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CORRELATIONS BETWEEN LEFT VENTRICULAR EJECTION FRACTION REDUCTION AND HEART RATE VARIABILITY

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ABSTRACT. The decrease of heart rate variability after acute myocardial infarction has been proved to be a predictor of both sudden death from any cause and sudden cardiac death. Decreased left ventricle ejection fraction is a negative prognostic factor in patients with acute myocardial infarction. Considering this, we intended to prove that there is a correlation between the decrease in the sinus rhythm variability and the degree of reduction of the left ventricle ejection fraction. We measured seven time domain parameters of heart rate variability in patients with acute myocardial infarction (7-10 days after the onset of the infarction; and low ejection fraction of the left ventricle. Parameters of the heart rate variability decreased progressively with the decrease of left ventricle ejection fraction. For patients with LVEF<20%, the decrease of the parameters was statistically significant. The inclusion of patients with severely altered systolic function among acute myocardial infarction surviving patients may alter the prognostic value of heart rate variability indices.
KEYWORDS: heart rate variability, left ventricular ejection fraction, prognostic factor, sinus rhythm variability.

INTRODUCTION

The autonomic nervous system plays an important role in modulating the circulatory response and the heart rate. Disturbances in the control of cardiovascular functions by the autonomic nervous system can contribute significantly to cardiac mortality (Krstacic et al., 2013). The most important application of determining the autonomic nervous system function, in recent years, is the stratification of the risk in ischemic cardiopathy (Danon et al. 2015). The predisposing effects for ventricular fibrillation, which sympathetic activation has, are well-known, as well as the effects of decreasing cardiac vulnerability to ventricular fibrillation that parasympathetic activity increase has (Hohnloser et al., 1986).

Analysis of heart rate variability (HRV) (Ingale et al., 2014, Mansier et al., 1996, Stoicescu et al., 2011) is a useful method of indirect measurement of the autonomic system effects on the heart. Its results have been shown to be a predictor of mortality after myocardial infarction. The contractility changes of the ventricular wall secondary to myocardial infarction are reflected by alteration of the left ventricular ejection fraction. It is known that the degree of decrease in the left ventricular ejection fraction is an independent prognostic factor in patients with acute myocardial infarction (Bustea et al., 2009).

The relationship between the decrease of sinus rhythm variability and death was first observed in patients with myocardial infarction four decades ago (Schneider et al., 1965), being subsequently confirmed by other researchers (Wolf et al., 1978). Kleiger et al. performed a large-scale prospective study demonstrating that reduction of sinus rhythm variability denotes an increased risk of death following myocardial infarction independent of other established risk variables (Kleiger et al., 1987). Modification of heart rate variability is also seen in other forms of ischemic cardiopathy when it is also associated with an unfavorable prognosis.

Although there are numerous studies on the prognostic value of low sinus rhythm variability after acute myocardial infarction, it is not known exactly whether the sinus rhythm variability is only a prognostic mortality factor or it is an aggravating and favoring mortality mechanism.

The objective of this study was to prove that there is a connection between the decrease in the sinus rhythm variability and the degree of reduction of the left ventricular ejection fraction.

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MATERIALS AND METHODS

The study was conducted in the Cardiology Clinic of Oradea County Emergency Clinical Hospital between January 2011 and May 2012, in accordance with the WMA Declaration of Ethical Helsinki-Medical Research Involving Human Principles for Subjects, and was approved by the Ethic Committee of the Faculty of Medicine and Pharmacy from the University of Oradea. We formed 2 groups: a study group consisting of consecutive patients with acute myocardial infarction admitted to the coronary unit of the Cardiology Clinic of the afore mentioned hospital and a control group consisting of subjects who addressed the cardiology ambulatory and who have been diagnosed as healthy. Patients from the study group were monitored for survival by telephone contact for three years from their inclusion in the study.

The study included patients aged between 18-80 years diagnosed with acute myocardial infarction, defined according to current criteria, whose onset is well known.

Exclusion criteria were considered: the presence of a limiting life expectancy condition; absence of sinus rhythm at the time of Holter ECG monitoring; the presence of a pacemaker; the presence of a preexcitation syndrome.

