entropy 2021
The Scientific Tool of the 21st Century
5-7 May 2021

UNIVERSITY OF BELGRADE FACULTY OF MEDICINE

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Sample entropy approach to the examination of cardio-respiratory coupling in response to cardiac resynchronization therapy

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Background and Aim

Cardiac resynchronization therapy (CRT) is a well-established therapy for symptomatic patients with heart failure and reduced left ventricular ejection fraction.

It is known that patients with heart failure (HF) have altered cardio-respiratory interactions, but it has not been examined whether resynchronization therapy leads to changes in coupling of cardiac and respiratory rhythm, and whether the success of this therapy leads to restoring of cardio-respiratory interactions. In these patients, in addition to sinus rhythm, different types of arrhythmias usually appear, which limits the application of linear methods in analysis of interbeat interval time series [1].

Therefore they should be analyzed with non-linear techniques and we applied the **sample entropy** approach in analysis of RR interval and respiratory signal time series[2].

Methods

Subjects

We studied 47 patients (14 females) with heart failure and CRT indication. They were 64 ± 2 years old. The study was approved by the Ethics Committee of Faculty of Medicine University of Belgrade, and each subject signed an informed consent. Measurements were performed before (baseline) and approximately 9 months after CRT device implantation (follow-up). After follow-up, patients were divided into two groups, responders (N = 27) and non-responders (N = 20), in relation to the response to CRT, which was assessed according to changes in certain clinical parameters.

Data acquisition

Baseline and follow-up experiments were conducted in the morning, between 7 and 10 a.m. in a quiet surrounding at the Pacemaker Center of the Clinical Center of Serbia. Baseline measurements were done immediately before device implantation in HF patients. Data were acquired from 20 minutes of ECG and respiratory signal measurement from relaxed subjects in supine position and at spontaneous breathing frequency (BIOPAC System, Inc, Santa Barbara, CA, USA). Respiratory signal (Resp) was obtained from transducer attached to the belt, which was used to measure abdominal expansion and contraction. Inter-beat (RR) intervals and inter-breath (BB) intervals were extracted from recorded signals using tool Pick Peaks from OriginPro 8.6 (OriginLab Corporation, Northampton, MA, USA). Heart rate (HR) and breathing frequency (BF) were obtained as a reciprocal value of subject mean RR interval and mean BB interval [3].

Data analysis

Sample entropy and cross sample entropy

Sample entropy (SampEn) and cross-sample entropy (cross-SampEn) are non-linear measures of time series regularity derived from the probability of finding a similar pattern within signal/signals [2]. The signal with a small number of simillar patterns is characterized by larger values of SampEn which indicated its higher unpredictability (irregularity). Similarly, coupling of two signals with a small number of similar patterns would result in high values of crossSampEn which indicated their high asynchrony i.e. low association between analyzed systems. SampEn and cross-SampEn were calculated with fixed input variables $m = 2$ (window size) and $d = 0.15 \cdot SD$ (tolerance, SD – standard deviation of time series) from whole time series (approximately about 1200 samples). For two equally equidistant resampled and normalized series the RR and the Resp, SampEn and crossSampEn were computed [3, 4].

Statistics

Statistical analyses were performed using the software package SPSS Statistics (version 17.0, SPSS Inc, USA). The results were given as mean ± standard error (SE). One-way ANOVA for 2 repeated measurements was performed for all quantities and one-way ANOVA for comparison between groups. For all analyses, probability values 0.05 were considered as statistically significant.

