The effect of an evening dose of a long-acting beta-blocker on the autonomic tone in patients with congestive heart failure

Ryszard Targoński[1], Janusz Sadowski[2]

[1] Department of Medical Sciences, Warminsko-Mazurski University, Olsztyn, Poland
[2] City Hospital, Olsztyn, Poland

Abstract

Background: Heart rate variability (HRV) indices are accepted markers of cardiac autonomic activity and have been used as indicators of beta-blockade effects in congestive heart failure (CHF) patients. In view of the high frequency of sudden cardiac death in the morning, there is a question whether the evening beta-blocker administration would be more efficient than a morning dose.

Aim: To compare HRV indices after morning or evening long-acting beta-blocker administration.

Methods: The study group consisted of 52 CHF patients (NYHA class II/III) in sinus rhythm. Time domain (TD) and frequency domain (FD) HRV analyses were performed for daytime, nighttime and a 24-hour period: first after the morning bisoprolol administration, and then after the same evening dose.

Results: After the evening dose the mean heart rate was significantly lower ($p = 0.01$), nighttime normal R-R intervals were significantly prolonged ($p = 0.008$) and the low frequency (LF)/high frequency (HF) ratio was significantly lower for: 24 h ($p = 0.0002$); daytime ($p = 0.003$) and nighttime ($p = 0.008$) with higher HF values in the 24-hour period ($p = 0.0007$) and in the daytime interval ($p = 0.006$).

Conclusion: An evening dose of a beta-blocker is more effective than a morning dose in reversing adverse changes in the autonomic nervous system activity in CHF patients.

Key words: heart failure, heart rate, beta blockade, autonomic nervous system

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Introduction

Congestive heart failure (CHF) is a well known trigger of abnormal neuroendocrine response leading to excessive norepinephrine plasma secretion and increased adrenergic activity [1]. Adrenergic stimulation produces short-term adaptive improvement of cardiac output. However, permanent baroreceptor excitation results in long-lasting adrenergic stimulation and subsequent progressive diminished susceptibility of beta 1 receptors due to prolonged decrease of cardiac output. This vicious circle leads to an increase in clinical symptoms of CHF and may induce cardiac arrhythmias, resulting in sudden cardiac death (SCD) [2].

Numerous international large-scale randomised trials have shown that prolonged beta-blocker administration in CHF patients significantly improved their long-term prognosis, presumably due to a decrease in sympathetic activity [3-6].

Heart rate variability (HRV) is one of the simplest examinations widely used to assess autonomic nervous system activity [7, 8]. In spectral HRV analysis, the high frequency band (HF) reflects vagal activity, and the low frequency band (LF) is modulated by both sympathetic and parasympathetic systems [7]. A fluctuating daily HF/LF ratio is a well established indicator of the sympatho-vagal balance [9].

At the early stage of CHF, a relative increase in the LF band and reduction of the HF band as well as depression of the total power (TP) spectrum have been observed [9]. More advanced stages of CHF are accompanied by a decline in both LF and HF bands arising from improper central autonomic system regulation and diminished reactivity of beta adrenergic receptors [10, 11]. It has been shown that in the case of left ventricular (LV) dysfunction, the HF and LF/HF ratios were both substantially reduced along with regression of their daily fluctuations [9]. These

Address for correspondence:
Ryszard Targoński MD, PhD, Wydział Nauk Medycznych, Uniwersytet Warmińsko-Mazurski, ul. Żołnierska 14c, 10-561 Olsztyn,
tel.: +48 89 524 61 54, fax: +48 89 524 61 54, e-mail: rtarg@op.pl
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data suggest that disturbances in autonomic activity in CHF are due to a decrease in the activity of the parasympathetic system and a relative increase in sympathetic activity, especially during the night-time.

Diabetes mellitus (DM) is a well known factor with an important impact on the autonomic nervous system which is manifested by a reduction in HRV parameters [12, 13]. Its effect on HRV parameters in CHF has not been well established.

