

Arterial hypertension and heart failure with preserved ejection fraction – associations between echocardiography and heart rate variability

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Abstract

Background: Assessment of heart rate variability provides noninvasive information regarding the autonomic regulation of the heart. Lower HRV is associated with established cardiovascular disease, probably due to autonomic imbalance secondary to an increased sympathetic output.

Methods: We performed a retrospective study on 69 hypertensive patients with and without heart failure, which included time domain parameters extracted from 24-hour ECG Holter tracings and echocardiographic data.

Results: Patients with heart failure showed lower HRV for short-term indices: SDANNi (94.8 ± 34.9 vs. 114.6 ± 43.5 , $p=0.044$), but not in terms of 24-hour evaluation by SDNN, as this did not reach statistical significance (109.4 ± 36.8 vs. 122.2 ± 43.1 , $p=0.197$). The maximum QT interval (509.5 ± 78.8 vs. 471.1 ± 56.2 , $p=0.022$) was higher in patients with heart failure. There were some correlations between echocardiographic data and HRV: SDNNi, rMSSD and pNN50 respectively and left atrium size ($r = 0.252$, $p = 0.041$; $r = 0.307$, $p = 0.012$; $r = 0.320$, $p = 0.009$), as well as right atrium size ($r = 0.291$, $p = 0.020$; $r = 0.316$, $p = 0.011$; $r = 0.296$, $p = 0.018$) but not right ventricle size ($r = 0.165$, $p = 0.194$; $r = 0.153$, $p = 0.229$; $r = 0.146$, $p = 0.251$).

Conclusion: Our study confirms a loss of HRV, particularly a reduction in short-term time domain parameters and a prolongation of the maximum QT interval in patients with heart failure with preserved ejection fraction in comparison to patients without HF.

Keywords: heart rate variability, arterial hypertension, heart failure, heart failure with preserved ejection fraction, echocardiography, 24-hour ECG Holter, autonomic nervous system, SDNN, rMSSD, SDANNi

Introduction

The autonomic nervous system regulates heart rate response to environmental and psychological stimuli by maintaining a dynamic equilibrium between sympathetic and parasympathetic influences. While

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the heart rate (HR) is equal to the total number of heartbeats measured over a minute, heart rate variability (HRV) is the extent to which the time interval between consecutive heartbeats varies [1].

Assessment of heart rate variability provides noninvasive information regarding the autonomic regulation of the heart [2, 3] and is performed through the use of electrocardiography. Long term electrocardiographic recordings such as those obtained through 24-hour ECG Holter monitoring provide HRV information through time and frequency domain parameters [4].

Frequency domain parameters are obtained by dividing the heart rate signal into frequencies and measuring their relative intensity as power [4]. Total power is the variance of all normal sinus beat (NN) intervals, thus expressed in milliseconds, and is further divided, according to frequency, into very-low-frequency (VLF), low-frequency (LF) and high frequency (HF) ranging across 0.0033-0.04 Hz, 0.04-0.15 Hz and 0.15-0.40 Hz respectively. According to the frequency range analyzed, information is obtained regarding sympathetic (LF) or parasympathetic activity (HF) and their ratio (LF/HF) [1, 2, 4].

Time domain parameters are either measured or calculated and provide information on long (24-hour) or short-term (5-minute) intervals that make up the ECG recording, and as such, are expressed in milliseconds. Short-term interval parameters are a reflection of inter-beat variance and are closely correlated with parasympathetic nervous system activity, while 24-hour measurements also take into account the circadian rhythm and physical activity [1-4].

The standard deviation is measured between consecutive normal sinus beats (NN) (SDNN) i.e. with exclusion of ectopic beats on a 24-hour strip. Other parameters are extracted after dividing the recording into 5-minute segments: the standard deviation of the average NN intervals (SDANN) and the mean of the standard deviations of all NN intervals (SDNNi). Calculated indices are: the root mean square of successive differences between NN intervals (rMSSD) and the percentage of adjacent NN intervals that differ from each other by more than 50 ms (pNN50) [1].

