Effects of Beta Blocker Therapy on RR Interval Correlations During Exercise

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Abstract

The effects of beta blockers (BBs) on heart rate (HR) and HR variability (HRV) are well known in general, but RR interval (RRI) correlations during an exercise test have not been previously studied in detail. We analyzed RRIs extracted from Mason–Likar modified 12-lead ECG recordings during a clinical exercise test ($N = 2257$, of which 1227 with BBs) from the FINCAVAS database. We computed the short-term scaling exponent α_1 of detrended fluctuation analysis (DFA) in one-minute segments before, during and after exercise. Several confounding factors such as age, sex, diseases and medication were taken into account with propensity score matching.

During rest, BBs significantly reduced the DFA scaling exponents, but the effect was opposite in the recovery phase. Thus, BBs were found to limit the α_1 range. However, propensity score matching accounting for the confounding factors was found to diminish the differences. The dependency of the scaling exponents on the HR was found to be similar in both groups, and disappeared during the exercise.

1. Introduction

Since the amount of wearable devices collecting data has increased significantly in the customer market during the past years, the need for advanced analytics for different physiological measures, such as heart rate (HR) variability (HRV) has increased. HRV has been proved to be a great measure to evaluate cardiac health, sleep analytics and physical exercise [1]. However, cardiac diseases are fairly common in the population and they are often treated with different medications, such as beta blockers (BBs), which are effective in preventing heart failure [2]. However, BBs also reduce the HR, cause possible negative inotropic effects on both peripheral skeletal muscles and airway smooth muscles which leads into exercise intolerance due to dyspnea and fatigue [3]. These changes in HR also affect many of the HRV parameters, and due to the correlation between these two parameters [4] the use of HRV in the early detection of cardiovascular diseases in patients with BB medication is limited in early detection of cardiovascular diseases in patients with BB medication.

Here we studied how the RR interval (RRI) correlations are affected by BB treatment before, during and after a controlled exercise test. We utilized detrended fluctuation analysis (DFA) [5–7] to study the RRI correlations between subjects with and without BB medication. DFA has been previously shown to yield significant potential in disease detection [8–10].

2. Data and preprocessing

The data was collected from the clinical FINCAVAS study [11] 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 in compliance with the Declaration of Helsinki. The data from the study has been already used in several publications [12].

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. We included only the subjects that had enough data for 1 min segments in all the following phases: (i) 80 sec data in resting phase (60 sec segment and 20 sec break before exercise start) (ii) minimum of 2 min during exercise for 1 min segment at the start and (iii) end of the exercise, and (iv) 1 min from recovery [13]. These segments represent a good range of different intensities; rest, light exercise, hard

exercise and recovery immediately after hard exercise.

The 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 3 times the local standard deviations from local median calculated with kernel size of 51 beats. If more than 10% of the all beats were removed in total, the whole sample was discarded.

After the selection and preprocessing of the samples, we ended up with 2257 recordings, including 1227 samples with BB medication. The main statistics of the studied groups are shown in Table 1.

Table 1. Statistics for both control and BB groups of N (male=M/female=F) subjects presented as mean values (standard deviations).

	Control group	BB group
N (M/F)	1030 (530/500)	1227 (766/461)
Rest HR (BPM)	67.1 (11.6)	62.5 (11.7)
Max HR (BPM)	164.7 (18.5)	141.2 (26.7)
Recovery HR (BPM)	140.2 (20.3)	113.1 (23.7)
Age (years)	49.7 (13.5)	58.3 (10.8)
Fitness (MET)	8.7 (2.9)	6.9 (2.6)

3. Theory and methods

We analyzed the DFA [5–7] scaling exponents, which describe the *collective* correlations of the RRI time series compared to the *pointwise* correlations measured by the autocorrelation function [14]. The DFA short-scale correlations (scales 4-16) have been shown to yield good distinguishability for HRV analysis [9]. Thus, we focused on the respective short-scale correlations to achieve the best distinguishability between subjects with and without BB medication in all excercise test phases. In addition, we used maximally overlapping windows due to better statistical performance [15] and second-order detrending, which has been shown to improve distinguishability between healthy controls and subjects with cardiac diseases [9]. To summarize, we utilized second-order DFA short-scale scaling exponents (DFA-2 α_1) in the discrimination.

For the statistical analysis we utilized propensity score matching (PSM) [16] to remove bias caused by multiple confounders. The analysis was completed with PsmPy package [17] using k-nearest neighbors matching with replacement. The effect size of the confounders was analyzed using Cohen's d [18].

