, such as heart rate (HR) variability (HRV), has grown. HRV has been proven to be a valuable metric for evaluating cardiac health, sleep quality, and physical exercise -related issues [4]. Recently developed HRV methods, in particular, have shown great promise in assessing overall cardiac risk, including the risk of SCD [5].

In this study, we examined how HRV methods developed for detailed analysis of RR interval (RRI) correlations detection before, during, and after a controlled exercise test can be applied to detect SCD. We utilized detrended fluctuation analysis (DFA) [6, 7] and dynamical DFA (DDFA) [8] to study the RRI correlations. DFA has previously shown significant potential in disease detection [9–11] and in detecting SCD [5]. In this work we investigated if a dynamical approach with DDFA provides further insight into the analysis.

2. Data and preprocessing

The data was collected from the clinical FINCAVAS study [12] of subjects undergoing clinical exercise testing at Tampere University Hospital. The study protocol was approved by The Ethics Committee of Tampere University Hospital District and is in compliance with the Declaration of Helsinki. All patients have given written informed consent and the data from the study has been already used in several publications [13]. Clinical data was collected using standardized questionnaires, interviews and reviews of patient records.

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The RRIs were extracted from Mason–Likar modified 12-lead ECG recordings during a clinical exercise test. During the study 4386 exercise tests were completed, but multiple tests from same subject were removed and patients with pacemakers or implantable cardioverter-defibrillators and missing metadata were excluded, reducing the number of subjects to 3770.

llThe RRI data was filtered by removing all the beats defined as abnormal by the workstation CASE80000ws (v.1.71; GE Medical Systems, Waukesha, Wisconsin, USA). Of the remaining intervals we removed those that differed by more than 20% from the previous and succeeding beats. Finally, we removed all the beats that differed by more than three times the local standard deviations from local median calculated with kernel size of 51 beats. Subjects with more than 10% of the intervals removed after the preprocessing were removed from the analysis.

After the selection and preprocessing of the samples, we ended up with 3406 recordings, including 86 samples with SCD during the follow-up. The main statistics of the studied population are shown in Table 1. The subjects who experienced sudden ventricular fibrillation and hemodynamic collapse within 1 hour of symptom onset, were included into SCD population even when they were successfully resuscitated [5].

Table 1. Statistics for the studied population

N (male/female)	3406 (2013/1393)
1min HR recovery (BPM)	25 ± 11
Age (years)	55 ± 13
Fitness (MET)	7.8 ± 2.9
Beta Blockers (no=N/yes=Y)	1571/1835
Diabetes (N/Y)	2923/483
Stroke (N/Y)	3223/183
Atrial Fibrillation (N/Y)	2972/434
Myocardial Infraction (N/Y)	2510/896

3. Theory and methods

Detrended fluctuation analysis [6, 7] scaling exponents describes the *collective* correlations of the analysed time series contrary to the autocorrelation function, which describes the *pointwise* correlations [8]. The DFA short-scale correlations (scales 4-16) have been shown to yield good distinguishability for cardiac conditions and SCD [5, 10]. In our recent work we have shown how using maximally overlapping windows [14] and second-order detrending results in improved distinguishability between healthy controls and subjects with cardiac diseases and SCD [5, 10].

In this work we utilize DDFA to calculate the *dynamical* scaling exponent $\alpha(t, s)$ as a function of scale s and time t [8]. In order to study how the exercise intensity affects $\alpha(t, s)$, we aggregated the results as a function of HR. Since the exercise test is a controlled procedure and individuals have different resting and maximal HRs, they were quantile-transformed into 10 bins between 0 and 1, which correspond to the lowest and highest HRs, respectively. The quantile HR-dependent scaling exponents $\alpha(\mathrm{qHR}, \mathrm{s})$ were calculated from averaged values of $\alpha(t, s)$. The methodology is explained in more detail in Ref. [8].

The hazard analysis was completed with Fine–Gray subdistribution hazard model, and other causes of death (N=445) were modeled as competing risks. The duration of the follow-up period was used as a time scale in the analysis. The confounding factors were chosen based on the univariate Fine–Gray model of Ref. [5] (excluding the HRV measures) and taken into account with the multivariable hazard model.