A pathological increase or loss of variation may occur with the development of illness [4]. As opposed to healthy subjects, lower HRV seems to

be associated with chronic inflammation, diabetes, hypertension, dyslipidemia and established cardiovascular disease (heart failure, myocardial infarction, stroke, sudden cardiac death), probably due to autonomic imbalance secondary to an increased sympathetic output [1, 4-6]. Moreover, impaired autonomic activity after myocardial infarction has been regarded as an independent predictor of mortality [7].

The aim of this paper is to evaluate differences in HRV parameters in hypertensive patients with and without heart failure and their correlation to echocardiographic parameters.

Material and Methods

Patients

The study population consisted of 69 hypertensive patients admitted to the Internal Medicine and Cardiology Department between January 2017 and December 2018. Laboratory assays including NT-proBNP levels, as well as echocardiographic data and 24-hour ECG Holter monitoring reports were provided for all patients. The exclusion criteria were as follows: refusal to give informed consent, poor echocardiographic window and uninterpretable Holter reports due to excess noise.

According to the 2016 ESC guideline for the diagnosis of heart failure, patients were separated into two groups: those without evidence of heart failure and those diagnosed with heart failure – with either reduced (HFrEF), mid-range (HFmrEF) or preserved ejection fraction (HFpEF).

Echocardiographic study

Echocardiographic data was collected according to available guidelines including cardiac chamber size, left ventricular ejection fraction (determined through biplane Simpson's method), septal and lateral mitral annular plane systolic excursion (MAPSE), and parameters of diastolic dysfunction: early (E) and late (A) mitral filling velocities, E/A ratio (measured through the use of Doppler echocardiography), as well as diastolic septal and lateral mitral annular velocities (tissue Doppler echocardiography). All echocardiographic studies were performed by a single cardiologist in order to limit interobserver variability.

24-hour ECG Holter recordings

24-hour ECG Holter recordings were obtained for all patients by use of an ambulatory ECG record system providing 12-lead ECG information (DMS 300-3A Holter ECG recorder with a 7-lead 3-channel orthogonal hookup). The recorded information was analyzed automatically and edited to eliminate ectopic beats and artifacts by a single cardiologist. HRV was assessed through the use of time-domain indices such as SDNN, SDANN, SDNNi, rMSSD and pNN50.

Statistical analysis

Statistical analysis was performed with the use of IBM® SPSS for Windows version 20. Continuous variables were defined as average \pm standard deviation and their relationships evaluated using one-way ANOVA for analysis of variance, as well as bivariate correlations for strength of association. Categorical data were defined as frequencies and percentages and compared using the Chi-squared test. A p-value <0.05 was considered statistically significant.

Results

A total of 69 patients (47 females, 22 males; mean age, 68.92 ± 9.92 years; age range, 50 - 96 years) were enrolled.

All had preexisting arterial hypertension either grade 2 (26.1%) or grade 3 (73.9%) and were undergoing treatment with at least one of the following: angiotensin-converting-enzyme inhibitor (ACEi - 59.4%), angiotensin-receptor blockers (ARBs - 31.9%), calcium-channel blockers (CCB - 34.8%), beta-blockers (68.1%), diuretics (50.7%) or mineralocorticoid receptor antagonists (MRAs - 7.2%). None of the patients had grade 1 HTN.

In terms of traditional cardiovascular risk factors, 43.5% of patients had type 2 diabetes mellitus, 36.2% were obese, 36.2% had a long-standing history of smoking, 95.7% had dyslipidemia (89.9% under treatment with statins) and 76.8% had a very high cardiovascular risk defined either through known cardiovascular disease or a 10-year risk of fatal cardiovascular disease (CVD) above 10% according to the SCORE risk chart (additional information provided in Table 1).