An analysis of patients from the CIBIS II trial who died at night of SCD showed that their heart rate routinely measured in morning hours did not change over time either in the placebo or in the bisoprolol group [14]. It seems reasonable to assume that the level of the night and the early morning beta blockade was not sufficient to prevent these terminal events [14].

Numerous epidemiological studies have provided data which show that the early morning hours are a particularly vulnerable period for SCD incidents [2, 15]. Therefore, an abnormally high adrenergic tone in these hours may exert an adverse impact on the clinical course of CHF patients [2].

There is a question whether evening long-acting beta-blocker administration, with its maximal efficacy during the night and the early morning hours, is more effective than a morning dose in the modulation of HRV parameters. Accordingly, the aim of this study was to compare HRV indices after morning or evening long-acting beta-blocker administration and the impact of DM on HRV.

Methods

Fifty-two patients (30 male and 22 female, average age of 67.2 ± 10.6 years), who were in sinus rhythm and had CHF (class II-III in NYHA classification), were included in the study. Clinical characteristics are listed in Table I. All of them received ACE inhibitors, diuretics, including potassium-saving drugs, and a long-acting beta-blocker – bisoprolol in a dose of 5 mg once a day. The study conformed with the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects, Edinburgh, 2000). All patients signed written informed consent and agreed to participate in the study. The study was approved by the local Ethics Committee.

Table I. Baseline characteristics of patients (n = 52)

Age [years]	67.2 ± 10.6
Male gender, n (%)	30 (57.7)
Documented ischemic heart disease, n (%)	36 (69.2)
Idiopathic dilated cardiomyopathy, n (%)	5 (9.6)
Valvular heart disease, n (%)	7 (13.5)
Hypertension, n (%)	34 (65.4)
Diabetes mellitus, n (%)	20 (38.5)
Chronic renal disease, n (%)	7 (13.5)
Left ventricular ejection fraction [%]	37.5 ± 7.1

During the first period of 5 days, beta-blocker was administered in the morning (8:00-9:00 a.m.); this was followed by a 24-hour Holter recording. The administration time was subsequently changed to evening hours (5.00-6.00 p.m.), with the dosage maintained at the same level. After 72 h, a 24-hour Holter monitoring was again performed.

The 24-hour Holter monitoring was performed with 3-channel Medilog MR-63 cassette recorders, manufactured by the Oxford company (UK). The data were analysed with a Medilog Suprima Oxford ECG analysis system. We excluded all interferences, artefacts, premature beats, paroxysmal supraventricular and ventricular tachycardias and post-extrasystolic pauses from further analysis. Recordings with various interferences and/or extrasystolic beats (> 20%) were excluded from the HRV analysis, and the examination was repeated [7]. The tapes were subsequently analysed for HRV by the Holter Medilog Suprima software. The data to be analysed were obtained from the tachogram. The discarded fragments were interpolated by calculating the mean value.

The time-domain HRV analysis was performed for each registration in three time intervals (the 1st covered the whole 24-hour period; the 2nd covered the daytime hours 10:00 a.m. – 7:00 p.m.; the 3rd covered the night hours 11:00 p.m. – 6:00 a.m.) [14, 16]. The following parameters were assessed: NN (the mean RR interval), SDNN (standard deviation for all the selected RR intervals), SDANNi (standard deviation of 5 min means of selected RR intervals), rMSSD (square root of the mean square of consecutive differences in RR intervals), pNN50 (percentage of intervals which differ by at least 50 ms from the previous interval).

The frequency-domain analysis was conducted for three time intervals (the 1st covered the whole 24-hour period; the 2nd covered the daytime hours 10:00 a.m. – 7:00 p.m.; the 3rd covered the night hours 11:00 p.m. – 6:00 a.m.) [16]. The following parameters were assessed: TP (total power), HF (high frequency), LF (low frequency), VLF (very low frequency), ULF (ultra low frequency), LF/HF (LF/HF ratio).

Assessment of ventricular arrhythmias in the form of ventricular extrasystoles, couples and all types of ventricular tachyarrhythmias was also performed.

