Effects of Beta-Blocker on Heart Rate Variability in Heart Failure with Preserved Ejection Fraction

Shiza Saleem[1], Mohanad Alkhodari[1,2,] Leontios J Hadjileontiadis[1,2] and Ahsan H Khandoker[1,2] and Herbert F Jelinek[1,2]

[1]Department of Biomedical Engineering, Khalifa University, Abu Dhabi, United Arab Emirates
[2]Healthcare Engineering Innovation Center, Khalifa University, Abu Dhabi, United Arab Emirates

Abstract

Heart failure is characterized by sympathetic activation and parasympathetic withdrawal leading to an abnormal autonomic modulation. Beta-blockers (BB) inhibit overstimulation of the sympathetic system and are indicated in heart failure patients with reduced ejection fraction. However, the effect of beta-blocker therapy on heart failure with preserved ejection fraction (HFpEF) is unclear. This study investigated the effect of BB therapy on heart rate variability (HRV) features as a measure of risk of an abnormal cardiac event. ECGs of seventy-three patients with HFpEF > 55% were recruited. Fifty-six patients in the BB group and 17 patients in the without BB group. HRV analysis was performed for recordings between 6-10 am and 6-10 pm, which are times associated with increased risk of cardiac events. The result shows that RMSSD (p=0.011), HF power (p=0.012), and VLF power (p=0.047) were significantly higher during the 6 – 10 am interval. Sample entropy (p=0.016), and the novel fragmentation measures PIP (p=0.015), IALS (p=0.015) and PSS (p=0.008) were significantly higher between 6 – 10 pm. Beta-blocker therapy increases HRV measures in the HFpEF group depending on the feature investigated indicating an overall decreased risk of a cardiac event and a possibly beneficial effect of beta-blockers, especially during the morning hours that is characterized by a sympathetic surge.

1. Introduction

Heart rate variability (HRV) is characterized by periodic and nonperiodic oscillations. It provides valuable information about the state of the autonomic nervous system (ANS), which regulates cardiac activity through its two main divisions, the parasympathetic nervous system (PNS) and the sympathetic nervous system (SNS) [1]. HRV, therefore, reflects a reciprocating sympathovagal balance between the PNS and the SNS. HRV measures not only represent the variability but also provide information about the heart rate (HR) [2]. Decreased HRV is associated with cardiac pathology including heart failure and can be used to assess cardiac health. Chronic heart failure is indicated by diastolic dysfunction with impaired left ventricular ejection fraction (EF) including preserved ejection fraction (HFpEF). Epidemiological data shows that approximately 50% of heart failure patients fall into the HFpEF category [3]. Sympathetic activation and parasympathetic withdrawal to compensate for a weakened heart muscle are a part of the clinical presentation leading to alterations in the cardiac rhythm associated with heart failure [1].

Beta-blockers inhibit adrenergic activity of the sympathetic nervous system and are primarily used as a treatment therapy for heart failure with reduced EF (HFrEF). Studies have shown significant benefits from the treatment with increased survival rates and reduced hospitalizations in this patient group [3], [4]. A meta-analysis of BB treatment for HFpEF demonstrated a reduction in all-cause mortality but not the number of hospitalizations [3]. However, there are no clear guidelines or consensus on the use and effect of BB for HFpEF.

The present prospective study was undertaken to investigate the effect of BB therapy on patients with HFpEF for hours of the day associated with increased risk of a cardiac event.

2. Methods

2.1. Dataset and Patient enrollment

The heart failure dataset used here included 24-hour Holter ECG recordings with a sampling frequency of 200 Hz for 271 patients using a three pseudo-orthogonal lead configuration (X, Y, Z). The dataset was obtained from the Intercity Digital ECG Alliance (IDEAL) study of the University of Rochester Medical Center Telemetric and Holter ECG Warehouse (THEW) archives [6]. All

participants submitted an informed consent before enrolling in the study. The Research Subject Review Board of the University of Rochester approved the protocol.

The eligibility criteria of the IDEAL study included having exercise-induced ischemia, >75% narrowing of at least one vessel, myocardial infarction (MI), stable ischemic heart disease, and sinus rhythm. All patients in the dataset were stable since their latest cardiac event (2+ months ago). All patients with dilated cardiomyopathy, unstable angina, congestive heart failure (CHF), previous coronary artery bypass surgery (CABG), and cerebral/renal vascular diseases were excluded from the study.

In the current study, only patients with HFpEF > 55% according to the American Society of Echocardiography and the European Association of Cardiovascular Imaging (ASE/EACVI) were considered [7]. All patients taking medication (ACE-inhibitors, Anti-arrhythmic and Diuretic) other than betablockers were removed from the study. This resulted in a total of 73 patients among which 56 patients were using beta-blockers (BB) and 17 without beta-blocker medication (NBB). The demographical data for each group are shown in Table 1. HRV was calculated for each hour of the Holter ECG recordings.