The confounders included the following: (i) demographic variables: age, sex and smoking; (ii) physiological measurements: recovery HR, rest HR, standing HR, maximal HR and physical fitness; (iii) medication: ACE inhibitors, alpha blockers, angiotensin receptor blockers, calcium channel blockers, digitalis, diuretics, lipids, nitrates; (iv) diseases: congenital heart disease, left and right bundle branch blocks, left ventricular hypertrophy, valvular, ventricular pre-excitation, cardiomyopathy, long QT, atrial fibrillation, diabetes, myocardial infarction and stroke. Statistical signifigance was tested with p-values calculated using Welch's t-test and distinguishability with receiving operating characteristics (ROC) area under curve (AUC).

4. Results and discussion

DFA-2 α_1 results for different exercise segments are shown in Fig. 1 for the whole dataset **(A)** and propensity score matched results **(B)**. When the confounding factors are not taken into account, there is clear reduction in DFA-2 α_1 values for BB group compared to the control group. On the other hand, during high intensity exercise and recovery these differences disappear, and in the recovery phase the results are even slightly inverted. This leads to smaller range of DFA-2 α_1 values between rest and high-intensity exercise for the BB population as seen in Fig. 2**(A)**. This means that the BB group has limited extremes in the α_1 distribution. The AUC value of 0.71 shows decent distinguishability between the groups.

In addition, we considered the confounding factors, since the control and BB groups are inherently different, and the BB patients have a large variety of reasons behind the use of medication. Similar differences remained in subgroup analysis for each confounder. The combined effect of all the confounders listed in Sec. 3 is tested with PSM. The test population consisted of 938 BB subjects that had all the required metadata. PSM utilized matching with replacement, resulting into control group of 314 unique subjects. Propensity logits had similar distributions after matching (Kolmogorov-Smirnov test p-value $= 0.99$), and the effect size for all cofounders was < 0.2 measured by Cohen's d. However it is important to note that a very good mathematical match does not assure perfect epidemiological match. In Figs. 1**(B)** and 2**(B)** we show that the differences between the groups diminish.

We also checked how each individual confounder affected the AUC value shown in Fig. 2**(B)** by using age, sex and smoking as base confounders and testing every other one by one with PSM. None of those confounders led to huge differences alone. Therefore, the effect noticed in DFA-2 α_1 is caused by multiple sources that differ between the compared groups.

However, some of these confounders are also affected by BBs, most importantly the HR. BBs reduce both resting and max HR, affecting also the scaling exponents. Figure 3 shows DFA-2 α_1 as a function of average HR for

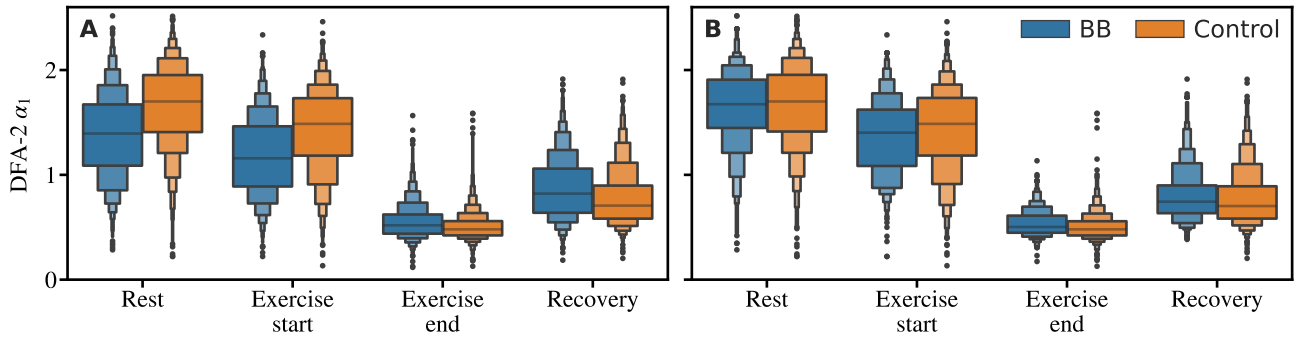

Figure 1. Second-order detrended fluctuation analysis short-scale scaling exponents (DFA-2 α_1) for different exercise stages for (**A**) BB group (N=1227) and control group (N=1030) (**B**) with propensity score matched BB group (N=938), where the control group is matched with replacement.