Statistical analysis

The data for each parameter were analysed using the STATISTICA 7.1 software pack (StatSoft Inc. Tulsa, OK., USA), calculating the mean and SD. The paired Student's t-test was used for continuous variables to determine the significance of differences (p value) after the morning and evening drug administration for each parameter of HRV. The distributions of all frequency domain HRV variables were skewed and not normally distributed so the natural log transformation of these measures was applied before statistical analyses were performed. A p value of ≤ 0.05 was adopted as statistically significant.

Results

The patients who were treated with the evening dose of beta-blocker had a slower heart rate in the 24-hour analysis than when they were given the drug in the morning (66.1 ± 9.4 vs. 63.6 ± 8.1 beats/min; p = 0.01) (Figure 1). The evening dose significantly prolonged the NN interval during 24-hour monitoring (918.6 ± 122.4 vs. 950.5 ± 118.5 ms; p = 0.01) with a significant difference in the night hours (995 ± 136.4 vs. 1039.3 ± 139.2 ms; p = 0.008). After the evening dose, a trend towards higher values of SDNN (120.7 ± 29 vs. 125.9 ± 34.3; p = 0.1), SDANNi (107 ± 27.8 vs. 112.6 ± 32.2; p = 0.1) and pNN50 level (7.21 ± 7.88 vs. 8.63 ± 6.37%; p = 0.07) in the 24-hour monitoring was also observed (Table II).

The analysis of HRV spectrum showed that the patients who were treated with the evening dose of beta-blocker had a significantly lower LF/HF ratio in the 24-hour recording (2.24 ± 1.72 vs. 1.78 ± 1.29; p = 0.0002), during daytime hours 10:00 a.m. – 7:00 p.m. (2.59 ± 2.18 vs. 2.12 ± 1.7; p = 0.003) and at night 11:00 p.m. – 6:00 a.m. (2.21 ± 1.76 vs. 1.77 ± 1.3; p = 0.008) as compared to the period when they received the drug in the morning. The decrease in the LF/HF ratio after the evening drug administration resulted mainly from the increase in the HF component. Significantly higher values of HF band were observed in the 24-hour monitoring (5.26 ± 0.96 vs. 5.54 ± 0.85; p = 0.0007) and in the daytime interval (4.92 ± 1 vs. 5.19 ± 0.92; p = 0.006). A similar tendency after the evening dose of bisoprolol was observed in the analysis of the nighttime interval (5.49 ± 1.1 vs. 6.06 5.7 ± 0.85; p = 0.08) (Table III).

Diabetic patients did not have any beneficial effect of the morning to evening drug administration shift. Evening drug administration did not result in significantly beneficial HF spectrum modulation during the 24-hour period and during the day in diabetic patients in contrast to non-diabetic patients. The presence of DM had no influence on the change in LF/HF ratio in 24-hour analysis. At night, the LF/HF ratio was more beneficially modulated in diabetic patients in comparison to non-diabetic subjects when the drug was administered in the evening.

The timing of bisoprolol administration had no effect on ventricular arrhythmia occurrence.

Discussion

The present study showed that the evening application of a beta-blocker with a prolonged effect resulted in a significant slowing down of the heart rate at night and during the 24-hour monitoring period in comparison to the morning dose. No differences in heart rate were observed during the day, regardless of the morning or evening drug administration time. This heart rate slowdown following the administration of a beta-blocker is thought to improve the metabolism of the cardiac muscle by increased oxygen supply during the extended diastole with simultaneous

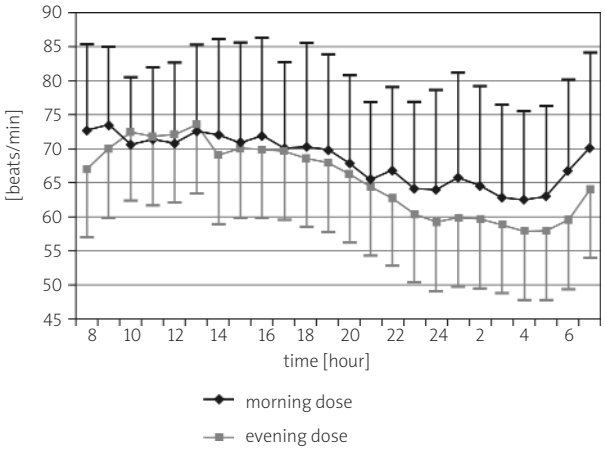

Figure 1. Plots of 24-hour heart rate values following the morning and the evening dose of bisoprolol

reduction in workload [17-19]. A direct relationship has been found between the degree of heart rate reduction and the lifespan extension in patients with CHF [18, 20].