The confounders included in the multivariable analysis were the following: (i) demographic variables: age and sex; (ii) physiological measurements: recovery HR and physical fitness; (iii) medication: beta blockers; (iv) diseases: atrial fibrillation, diabetes, myocardial infarction and stroke. The recovery HR and physical fitness were standardized to zero mean and unit variance, i.e, the hazard ratio of these measures corresponds to the risk change related to a 1-SD change in the measure. For age, the hazard ratio corresponds to the risk increase in age (in years).

4. Results and discussion

Figure 1 shows the aggregated DDFA scaling exponents $\alpha(\mathrm{qHR}, \mathrm{s})$ over all the subjects, split between different end points. The aggregation is done by calculating the mean of the subject means in each of the bins so that each subject has similar weight in the aggregated figure. The subjects alive at the end of the follow-up are shown in Fig. 1 (a). This illustrates the normal behavior of the scaling exponent as the HR increases: the scaling exponent is high at low HRs, but anticorrelations ($\alpha < 0.5$) start to appear around scale 10 as the HR increases. These anticorrelations further spread into other scales as the HR increases to the maximum.

The most important and prominent feature of the SCD case in Fig. 1 (b) is the reduced scaling exponent at the lowest HRs, i.e., at rest. Fig. 2 shows the difference between the scaling exponents of the subjects who were alive after the follow-up and those who had SCD. The most prominent area is at the low HRs with scales around 8-12. This result is similar to those reported in a previous study utilizing the DFA short-scale scaling exponent [5].

The univariate hazard ratios for each scale and quantile HR combination of $\alpha(\mathrm{qHR}, \mathrm{s})$ are shown in Fig. 3 (a). They align with previous results, with the lowest quantile HR of 0–0.1 (during rest before the exercise test) giving the most prominent univariate hazard ratio of 0.43 (95% CI 0.34–0.54, $p = 3 \times 10^{-12}$) obtained with scale 8 [5].

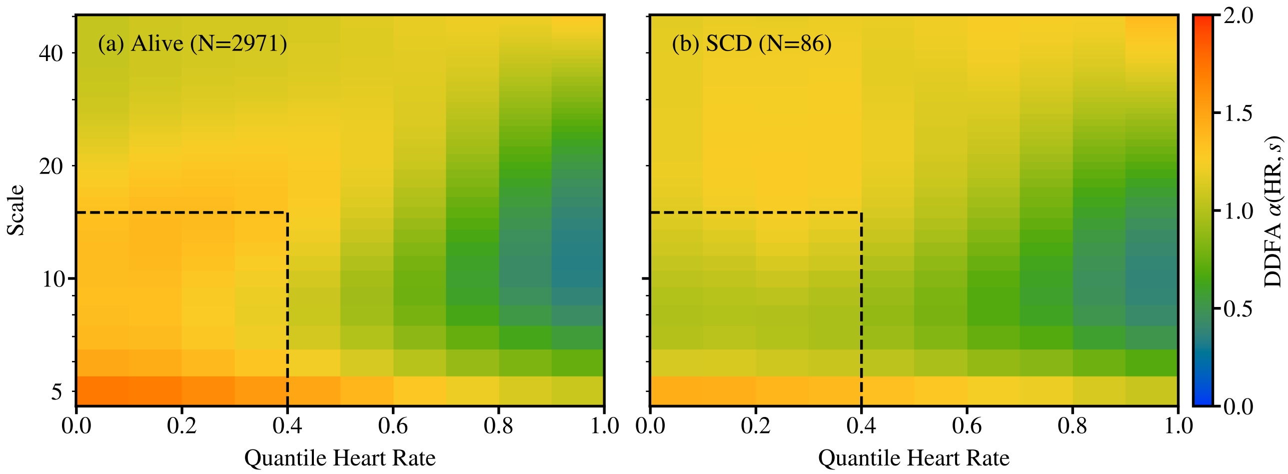

Figure 1. Aggregated dynamical detrended fluctuation analysis (DDFA) scaling exponents $\alpha(\mathrm{HR}, \mathrm{s})$ as functions of the heart rate (HR) and scale s for (a) subjects that were alive at the end of the follow-up and (b) subjects that suffered a sudden cardiac death (SCD) during the follow-up period.