Results and Conclusion

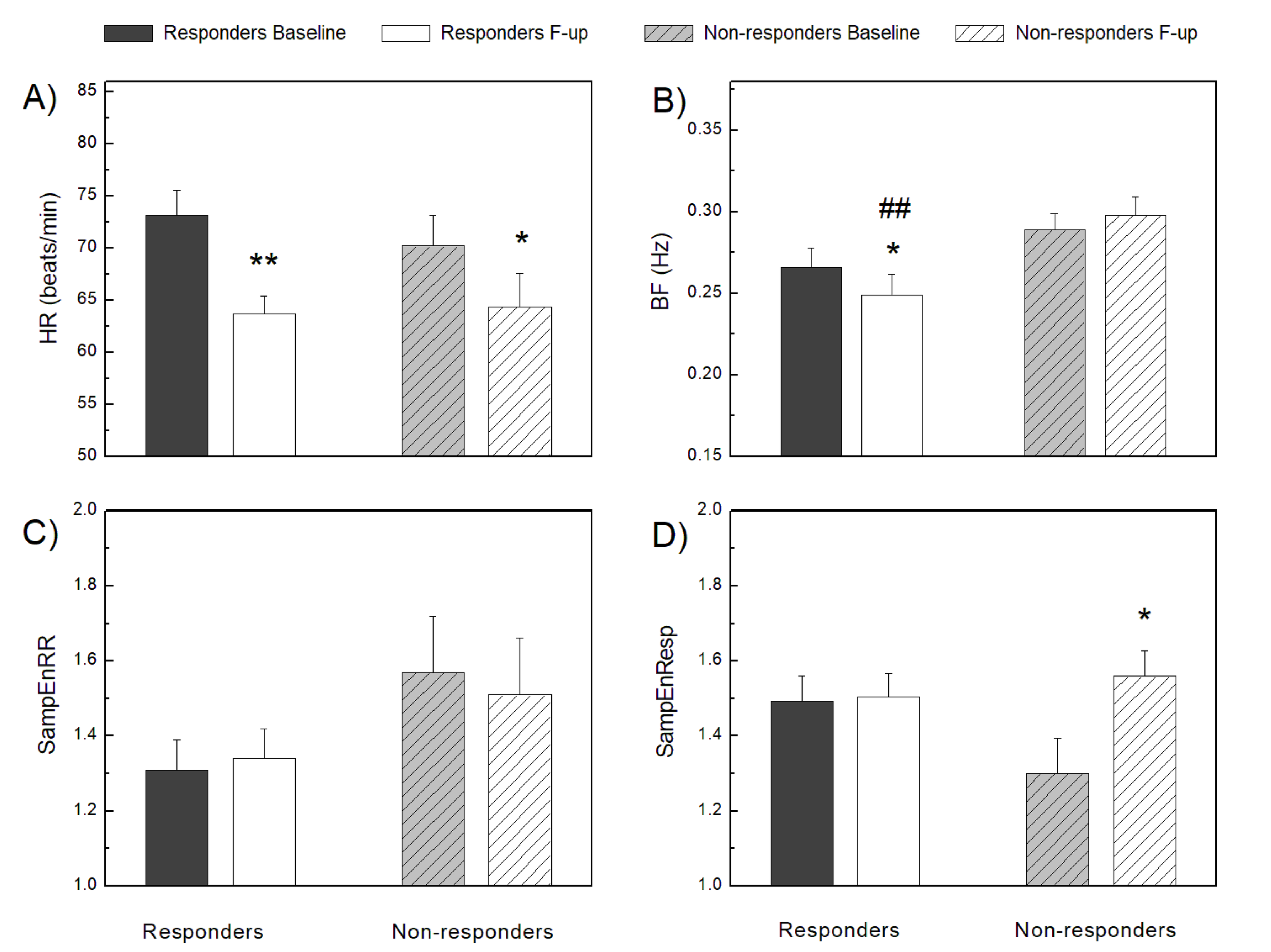
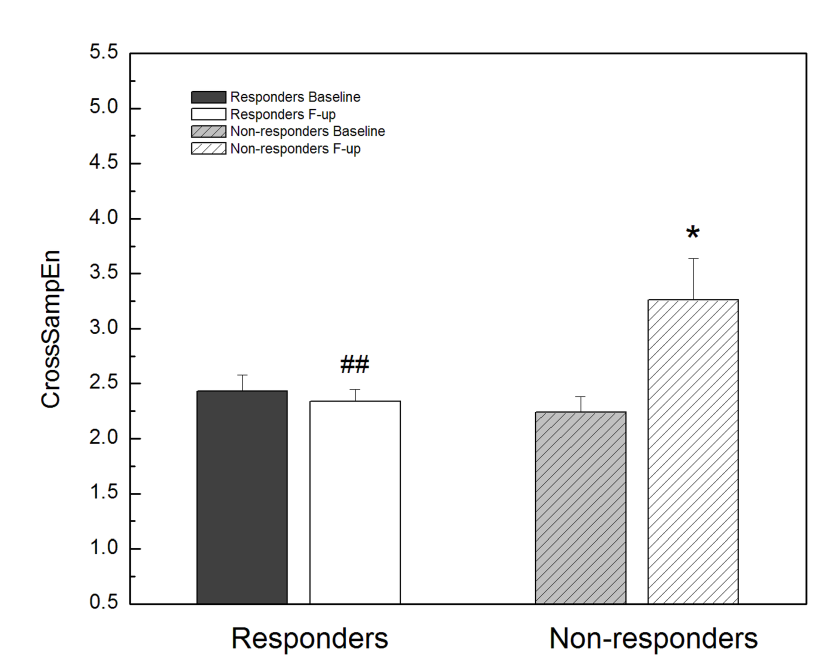


Figure 1. Effect of CRT on heart rate - HR (A), breathing frequency – BF (B), sample entropy of RR intervals – SampEnRR (C), and respiratory signal - SampEnResp (D), in responders and non-responders. Values are mean + standard error of the mean. ** $p < 0.01$, * $p < 0.05$, Follow-up vs. Baseline, ## $p < 0.01$, Responders vs. non-responders in follow-up

- **Responders to CRT showed significant decrease in heart rate and breathing frequency, while non-responders showed only a significant decrease in heart rate.**
- **In both groups, there was no difference in SampEnRR between baseline and follow-up. SampEnRR was higher in non-responders compared with the responders, but not statistically.**
- **In the non-responders group, a significant increase was obtained in SampEnResp and CrossSampEn (Fig. 2).**

Figure 2. Cross sample entropy (CrossSampEn) between RR interval series and respiratory signal series in the group of responders and the group of non-responders after cardiac resynchronization therapy. Values are mean + standard error of the mean. *$p < 0.05$, Follow-up vs. Baseline, ##$p < 0.01$, Responders vs. non-responders in follow-up



Conclusion

Compared to responders, in non-responders to CRT, respiratory rhythm is not adapting to changes in cardiac dynamics, which resulted in higher asynchrony of cardio-respiratory coupling.

References

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