Study design

Patients included in the study were treated according to guidelines in force at that time, doctors being encouraged to provide the most appropriate treatment for each patient. Due to the absence of an angioplasty laboratory (at the time of the study) revascularization therapy in eligible patients was performed with a thrombolytic drug agent. Patients were monitored with Holter ECG for 24 hours, 7-10 days after the onset of acute myocardial infarction. On the day of Holter monitoring, the left ventricle ejection fraction was determined by echocardiography and the laboratory analyzes were repeated. During the entire period of hospitalization the patients were monitored ECG and BP. Patients were called to periodic cardiologic control at 3 months and monitored for survival by telephone contact for an average of 45 months (36-54 months). In deceased patients data were requested about the way and nature of death. A subgroup of patients who underwent revascularization surgery was formed from the study group. To these, Holter ECG monitoring was performed at 1 month, 3 months and one year postoperatively.

Holter monitoring and record processing

The Working Group of the European Cardiology Society and the North American Pacing and Electrophysiology Society (Task Force of the European Society of Cardiology and The North American Society of Pacing and Electrophysiology, 1996) has set up an algorithm to follow for the recorded results to be comparable to each other.

Measuring the variability of sinus rhythm

The parameters used to measure sinus rhythm variability were those of the time domain. Table 1 describes the parameters of the time domain determined in the study.

Table I. Parameters of the time domain determined in the study

The variable	Unit.	Description
Mean NN	ms	Average of NN intervals
SDNN	ms	Standard deviation of all NN intervals
SDANN	ms	Standard deviation of the average of NN intervals in all 5 minute segments of the entire recording
RMSSD	ms	The square root of the mean of the sum of the squares of differences between adjacent NN intervals
SDNNidx	ms	Mean of the standard deviations of all NN intervals for all 5 min segments of the entire ecording
NN50	-	Number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording
pNN50	%	NN50 count divided by the total number of all NN intervals

Mean NN - average of all normal RR intervals; **SDNN** (the standard deviation of all normal RR intervals) - the most commonly used parameter in clinical trials and it is influenced by the duration of the recording; **SDANN** is determined by grouping NN intervals into five-minute segments (288 segments are obtained for records of 24-hour). The average NN range is calculated for each 5-minute segment, SDANN being the standard deviation of these averages. For calculating the **SDNN index**, the standard deviation of NN intervals over 5-minute segments is made and their average is calculated. This index is important for determining the sinus rhythm variability for cycles shorter than 5 minutes; **RMSSD** is obtained by calculating the square root of each NN interval of the entire 24-hour record. The average of these square roots is derived and from the obtained result is extracted the square root again; **NN50** - the number of all pairs of adjacent NN intervals that vary by more than 50 ms. Three variants are possible by counting all pairs of intervals or only pairs in

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which the first or second interval is longer; **pNN50** - the percentage of these intervals from the entire record, provides information about autonomous vagal tonus along with rMSSD.

Establishing the diagnosis of acute myocardial infarction

The diagnosis of myocardial infarction was established according to the guidelines in force at the time of patient recruitment. The presence of two of the following three criteria gave the positive diagnosis of acute myocardial infarction: typical retrosternal pain lasting at least 30 minutes or more; electrocardiographic signs of acute myocardial infarction; characteristic enzymatic changes (in order of preference and availability: troponin I, creatine kinase MB, creatine kinase) (Antman et al., 2000).

Measurement of LVEF

Measurement of the left ventricular ejection fraction was done using a standard echocardiograph using a 2.5 MHz echocardiogram probe. The determination was made from the four-chamber apical view, Simpson's biplanar method, on Holter ECG monitoring day, but by different operators.

Statistical analysis

In order to elaborate a consistent and relevant statistical study we studied the medical statistics from the specialized Anglo-Saxon literature (Altman, 1999).

Data obtained were showed as means ± standard deviations and frequency ranges (table I). The Student's t and x^2 tests allowed to calculate the statistical significance (assigned at a $P< 0.05$).

RESULTS AND DISCUSSIONS

The study group consisted of 164 patients with an average age of 62±10 years (ranging from 36 to 79 years). It predominated the inclusion of men these representing 73% of patients, which demonstrates the prevalence of myocardial infarction in the male population. 36.6% of the patients were hypertensive, 37.8% had dyslipidemia and 28% were diabetic patients.