2.2. Pre-processing

HRV data for each hour was preprocessed using the hybrid SDROM-adaptive filtering technique to decrease abnormalities in the data [7]. The starting point of the 24-hour circadian rhythm for this study was fixed at 12:00 am using Cosinor fitting analysis [7].

A cosine function was fitted for each hour of HRV data by deriving the midline estimating statistic of rhythm (MESOR-M), amplitude (Amp), and acrophase (AC). The 24-hour AC was changed to angle data (360/24) and the reference angle 0° was assigned to the starting time of 12:00 am with an increase of 15° for every hour.

2.3. Heart rate variability features

The time periods of interest were 6 – 10 am and 6 – 10 pm. Ten HRV measures for both groups were calculated for 4-hour and 2-hour windows using the Cosinor model.

Time-domain features, which define the interbeat interval variability, included standard deviation of the N-to-N intervals (SDNN) and the root mean square of differences between successive N-to-N intervals (RMSSD).

The frequency domain measures describe the distribution of power into the following discrete frequency bands: high-frequency (HF, 0.15–0.4 Hz), low-frequency (LF, 0.04–0.15 Hz), and very low-frequency (VLF, 0.0033– 0.04 Hz) [8]. Sample entropy (SampEn) was determined as a nonlinear measure [8]. The novel fragmentation measures which represent the sinoatrial node dynamics, were investigated for determining effectiveness of BB therapy for HFpEF included PIP (percentage of inflection points in the N-to-N interval), IALS (inverse average length of segments), PSS (percentage of short segments), and PAS (percentage alternation segments) [9].

Table 1. Demographic characteristics

Characteristics[a,b,c]	With β-blockers (n=56)	Without β-blockers (n=17)
Age (years)	56.60±12.80	57.90±10.48
Gender (Male/Female)	47/9	15/2
BMI	26.50±3.97	25.70±3.07
LVEF	66.60±5.75	65.80±7.45
Mean Heart Rate	65.68±8	73.13±9.59

[a]Data are expressed as mean±SD
[b]No significant difference found in the characteristics between the two groups
[c]BMI: Body mass index (Kg/m^2), LVEF: left ventricular ejection fraction (%)

2.4. Statistical Analysis

Statistical differences between the two groups for the HRV measures was determined using the nonparametric Mann Whitney U test with significant p value set at less than 0.05. In addition, the relative percentage change in the mean HRV features of all patients of the BB group relative to the mean HRV features of NBB group (% ΔHRV_{RBB}) was calculated as a measure of change between the two groups, i.e.:

$$\% \, \Delta HRV_{RBB} = \frac{HRV_{BB} - HRV_{NBB}}{HRV_{NBB}} \, x \, 100, \quad (1)$$

where HRV_{BB} are the HRV features for BB group and the HRV_{NBB} refers to the HRV measures for NBB group. All the analysis in the study was undertaken in Matlab 2022a (MathWorks).

3. Results

Research has shown that an increased risk of cardiac events occurs at certain periods of the circadian rhythm [10]. Therefore, in this study, the action of BB was investigated for the high-risk period of 6 – 10 am and 6 – 10 pm of the day. A 2- and 4-hour window of the HRV data was used to investigate the short term and long-term effects on HRV.

3.1. Two-hour window

Table 2: P value and % ΔHRV_{RBB} for two-hour window for the ten HRV measures. Significant p values in bold ($p<0.05$).

HRV metrics	6 - 8 am		8 - 10 am		6 - 8 pm		8 - 10 pm	
	p value	% ΔHRV_{RBB}	*p* value	% ΔHRV_{RBB}	*p* value	% ΔHRV_{RBB}	*p* value	% ΔHRV_{RBB}
SDNN	0.270	17.29	0.149	12.92	0.474	-10.45	0.161	12.71
RMSSD	**0.002**	60.06	0.058	19.44	1.000	-6.03	0.699	7.51
HF	**0.004**	286.15	**0.042**	36.50	0.404	30.92	0.577	27.60
LF	**0.036**	104.06	0.415	13.00	0.979	5.07	0.977	-1.48
VLF	**0.020**	61.87	0.165	20.09	0.260	19.88	0.283	23.33
SampEn	0.084	15.29	0.588	-1.57	**0.003**	31.05	0.415	5.42
PIP	0.056	9.42	0.318	4.83	0.145	9.33	**0.007**	18.00
IALS	0.056	9.43	0.318	4.83	0.145	9.30	**0.007**	18.01
PSS	0.054	15.42	0.385	6.04	0.181	14.94	**0.004**	29.31
PAS	0.364	36.46	0.331	34.52	0.466	21.89	0.270	32.86

Table 2 illustrates the p values from the Mann Whitney test. For 6 – 8 am RMSSD, HF power, LF power and VLF power were significantly different between the two groups. For the period between 8 – 10 am only HF power showed a significant difference. No significant difference was seen during 6 – 10 pm for these measures. However, for the evening period significant changes were observed for sample entropy between 6 – 8 pm and for the fragmentation measures between 8 – 10 pm. PIP, IALS, and PSS demonstrated significant changes between the two groups.