Moreover, 75.4% of patients had atherosclerosis (coronary artery disease, peripheral artery disease, carotid plaque) of whom 42.0% had a known history of coronary artery disease (acute coronary syndrome, percutaneous coronary intervention or stable angina). A diagnosis of atrial fibrillation had been made in 29.0% of patients and 30% of them were undergoing treatment with amiodarone.

Out of the 69 patients enrolled, 31 (44.9%) had clinical signs and symptoms of heart failure (HF) and among those, 25 (80.6%) were diagnosed with heart failure with HFpEF, 4 (12.9%) with HFmrEF and 2 (6.4%) with HFrEF based on laboratory and echocardiographic data.

Heart failure patients were generally older (74.2 ± 9.0 vs. 64.5 ± 8.4 , $p < 0.001$). There was a female predominance in both groups, without significant differences (34.8% vs. 33.3%, $p = 0.134$). In terms of cardiovascular risk factors - diabetes ($p = 0.799$), obesity ($p = 0.907$), smoking status ($p = 0.535$), dyslipidemia ($p = 0.439$) and degree of HTN (0.089) - there were no significant differences in distribution across the two groups.

In terms of echocardiographic parameters, though only 29.0% of patients had been previously diagnosed with atrial fibrillation - two patients (2.8%) had AF for the entire time of the ECG Holter recording - HF patients exhibited left atrial enlargement, both in terms of LA transverse diameter (43.1 ± 6.5 vs. 37.2 ± 3.8 , $p < 0.001$; Figure 1 - Panel A) and volume (86.7 ± 39.3 vs. 61.5 ± 20.8 , $p = 0.002$). Moreover, patients with heart failure also exhibited decreased MAPSE of both the lateral (12.0 ± 2.8 vs. 14.0 ± 2.0 , $p = 0.004$) and septal wall (9.6 ± 2.6 vs. 12.5 ± 2.0 , $p < 0.001$; Figure 1 - Panel B). There seemed to be a difference between patient groups in terms of mid-right ventricular (34.6 ± 5.7 vs. 31.7 ± 3.7 , $p = 0.020$) and right-atrial diameter (38.1 ± 8.0 vs. 33.2 ± 3.8 , $p = 0.003$) with HF patients exhibiting slightly larger right-sided chambers and more frequent tricuspid regurgitation (23.2% vs. 14.5%, $p = 0.031$), and consequently, higher trans-tricuspid gradients (33.4 ± 10.3 vs. 23.3 ± 8.0 , $p = 0.009$).

There seems to be a loss in heart rate variability with heart failure, but only for short-term indices: SDANNi (94.8 ± 34.9 vs. 114.6 ± 43.5 , $p = 0.044$; Figure 2), as the 24-hour evaluation by SDNN (109.4 ± 36.8 vs. 122.2 ± 43.1 , $p = 0.197$) did not reach statistical significance. Moreover, the maximum QT