Demographics of patients with significantly low ejection fraction compared to those of the entire study group are shown in Table II.

Table II. Demographic and clinical characteristics

Patients variables	Study group		Patients with LVEF <40%	
	n=164	%	n=42	%
Age (average±SD)	62±10		61 ±12	
Sex (male)	120	73.2	30	71.4
Dyslipidemia	62	37.8	16	38.1
Diabetes	46	28	12	28.6
HBP	60	36.6	16	38.1
Inferior AMI	78	47.6	14	33.3
Anterior AMI	44	26.8	16	38.1
Anteroseptal AMI	34	20.7	8	19.0
Anterolateral AMI	8	4.9	4	9.5
LVI (Killip class > 2)	66	40.2	40	95
Primary FiV	10	6	6	13.4
Nonsustained TV	20	12.2	8	19.0
Sustained TV	4	2.4	2	4.8
Multiple ExV	18	11	0	0

It is noted an anterior location of myocardial infarction in higher percentages (38%; in patients with low LVEF compared to the study group (27%; as well as a higher incidence of primary ventricular fibrillation (13% versus 6%). Most patients (95%; with low ejection fraction experienced acute left ventricular failure.

Distribution of patients with significantly low LVEF depending on the clinical manifestation of acute left ventricular insufficiency (as assessed by Killip class) is shown in Figure 1.

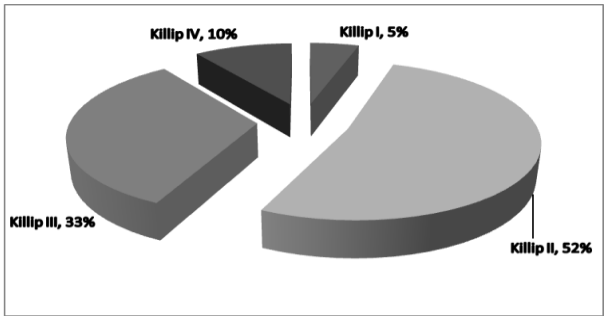

Figure 1. Distribution of patients with LVEF <40% according to Killip class

It is noted in these patients increased percentage of Killip class II and III left ventricular failure phenomena, as opposed to all the patients in the study group where the majority of patients had no symptoms of acute left ventricular insufficiency.

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From the data of the applied treatment for these patients, we note that diuretics were used in 53% of patients, nitrate derivatives were administered to 76% of patients, and 86% of patients were treated with angiotensin II converting enzyme inhibitors. It is observed that these classes of drugs, listed in Table III, were used more frequently in patients with altered left ventricular ejection fraction compared to all patients.

Table III. The therapeutic classes used in the two groups of patients

The variable	Study group		Patients with LVEF <40%	
	n=164	%	n=42	%
Thrombolised patients	88	53.7	21	52.4
Treatment with				
Aspirin	162	98.8	42	100
Beta blockers	144	87.8	38	90.5
Statins	156	95.1	40	95.2
ACE inhibitors	128	78	36	85.7
Retard nitrate derivatives	100	61	32	76.2
Diuretics	30	18.3	22	52.4

Initially, we constituted two groups of all patients: one consisting of patients with an ejection fraction less than 50% and one including patients with an ejection fraction of over 50%.

Comparison of the time domain parameters of heart rate variability in patients with normal left ventricular ejection fraction and those with low fraction (including those with LVEF only slightly low; is shown in Table IV.

Table IV. Sinus rhythm variability parameters in the two groups of patients (LVEF <50%)

The variable	Present		Absent		p*
	Average	SD	Average	SD	
meanNN (ms)	831	123	900	134	0.01
SDNN (ms)	72	22	79	22	0.15
SDANN (ms)	54	16	59	16	0.15
SDNNidx (ms)	41	18	44	15	0.38
rMSSD (ms)	34	31	41	29	0.13
NN50	4651	5846	6345	7613	0.31
pNN50 (%)	5.07	6.53	7.44	8.79	0.19

All time domain parameters of sinus rhythm variability are lower in patients with altered LVEF compared to patients with normal ejection fraction. The decrease of the parameters is unitary and proportional. Figure 2 shows selected time domain parameters in patients with and without low ejection fraction and Figure 3 – mean NN in the same patients. Decrease of mean NN is statistically significant.