The results for % ΔHRV_{RBB} are also shown in Table 2. As a general trend the HRV_{BB} values were higher than the HRV_{NBB} for all time periods. However, sample entropy showed a decrease of 1.57% for the period of 8 – 10 am. Although the difference between the two groups was not significant for SDNN and RMSSD, a decrease of 10.45% and 6 % was observed between 6 – 8 pm. respectively. The hours of 8 – 10 pm indicated a slight decrease of 1.48 % in the LF power. A significant increase of HF power was also observed for the period of 6 – 8 am most probably due to the reduction of sympathetic activity following BB intervention. The LF power and VLF power were also much higher during this time. However, it is important to note that the % ΔHRV_{RBB} for HF power is 2.7 and 3.2 times higher than LF power and VLF power, respectively.

3.2. Four-hour window

The 4-hour window analysis of the HRV difference between the two groups demonstrated similar results as is seen in Table 3. The significant change observed in LF power for the 6 – 8 am period is diminished in the 4-hour window analysis. However, RMSSD, HF power and VLF power were significantly different between the BB and NBB group. The 6 – 10 pm results reaffirm the results of the 2-hour window analysis. Sample entropy, PIP, IALS and PSS were statistically significantly different ($p<0.05$).

There was also an increase in HRV_{BB} for all of the measures investigated in the 4-hour window as observed in Table 3. However, the percentage increase observed in HRV_{BB} was higher for the 6 – 10 am period for all HRV indices except fragmentation measures. The fragmentation measures on the other hand were higher during the evening hours of 6 – 10 pm.

4. Discussion and Conclusion

HRV analysis is proving to be a robust analytical method for risk stratification and prognosis of various cardiovascular conditions as well as chronic disease classification and progression. Reduced HRV has been used as a risk factor for mortality in patients with heart failure reflecting impaired autonomic control [1]. Although HRV metrics are known to be influenced by the chronotropic state [2], the current study found no significant correlation between the mean heart rate (HR) and HRV metrics except for PSS. Therefore, no further investigation was required to adjust HRV metrics for HR.

Treatment with beta-blockers improved the linear and nonlinear HRV measures in patients with reduced ejection fraction [11]. A study investigating the effect of propranolol on the HRV measures following acute myocardial infraction found significant changes in the RMSSD but not for SDNN [12]. The results of the current study confirm these findings.

The impaired sympathovagal balance in heart failure patients can be observed by the decrease in the HF power and an increase in the LF frequency [1]. The results of this study show an improved sympathovagal balance with significantly increased HF and consequently lowered LF/HF ratio for the BB group in comparison to the NBB patients. This may indicate a possible reduction in the sympathetic surge in the morning hours and a reduction in adverse cardiac event risk. The increase in short-term HRV

measures including RMSSD and HF power seen in this study suggest the recovery of parasympathetic tone in HFpEF patients undergoing beta-blocker therapy.

Table 3: P value and % ΔHRV_{RBB} for four-hour window for the ten HRV measures. Significant p values in bold ($p<0.05$).

HRV metrics	6 - 10 am		6 - 10 pm	
	p value	% ΔHRV_{RBB}	*p* value	% ΔHRV_{RBB}
SDNN	0.119	16.05	0.453	8.33
RMSSD	**0.011**	39.78	0.351	8.57
HF	**0.012**	134.11	0.190	40.83
LF	0.153	50.86	0.634	8.85
VLF	**0.047**	62.96	0.149	26.69
SampEn	0.393	51.74	**0.016**	32.14
PIP	0.128	6.81	**0.015**	24.92
IALS	0.128	7.46	**0.015**	22.23
PSS	0.165	7.46	**0.008**	22.22
PAS	0.371	11.42	0.149	35.92

A study that investigated HRV parameters and specifically the sympathetic shift in heart failure patients on beta-blocker treatment found that the nonlinear HRV measure of sample entropy was not significantly affected [13]. Traditional time domain measures, such as RMSSD, were found to be better predictors of the sympathetic shift in heart failure [13]. The short-term fragmentation measures were found to be higher in patients with coronary artery disease and outperformed the traditional linear measures and sample entropy in separating healthy subjects from patients [9]. However, the fragmentation measures are higher for the BB group. The effect of beta-blockers during the day and night time has also been previously reported, with greater effect during the day [14]. This pattern can also be observed in the current study especially for the frequency domain measures. The results for the hours of 6 – 10 am and 6 – 10 pm show a significant difference in the % ΔHRV_{RBB}.

Treatment of HFpEF patients with beta-blocker therapy increased the HRV measures in heart failure patients and improved the cardiac autonomic modulation during high-risk periods. In summary, analysis of the HRV measures for the beta-blocker therapy for heart failure with preserved ejection fraction has shown significant differences between the two groups at different time periods and indicates that beta blockers may be beneficial for this group of patients. HRV measures can be used as biomarkers and predictors for beta-blocker therapy.

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Shiza Saleem
PO Box 127788
Abu Dhabi, UAE
100052484@ku.ac.ae