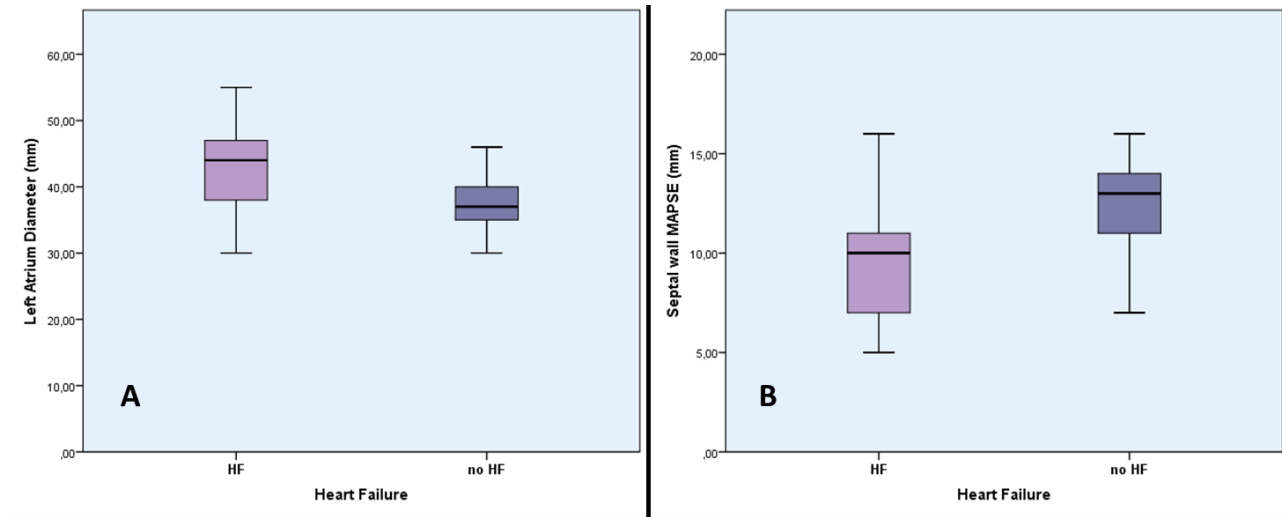


Figure 1. Panel A - Patients with heart failure were more prone to have left atrial enlargement than patients without heart failure; Panel B - Patients with heart failure exhibited decreased septal wall mitral annular plane systolic excursion (MAPSE) than patients without heart failure.

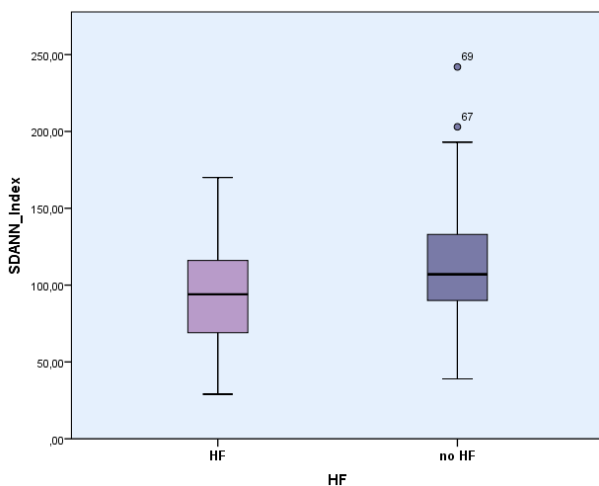


Figure 2. Patients with heart failure had lower SDANNi (the mean of the standard deviations of all NN intervals) than patients without heart failure.

interval (509.5 ± 78.8 vs. 471.1 ± 56.2 , $p=0.022$) seems to be higher in patients with heart failure, even after correction with Bazzett's formula (535.2 ± 76.1 vs. 501.0 ± 59.9 , $p=0.042$).

There seemed to be a correlation between age and SDNNi ($r=0.412$, $p<0.001$), rMSSD ($r=0.464$, $p<0.001$), pNN50 ($r=0.469$, $p<0.001$), as well as between NTproBNP levels and rMSSD ($r=0.517$, $p<0.001$) and pNN50 ($r=0.496$, $p<0.001$). In terms of correlations between echocardiographic data and HRV, we found statistically significant correlations between SDNNi, rMSSD and pNN50 respectively

and left atrium size ($r=0.252$, $p=0.041$; $r=0.307$, $p=0.012$; $r=0.320$, $p=0.009$), as well as right atrium size ($r=0.291$, $p=0.020$; $r=0.316$, $p=0.011$; $r=0.296$, $p=0.018$) but not right ventricle size ($r=0.165$, $p=0.194$; $r=0.153$, $p=0.229$; $r=0.146$, $p=0.251$) (Figure 3).

On subgroup evaluation, patients with heart failure exhibited a correlation between age and SDNNi ($r=0.488$, $p=0.005$), rMSSD ($r=0.467$, $p=0.008$) and pNN50 ($r=0.562$, $p=0.001$). Moreover, maximum QT interval correlated with right atrium size ($r=0.507$, $p=0.005$) and right ventricle size ($r=0.611$, $p<0.001$) in these patients.