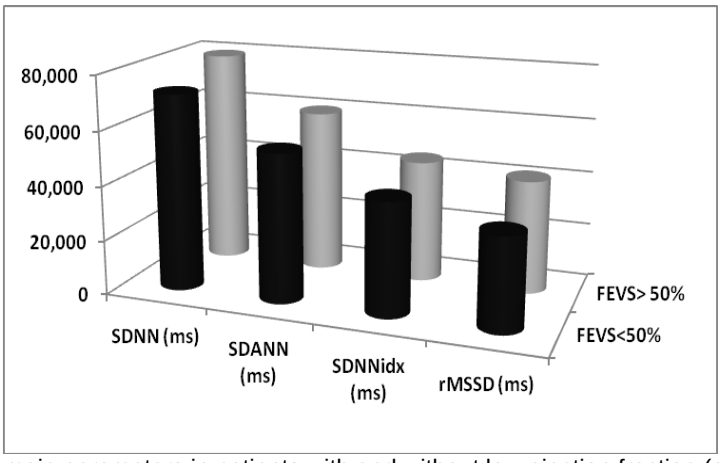

Figure 2. Selected time domain parameters in patients with and without low ejection fraction (above and under 50%)

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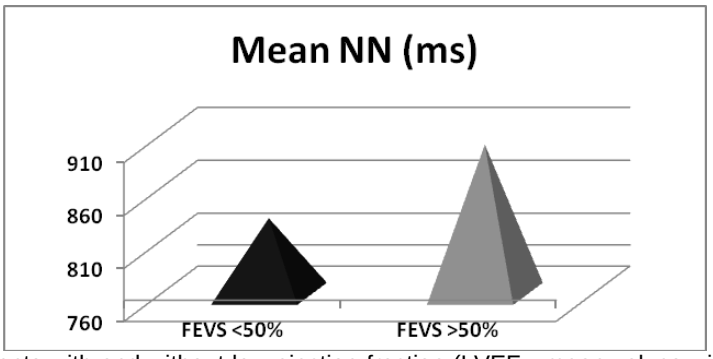

Figure 3. Mean NN in patients with and without low ejection fraction (LVEF - mean values with 95% confidence interval for mean errors)

In order to have a better image of the influence of ejection fraction reduction on heart rate variability we divided patients with low ejection fraction into the following categories: below 20%, 20-30%, 30-40% and 40-50%. The distribution of patients in the study group by categories of the left ventricle ejection fraction is shown in Figure 4.

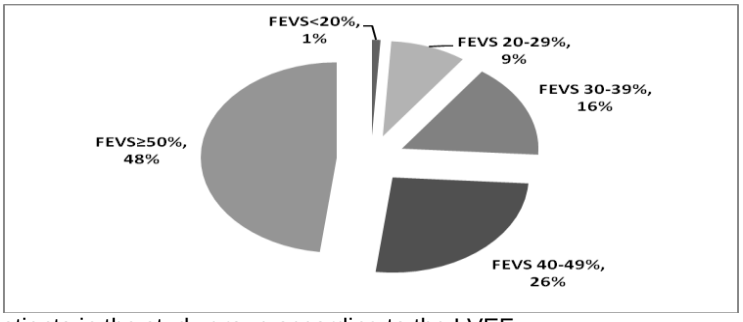

Figure 4. Distribution of patients in the study group according to the LVEF

It is noted that most patients (48%; had the ejection fraction within normal ranges. Of the patients with low ejection fraction half had only a slight reduction of it (26% of the whole lot;. Patients with severely diminished left ventricular ejection fraction were in low proportion (10% of all patients).

Table V shows time domain parameters in patients with LVEF in the 4 categories compared to patients with LVEF within normal ranges.