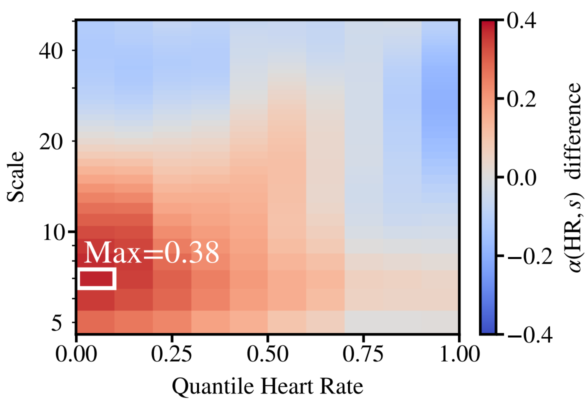

Figure 2. Difference in aggregated dynamical detrended fluctuation analysis (DDFA) scaling exponents $\alpha(\mathrm{HR}, \mathrm{s})$ as functions of the heart rate (HR) and scale s of Fig. 1 between the subjects that were alive at the end of follow-up and the subjects that suffered a sudden cardiac death.

This corresponds to a 2.4-fold risk of SCD compared to the alive population with one SD decrease in the DDFA scaling exponent. Similarly, the smallest multivariable hazard ratio is 0.52 (95% CI 0.40–0.69, $p = 5 \times 10^{-6}$) for the corresponding scale and HR. The univariate model also shows a decent hazard ratio of 1.52 at the highest HRs, but it almost completely vanishes in the multivariable model. We suspect this is due to the confounding factors significantly affecting physical performance and highly correlating with SCD.

5. Conclusion

Based on clinical exercise test data, the highest and lowest HRs are most valuable when using HRV data for the prediction of SCD. Individuals at risk of SCD exhibit RRI correlations that resemble those of a heart under stress, even during rest. The multivariable hazard ratio of 0.52 at the lowest HRs and scale 8 corresponds to a 1.9-fold increased risk of SCD compared to the alive population for each standard deviation decrease in the DDFA scaling exponent.

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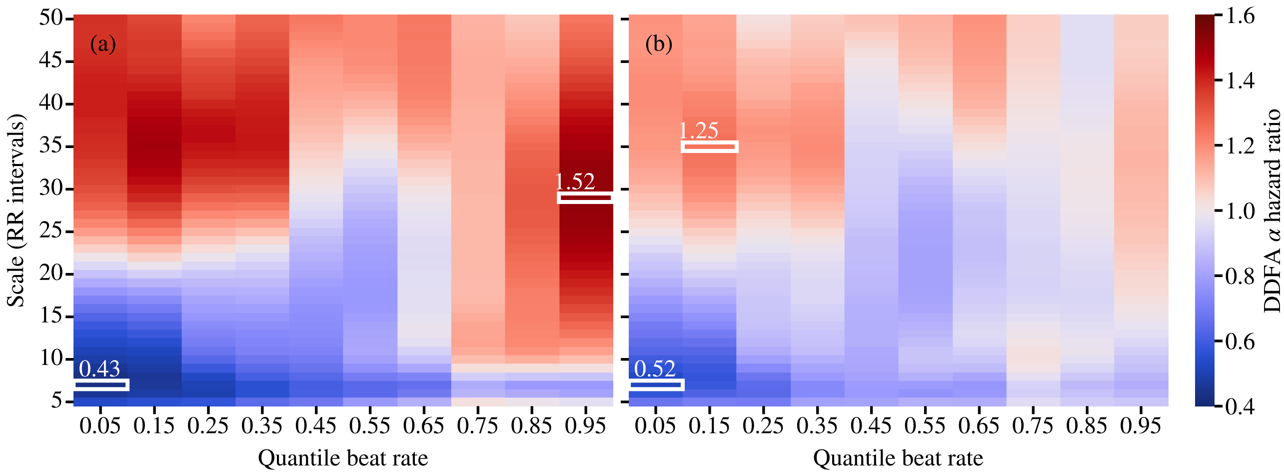

Figure 3. (a) Univariate and (b) multivariable hazard ratios of dynamical detrended fluctuation analysis (DDFA) scaling exponents $\alpha(\mathrm{HR}, \mathrm{s})$ as functions of the heart rate (HR) and scale s. Boxes with with outlines and numbers show the highest and lowest hazard ratios in the given scale and quantile HR space.

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