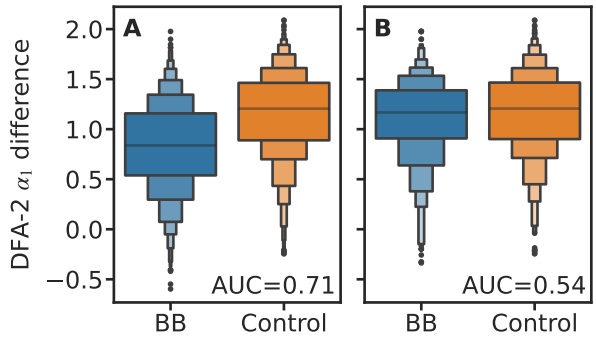

Figure 2. DFA-2 α_1 differences between rest and exercise end segments for (**A**) beta blocker group and control group (**B**) with propensity score matched BB group, where the control group is matched with replacement.

BB and control groups, respectively. During rest the BB group has smaller scaling exponents across the HR range as shown in Fig. 3(**A**). The BBs reduce the average HR with the scaling exponent, but with widened distribution in addition to shifting to lower values. Figure 3(**B**) shows the end of the exercise, where – despite different maximal HRs – the scaling exponents are very similar in both groups. Thus, maximal exercise seems to lead into similar scaling exponents despite different HRs. During the recovery, both groups yield similar scaling exponents but now with a clear decreasing trend as a function of HR as illustrated in Fig 3(**C**). This indicates faster recovery towards the resting values at lower recovery HRs. Finally, selective vs. non-selective BBs did not show statistically significant ($p > 0.1$) differences in any of the exercise stages.

5. Conclusion

Subjects with BB medication have lower DFA-2 α_1 during rest but similar values during maximal exercise despite different HRs, resulting into limited α_1 range for BB subjects. However, this difference is diminished in PSM matched groups. Different HR values between the groups do not fully explain the DFA-2 α_1 differences. To conclude, due to multiple confounding factors DFA-2 α_1 values differ between subjects with and without BB medication. Therefore, the presence of the BBs must always be taken into account when conducting HRV analysis with DFA.

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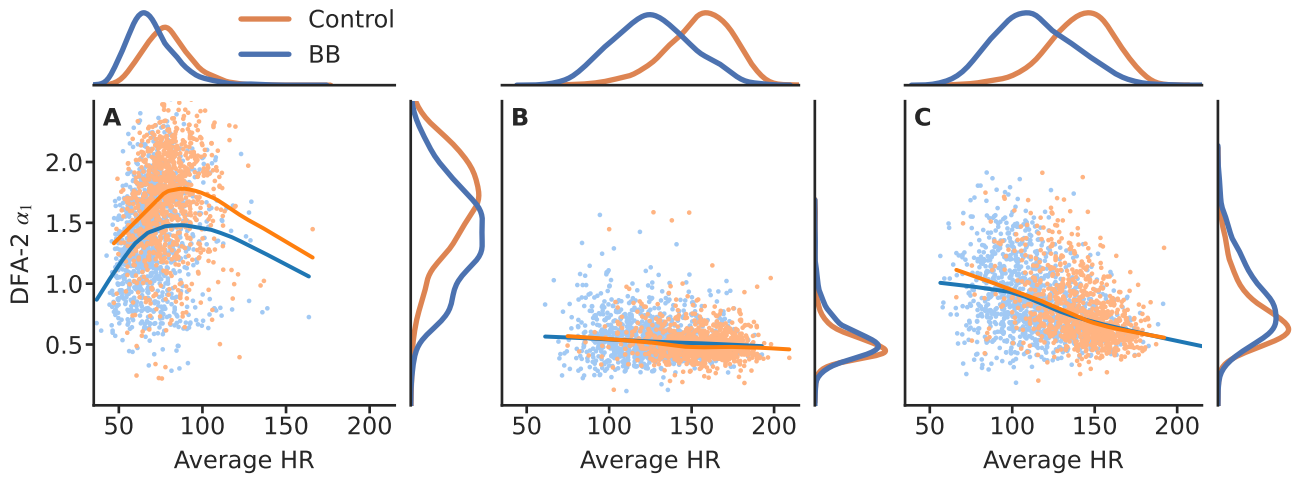

Figure 3. Differences in DFA-2 α_1 as a function of average HR between BB and control groups for (**A**) rest (**B**) exercise end (**C**) recovery. Line fits in the scatter plots are calculated with locally weighted scatterplot smoothing (LOWESS), and the marginal distributions are kernel density estimates.

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