The CIBIS II study revealed that the application of bisoprolol was the most beneficial for the patients with the greatest reduction in heart rate [18]. According to the findings of the COMET study, which assessed the total mortality of patients with CHF, better results were achieved in the treatment with carvedilol than with metoprolol tartrate [6]. Di Lenarda et al. [21] compared the effects of these two drugs in patients with idiopathic dilated cardiomyopathy and found no difference in the average daily heart rate despite their different pharmacokinetics. However, the presented daily heart rate analysis showed that the heart rate assessed during the period from the evening to early morning was persistently lower in patients who were given carvedilol. In our study group, the evening drug dose caused a significant slowdown of the night and morning heart rate as compared to the morning dose, which resembled the findings of Di Lenarda et al. [21]. Therefore, there is a question whether the reduced death rate in the patients on carvedilol from the COMET study should be linked to the similar prolonged nocturnal beta blockade, which is likely to result from a longer effect of carvedilol than that of metoprolol tartrate.

The evening dose of bisoprolol, as compared to the morning dose, caused more favourable modulation of the autonomic activity with a relative decrease of the sympathetic activation which manifested itself in a significant decrease of the LF/HF ratio in all of the three analysed periods. This was mainly due to the increased HF component in the 24-hour analysis and a relatively lower LF band increase. Bullinga et al. [22] observed that beta-blocker application was related to elevation of all components of the HRV spectrum and considered that the

Table II. Results of the time – domain HRV analysis

HRV parameter	All patients (n = 52)			Non-diabetic (n = 32)			Diabetic (n = 20)		
	Beta-blocker administered in the morning	Beta-blocker administered in the evening		Beta-blocker administered in the morning	Beta-blocker administered in the evening		Beta-blocker administered in the morning	Beta-blocker administered in the evening	
	mean (SD)	mean (SD)	p	mean (SD)	mean (SD)	p	mean (SD)	mean (SD)	p
NN [ms]	918.6 (122.4)	950.5 (118.5)	0.01	926.64 (125.66)	972.06 (126.21)	0.02	905.83 (119.14)	917.92 (96.45)	0.3
NN [day]	874.5 (128.5)	894.6 (120.7)	0.1	882.77 (136.15)	917.92 (131.22)	0.07	861.35 (117.32)	857.36 (92.81)	0.8
NN [night]	995 (136.4)	1039.3 (139.2)	0.008	1003.72 (130.27)	1065.79 (140.4)	0.01	981.09 (147.92)	996.93 (129.63)	0.4
SDNN [ms]	120.7 (29)	125.9 (34.3)	0.1	118.14 (29.91)	127.38 (36.74)	0.03	124.71 (27.69)	123.58 (30.79)	0.8
SDNN [day]	93.1 (26.9)	96.2 (26.6)	0.3	90.88 (30.74)	96.29 (28 .71)	0.1	96.59 (19.31)	96.04 (23.5)	0.9
SDNN [night]	92.7 (30.1)	92.5 (29.2)	1.0	91.58 (28.3)	91.77 (30.9)	0.9	94.47 (33.46)	93.63 (27.05)	0.8
SDANNi [ms]	107 (27.8)	112.6 (32.2)	0.1	104.71 (28.39)	114.19 (32.91)	0.04	110.66 (27.20)	110.15 (31.75)	0.9
SDANNi [day]	77.6 (24.5)	81.1 (25.3)	0.4	75.69 (27.59)	80.64 (26.76)	0.2	80.58 (18.87)	81.81 (23.35)	0.8
SDANNi [night]	71.2 (26)	69.4 (27.4)	0.6	70.45 (26.1)	67.34 (28.22)	0.6	72.37 (26.48)	72.62 (26.52)	0.9
pNN50 [%]	7.21 (7.88)	8.63 (6.37)	0.07	7.49 (8.3)	9.05 (6.88)	0.1	6.77 (7.37)	7.96 (5.59)	0.4
pNN50 [day]	5.6 (7.6)	6.39 (5.91)	0.3	5.82 (8.28)	6.36 (6.29)	0.6	5.24 (6.54)	6.43 (5.43)	0.4
pNN50 [night]	9.93 (11.1)	11.62 (9.1)	0.2	10.17 (10.18)	13.01 (10.25)	0.07	9.53 (12.59)	9.37 (6.39)	1
RMSSD [ms]	32.8 (19.6)	34.4 (13.4)	0.4	33.75 (21.95)	33.15 (14.73)	0.6	31.18 (15.57)	33.24 (11.27)	0.4
RMSSD [day]	28 (18.5)	29.94 (11.12)	0.3	28.58 (21.73)	30.27 (11.55)	0.6	27.06 (12.12)	29.43 (10.65)	0.3
RMSSD [night]	38.5 (27.2)	37.5 (17.3)	0.7	39.93 (28.23)	38.93 (19.85)	0.8	36.18 (26.09)	35.08 (12.16)	0.8