Based on SDNN values, patients were divided into three categories: <50 ms, $50-100$ ms and >100 ms. There were no differences between patients with (3.2%, 29.0%, 64.5%) and without HF (2.6%, 26.3%, 68.1%) in terms of SDNN-based risk stratification ($p=0.706$).

Discussion

Heart failure patients may exhibit hypotension and hypovolemia through inotropic failure and fluid redistribution which, in turn, lead to the compensatory activation of the sympathetic nervous system and decrease in vagal influence. Consequently, there is a higher risk for the development of arrhythmias, thus linking autonomic imbalance to premature cardiac death.

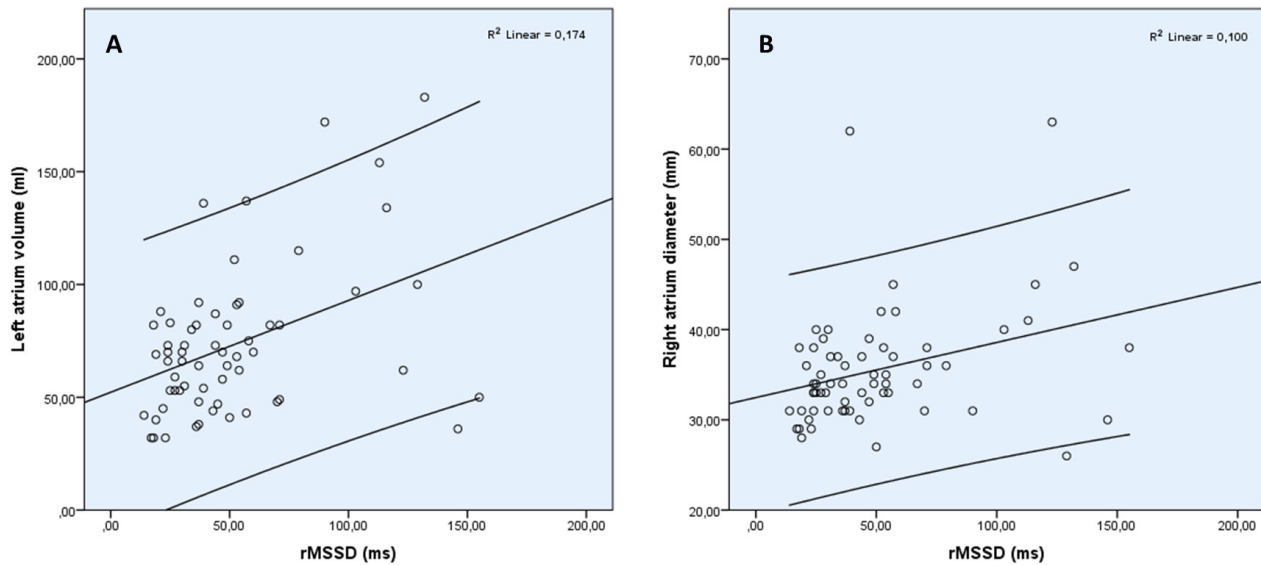


Figure 3. The root mean square of successive differences between NN intervals (rMSSD) values correlated with both left (Panel A) and right (Panel B) atrium size.

As patients with HF have more frequent non-sinus beats, it seems that, during unrestricted daily activities, time domain parameters are easier to obtain from 24-hour ECG Holter tracings, while frequency domain parameters become useful when assessed for short periods of time, under standard conditions [8].

Patients with heart failure have autonomic dysfunction, as exhibited by lower HRV, and a higher risk for progressive disease and cardiac death. Studies on patients with a history of acute myocardial infarction have used SDNN to categorize patients into risk groups and establish cutoff values [9]. As such, SDNN values below 50 ms, 50-100 ms and above 100 ms are associated with an increasingly better prognosis, and a lower risk of mortality. Moreover, the same cutoffs have been applied to HF patients, citing an annual mortality rate of 54.4%, 12.7% and 5.5% respectively [10].