Table V. Time domain parameters in patients with LVEF in the 4 categories compared to patients with LVEF within normal ranges

The variable	LVEF					
	average	SD	(p*)	average	SD	(p*)
	< 20%			20-30%		
meanNN (ms)	850	22	0.16	877	98	0.66
SDNN (ms)	39	9	0.05	73	24	0.51
SDANN (ms)	27	7	0.05	60	20	0.99
SDNNidx (ms)	26	8	0.09	37	15	0.26
rMSSD (ms)	18	2	0.15	30	13	0.35
NN50	334	13	<0.001	3917	3793	0.54
pNN50 (%)	0.40	1.1	<0.001	4.50	4.54	0.48
	30-40%			40-50%		
meanNN (ms)	810	109	0.03	828	141	0.05
SDNN (ms)	67	20	0.10	76	22	0.61
SDANN (ms)	51	16	0.11	56	15	0.37
SDNNidx (ms)	39	15	0.26	45	21	0.96
rMSSD (ms)	32	16	0.41	37	43	0.28
NN50	3860	5408	0.53	5591	6763	0.56
pNN50 (%)	4.26	6.45	0.39	5.98	7.34	0.37

* the Student test (t-test) for independent groups

Changes of these parameters present in different LVEF categories were compared with sinus rhythm variability indices in patients with LVEF within normal ranges (Figure 5).

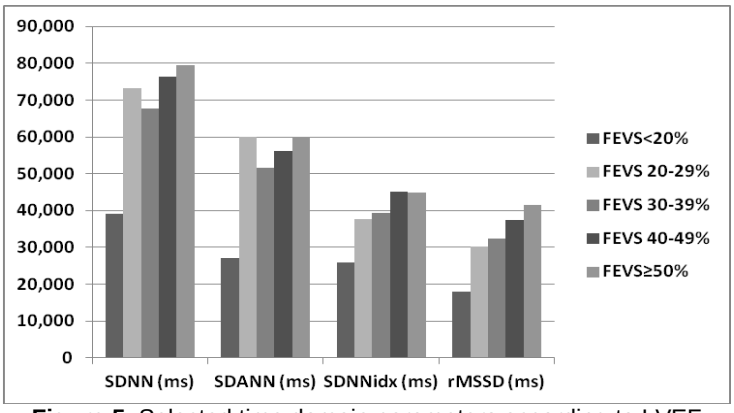

Figure 5. Selected time domain parameters according to LVEF

Although all time domain parameters of sinus rhythm variability showed a marked decrease in patients with LVEF <20%, only SDANN and SDNN reduction had statistical significance (from the global variability indices), as it can be seen in Figure 6.

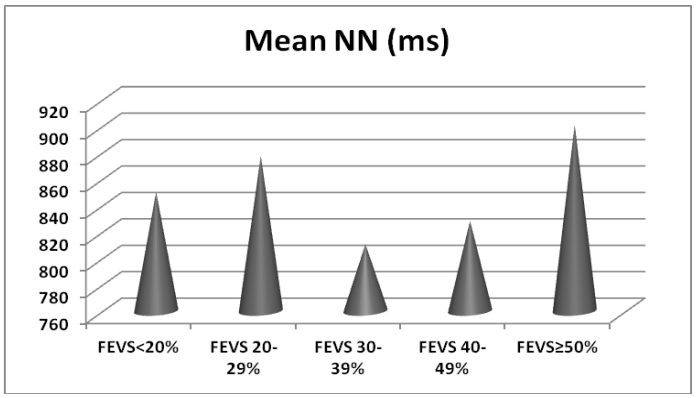

Figure 6. Mean NN according to LVEF (LVEF – average values with 95% confidence interval for errors of the mean)

The parameters of sinus rhythm variability that were determined showed a progressive decrease parallel to the decrease of the left ventricular ejection fraction. A discordant evolution showed the SDNN and SDANN parameters that were higher in LVEF category = 20-30% compared to adjacent categories. There is noticed an accentuated decrease of pNN50 in patients with LVEF <20% with statistical significance (Figure 7).