Abbreviations: see Methods section

Table III. Results of the frequency – domain HRV analysis

HRV parameter	All patients (n = 52)			Non-diabetic (n = 32)			Diabetic (n = 20)		
	Beta-blocker administered in the morning	Beta-blocker administered in the evening		Beta-blocker administered in the morning	Beta-blocker administered in the evening		Beta-blocker administered in the morning	Beta-blocker administered in the evening	
	mean (SD)	mean (SD)	p	mean (SD)	mean (SD)	p	mean (SD)	mean (SD)	p
TP [lnms^2]	7.88 (0.58)	7.9 (0.65)	0.6	7.81 (0.64)	7.89 (0.72)	0.3	7.98 (0.48)	7.92 (0.55)	0.5
TP day [lnms^2]	7.69 (0.57)	7.75 (0.59)	0.3	7.61 (0.62)	7.74 (0.65)	0.1	7.82 (0.44)	7.78 (0.49)	0. 6
TP night [lnms^2]	7.93 (0.7)	7.95 (0.7)	0.8	7.88 (0.7)	7.89 (0.81)	0.8	8.02 (0.68)	8.03 (0.5)	0.9
HF [lnms^2]	5.26 (0.96)	5.54 (0.85)	0.0007	5.21 (0.96)	5.57 (0.8)	0.002	5.32 (0.98)	5.49 (0.94)	0.2
HF day [lnms^2]	4.92 (1)	5.19 (0.92)	0.006	4.89 (1.02)	5.24 (0.84)	0.01	4.96 (1.01)	5.12 (1.04)	0.2
HF night [lnms^2]	5.49 (1.1)	5.7 (0.85)	0.08	5.48 (1.09)	5.71 (0.89)	0.2	5.5 (1.05)	5.69 (0.79)	0.4
LF [lnms^2]	5.87 (0.85)	5.9 (0.88)	0.6	5.77 (0.95)	5.86 (0.97)	0.3	6.02 (0.66)	5.99 (0.72)	0.7
LF day [lnms^2]	5.63 (0.87)	5.67 (0.78)	0.7	5.57 (0.97)	5.64 (0.92)	0.5	5.74 (0.66)	5.74 (0.56)	1
LF night [lnms^2]	6.06 (0.97)	6.06 (0.97)	0.9	5.98 (1.1)	6 (1.1)	0.8	6.18 (0.77)	6.14 (0.73)	0.8
VLF [lnms^2]	7.36 (0.48)	7.35 (0.57)	0.9	7.29 (0.52)	7.34 (0.65)	0.5	7.47 (0.39)	7.37 (0.43)	0.3
VLF day [lnms^2]	7.15 (0.63)	7.23 (0.58)	0.4	7.12 (0.54)	7.22 (0.64)	0.2	7.21 (0.76)	7.24 (0.47)	0.9
VLF nigh [lnms^2]	7.4 (0.64)	7.41 (0.69)	0.9	7.34 (0.62)	7.34 (0.79)	1	7.5 (0.67)	7.51 (0.52)	0.9
ULF [lnms^2]	5.95 (0.78)	5.88 (0.77)	0.4	5.89 (0.84)	5.89 (0.85)	1	6.05 (0.68)	5.86 (0.63)	0.2
ULF day [lnms^2]	5.79 (0.76)	5.83 (0.72)	0.7	5.64 (0.77)	5.78 (0.76)	0.2	6.05 (0.67)	5.9 (0.64)	0.4
ULF night [lnms^2]	5.6 (0.77)	5.52 (0.77)	0.5	5.53 (0.82)	5.46 (0.87)	0.5	5.71 (1.1)	5.63 (0.59)	0.7
LF/HF	2.24 (1.72)	1.78 (1.29)	0.0002	2.21 (2)	1.73 (1.49)	0.01	2.29 (1.17)	1.85 (0.93)	0.001
LF/HF [day]	2.59 (2.18)	2.12 (1.7)	0.003	2.55 (2.46)	2.01 (1.8)	0.01	2.66 (1.7)	2.28 (1.54)	0.01
LF/HF [night]	2.21 (1.76)	1.77 (1.31)	0.008	2.15 (2)	1.8 (1.53)	0.1	2.3 (1.32)	1.75 (0.9)	0.02