A 2019 study by Costa-Felix enrolled 59 patients with acute decompensated heart failure and further divided them according to LVEF into HFpEF and HFrEF. Patients with HFrEF seemed to have lower HRV parameters than patients with HFpEF [11].

In our analysis, there were no differences in terms of SDNN risk categories between patients in the two groups. This result may be a consequence of the greater proportion of patients with HFpEF than previously described in HRV literature.

Most HRV studies to date have enrolled few patients and have focused mainly on heart failure with reduced ejection fraction (< 40%) [12-14]. The largest study to date on HRV in HF patients, UK-HEART, enrolled 500 patients with mild to moderate symptoms of heart failure and a mean ejection fraction of $41 \pm 17\%$, though measured through M-mode, and excluded patients with T2DM [10].

There is little literature data regarding HRV in patients with HFpEF. Recently, Jian et al. conducted a retrospective study on 88 patients with HFpEF and HFrEF with impaired HRV in comparison to healthy controls which showed that only a low SDANNi was associated with an enlarged left atrium [15]. A 2012 study compared 42 patients hospitalized for diastolic heart failure with 10 healthy controls (LVEF $\geq 50\%$) and found that patients with heart failure, even after undergoing treatment, had lower HRV values than healthy volunteers [16]. Moreover, patients were divided into groups based on grading of diastolic dysfunction and HRV impairment was more profound as diastolic dysfunction progressed [16].

Our study found no significant difference between hypertensive patients with and without heart failure (the majority of whom had HFpEF) in terms of SDNN risk stratification, despite the differences in other HRV parameters (SDANNi). However, the

patients in our cohort were already under treatment with beta-blockers and ACEi, which have been shown to improve HRV parameters after as little as 3 months of treatment [17]. Our data seems to point to an association between most time-domain indices (SDANNi, SDNNi, rMSSD, pNN50) and enlargement of the all cardiac chambers, as well as an increase in the prevalence of functional tricuspid regurgitation.

Study Limitations

Some limitations should be noted. Firstly, the number of enrolled patients was small and they were all gathered from a single center, thus results may not be entirely applicable to larger populations. Secondly, the heart failure group was relatively inhomogeneous as patients with heart failure with mid-range or reduced ejection fraction were not excluded, though very few in number. Finally, lack of follow-up data has prevented us from extracting information regarding the risk of mortality in either group. Larger, prospective trials of patients with HFpEF are needed in order to establish the utility of HRV parameters in clinical practice.

Conclusions

Our study confirms a loss of HRV, particularly a reduction in short-term time domain parameter reduction and a prolongation of the maximum QT interval in patients with heart failure with preserved ejection fractions in comparison to patients without HF. To our knowledge, this is the first study to compare HFpEF patients with non-HF patients matched to comorbidities, and not healthy controls, in terms of HRV and its relationship with echocardiographic parameters.

Conflict of interests (financial or non-financial)

The authors declare that there are no conflicts of interest.

List of abbreviations used (optional)

ACEi – angiotensin-converting-enzyme inhibitor
ARBs – angiotensin-receptor blockers

CCB – calcium-channel blockers
HF – heart failure
HFpEF – heart failure with preserved ejection fraction
HfmrEF – heart failure with mid-range ejection fraction
HFrEF – heart failure with reduced ejection fraction
HR – heart rate
HRV – heart rate variability
HTN – arterial hypertension
MAPSE – mitral annular plane systolic excursion
MRAs – mineralocorticoid receptor antagonists
ms – milliseconds
N – normal sinus beat
NS – without statistical significance
pNN50 – the percentage of adjacent NN intervals that differ from each other by more than 50 ms
rMSSD – the root mean square of successive differences between NN intervals
SDANN – standard deviation of the average NN intervals
SDNN – standard deviation is measured between consecutive normal sinus beats
SDNNi – the mean of the standard deviations of all NN intervals
RAAS – renin-angiotensin-aldosterone system

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