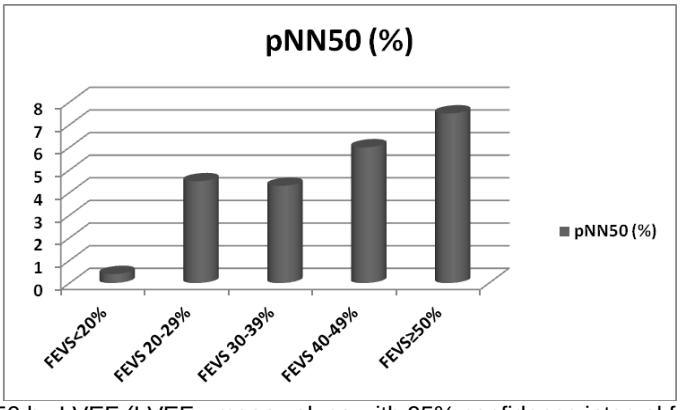

Figure 7. pNN50 by LVEF (LVEF - mean values with 95% confidence interval for mean errors)

Although all parameters of sinus rhythm variability in patients with reduced LVEF (<50%; were lower compared to patients with LV ejection fraction within normal range, only the mean NN decrease was statistically significant.

In case of separating patients by LVEF categories, the decrease in sinus rhythm variability parameters (with 2 exceptions; was parallel to the decrease of LVEF. For patients with severe left ventricular systolic impairment, the decrease in time domain indices was statistically significant.

Significant changes in heart rate variability parameters in patients with severely altered ejection fraction may influence the prognostic value of these indices. Literature data in this respect are contradictory. Thus, in an older research, UK-heart study (Nolan et al., 1998), performed on 433 patients with chronic heart failure (FEVS <40%; recruited from ambulatory, the decrease in SDNN was the most important predictor of death by heart failure. Bonaduce et al. confirms these results in a study conducted on 94 patients with heart failure, in which sinus rhythm variability retained the value of prognostic factor independent of mortality (Bonaduce et al., 1999).

Different results were obtained by Huikuri et al. (Huikuri et al., 2000) which found a decrease in the prognostic power of traditional parameters of measuring the variability of sinus rhythm. Information was obtained from 446 patients with acute myocardial infarction and LVEF ≤ 35%. None of these parameters had prognostic value independent of the occurrence of arrhythmias. It is assumed that the different results were due to the different modality of death in patients with low LV ejection fraction versus patients with normal left ventricular function. If the first group has as a potential decease mechanism a primary rhythm disorder or progressive heart failure, the second group presents as a possible death mechanism reinfarction or a recurrent acute ischemic event.

The research conducted by Makikallio et al. (Makikallio et al 2005) on 2130 patients with acute myocardial infarction, recruited from 2 centers in Germany and Finland, was designed to study the predictive value of variables derived from long-term Holter records (in patients who had an acute myocardial infarction and were treated according to contemporary guidelines; on sudden cardiac death occurrence. Patients were divided into two subgroups according to the left ventricular ejection fraction (above or below 35%). For the authors, the results were disappointing because in the subgroup of patients with LVEF ≤35% none of the traditional parameters of heart rate variability had independent predictive value of the occurrence of sudden death. In the group of patients with normal systolic function or only slightly diminished, time domain parameters did not have independent prognostic value (only spectral analysis had prognostic significance).

La Gerche et al. (La Gerche et al., 2012) show in one of their studies that exercises in athletes may be associated with arrhythmogenic cardiac remodeling of the right ventricle (RV). It was examined whether myocardial dysfunction after intense exercise affects RV more than the left ventricle (LV) and whether cumulative exposure to affective competition affects cardiac remodeling (including fibrosis) in well-trained athletes. In conclusion, it has been shown that intense exercise causes acute RV dysfunction, but not LV. Although short-term recovery seems complete, chronic structural changes and reduced RV function are evident in some of the most active athletes; long-term clinical significance justifies further studies

Unlike the studies listed above, Yoshikawa et al. (Yoshikawa et al., 1999) demonstrated, in a study conducted on 146 heart failure patients, that the sinus rhythm variability indexes showed no correlation with cardiac function, retaining its independent prognostic factor.

CONCLUSIONS

Parameters of sinus rhythm variability decreased progressively with the decrease of the left ventricular ejection fraction. For patients with LVEF <20%, the decrease of the parameters was statistically significant. The inclusion of patients with severely altered systolic function among patients surviving an acute myocardial infarction may alter the prognostic value of heart rate variability.

This is supported by part of the specialty studies, but there are also studies that state that the mortality independent prognostic value of the heart rate variability parameters in patients with heart failure is maintained.

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