Abbreviations: see Methods section

degree of the change may reflect higher treatment effectiveness. The patients with lower total HRV values had worse prognosis and heart failure symptoms were more advanced [9]. Patients with CHF who had an implantable cardioverter defibrillator (ICD) and who had a recorded episode of morning ventricular tachycardia did not show an increase in the vagal tone during the night sleeping hours, followed by its morning decrease, which was reflected by lower HF values [4]. What is more, increased vagal tone prevents life-threatening ventricular arrhythmias in ischaemic heart disease and CHF [22]. Therefore, an increase in the HF component after switching from the morning to the evening dose of bisoprolol seems to be further proof of the favourable modulation of the autonomic system.

Introducing beta-blockers in CHF treatment was a consequence of the discovery of its neuroendocrine nature. The therapeutic effectiveness of these compounds results from breaking the vicious circle which leads to excessive adrenergic stimulation. Further patho-physiological studies showed that stimulation of the adrenergic system in patients in the initial period of CHF precedes stimulation of the renin-angiotensin-aldosterone system. Clinical significance of this pathophysiological background was verified in the CIBIS III trial [4]. The observed reduction of death risk and prevention of sudden cardiac death in the beta-blocker first arm confirmed the significance of the knowledge of this pathophysiological pathway for choosing the optimal sequence of implemented drugs.

The presence of DM in our patients significantly decreased some parameters of time domain analysis and hampered HF value increase in comparison to non-diabetic patients following drug administration shift from morning to evening. It is a well known fact that development of DM with subsequent autonomic diabetic neuropathy has an important impact on HRV [13]. The earliest sign of cardiac autonomic diabetic neuropathy is a reduction in HRV. The differences described in our study probably result from the development of diabetic neuropathy affecting the autonomic nervous system.

Our results may be limited by the fact that the HRV analyses were conducted with a relatively low bisoprolol dose given in an unchanged sequence for all patients (e.g. morning dose administration was always followed by the evening dose). Nonetheless, the favourable modulation of the autonomic nervous system following an evening drug dose can be another encouraging pathophysiological argument for further studies, which may contribute to planning more effective therapy of CHF.

The next limitation is that daytime (10:00-19:00) and night-time (23:00-06:00) periods were planned according to the publication by Galinier et al. [16]. The presented whole-day heart rhythm graph and data from papers reporting SCD frequency strongly suggest that detailed analysis of this period is of great importance. We hope that introducing digital recording, reducing the number of leads and noise recordings in this specific period will enable us to perform more comprehensive analysis.

Conclusion

An evening dose of a beta-blocker is more effective than a morning dose in reversing adverse changes in the activity of some components of the autonomic nervous system, assessed by the HRV in CHF patients.

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Ocena wpływu wieczornej dawki długo działającego beta-blokera na układ autonomiczny chorych z zastoinową niewydolnością serca

Ryszard Targoński[1], Janusz Sadowski[2]

[1] Wydział Nauk Medycznych, Uniwersytet Warmińsko-Mazurski, Olsztyn
[2] Miejski Szpital Zespolony, Olsztyn

Streszczenie

Wstęp: Zastoinowa niewydolność serca jest istotną przyczyną zaburzeń neurohormonalnych, poprzez nadmierną stymulację układu współczulnego, wiodących do wzrostu częstości nagłych zgonów. Wskaźniki zmienności rytmu serca (HRV) są akceptowanymi wykładnikami napięcia układu autonomicznego i mogą być stosowane do oceny wpływu beta-blokady u chorych z zastoinową niewydolnością serca. W związku z większą częstością nagłych zgonów sercowych w godzinach rannych powstaje pytanie, czy wieczorna dawka długo działającego beta-blokera nie jest bardziej skuteczna od dawki porannej.

Cel: Porównanie wskaźników HRV po porannym i po wieczornym podaniu długo działającego beta-blokera.

Metody: Badaniem objęto 52 pacjentów (30 mężczyzn i 22 kobiety, średnia wieku 67,2 ± 10,6 roku) z zastoinową niewydolnością serca w II i III klasie wg NYHA, z rytmem zatokowym, otrzymujących pełne leczenie, w tym inhibitory konwertazy angiotensyny (ACE-I), spironolakton, diuretyki pętlowe i beta-bloker. W pierwszym okresie, trwającym 5 dni, beta-bloker podawany był w godzinach rannych (8:00–9:00), po czym dokonywano 24-godzinnej rejestracji EKG metodą Holtera. Następnie zmieniano czas podawania tej samej dawki długo działającego beta-blokera na godziny wieczorne (17:00–18:00) i po następnych 72 godz. ponownie wykonywano 24-godzinną rejestrację EKG metodą Holtera. Analiza HRV została przeprowadzana w dwóch zakresach: analizy czasowej i częstotliwościowej. Oceniono 3 okresy czasowe – okres dzienny, nocny i wyniki rejestracji całodobowej po 5-dniowym stosowaniu dawki rannej i następnie po 3 dniach stosowania dawki wieczornej.

Wyniki: Po podaniu dawki wieczornej średnia częstotliwości rytmu w rejestracji całodobowej była znamiennie niższa ($p = 0,01$), a interwały NN w nocy były istotnie statystycznie wydłużone ($p = 0,008$). Iloraz niskich częstotliwości (LF) do wysokich częstotliwości (HF) był statystycznie istotnie niższy w rejestracji 24-godzinnej ($p = 0,0002$), w okresie obejmującym aktywność dzienną ($p = 0,003$) i w nocy ($p = 0,008$), a wartości HF okazały się znamiennie wyższe dla rejestracji 24-godzinnej ($p = 0,0007$) i rejestracji dziennej ($p = 0,006$).

Wnioski: Dawka wieczorna beta-blokera skuteczniej niż poranna odwracała niekorzystne zmiany niektórych wskaźników napięcia układu autonomicznego ocenianych na podstawie HRV wśród chorych z zastoinową niewydolnością serca.

Słowa kluczowe: niewydolność serca, częstotliwość rytmu, beta-blokada, autonomiczny układ nerwowy

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Adres do korespondencji:
dr n. med. Ryszard Targoński, Wydział Nauk Medycznych, Uniwersytet Warmińsko-Mazurski, ul. Żołnierska 14c, 10-561 Olsztyn,
tel.: +48 89 524 61 54, faks: +48 89 524 61 54, e-mail: rtarg@op.pl
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