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HEART RATE VARIABILITY IN PATIENTS WITH CHRONIC RHEUMATIC HEART DISEASE

Abstract

Objective. Evaluation of heart rate variability in patients with rheumatic heart disease. **Material and methods.** The study enrolled 230 patients, of whom 156 patients with mitral stenosis (CRHD), 36 patients with mitral valve regurgitation, and 38 patients with acquired aortic stenosis were selected. CHF functional class was determined using a 6-minute walk test according to the standard method; there were no patients with FC IV. HRV values were obtained using the Kardiotehnika-04-3R (M) cardiorespiratory monitor with an estimation of time domain and frequency domain. **Results.** The CRHD patients had lower HRV indicators in the time (SDNN — 126.38 ms, SDANN — 112.07 ms, RMSSD — 32.79 ms) and frequency domain (VLF — 2,098.59 ms²; LF — 865.39 ms², HF — 323.48 ms²) compared with patients with mitral valve regurgitation and aortic stenosis. Evaluation of HRV within patients with CRHD, depending on the presence or absence of combined mitral-aortic stenosis, did not show differences in the general and sympathetic tone of the ANS. In patients with combined mitral-aortic stenosis, only a decrease in parasympathetic tone was revealed: RMSSD — 31.18 ms, HF — 286.36 ms². Stratification of patients according to FC CHF showed an increase in parasympathetic tone: RMSSD was 26.67 ms for FC I and 43.69 ms for FC III; HF was 254.67 ms² for FC I and 541.23 ms² for FC III. The sympathetic and general tone of the ANS was minimal in patients with FC II CHF. A study of the change of indicators over 5 years did not demonstrate a significant increase in the time domain, and the main indicators of the frequency domain decreased significantly: VLF from (1,882.73 ± 119.48) to (1,603.54 ± 99.22) ms²; HF from (334.34 ± 33.13) to (252.87 ± 17.84) ms², LF from (819.48 ± 94.41) to (647.01 ± 42.50) ms². A decrease in the frequency domain was also observed when comparing the HRV results of survived and deceased patients. **Conclusions.** The patients with CRHD had lower values of the ANS tone in comparison with patients with other acquired heart valve disease. The smallest values of the general tone of the ANS and SNS were observed in those studied with CRHD with FC II CHF, and the activity of the PNS was maximum at FC III. After 5 years of follow-up, only the frequency indices of HRV were significantly reduced.

Key word: *rheumatic heart disease, heart rate variability, chronic heart failure*

Conflict of interests

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AS — aortic stenosis, ANS — autonomic nervous system, HRV — heart rate variability, MVR — mitral valve regurgitation, PNS — parasympathetic nervous system, SNS — sympathetic nervous system, FC — functional class, CRHD — chronic rheumatic heart disease, CHF — chronic heart failure, HF — high-frequency component of the spectrum, LF — low-frequency component of the spectrum, pNN50 — percentage of NN50 of the total number of successive NN interval differences, RMSSD — root mean square of successive NN intervals, SDNN — standard deviation of NN intervals for

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the considered period, SDNNidx — average standard deviations for all 5-minute sections, VLF — very-low-frequency component of the spectrum.

Heart rate variability (HRV) assessment in various conditions has been of interest for many years. In cardiology, this is because low HRV values are associated with the risk of sudden cardiac death and the number of ventricular arrhythmias [1]. Rhythms with low variability are observed in case of impairment of the autonomic regulation of the heart function and damage to the automatic cells of the main pacemaker [2]. An increase in the activity of the sympathetic nervous system (SNS) with a change in baroreflex effects on the heart function is considered one of main mechanisms of hypertension development, which leads to left ventricular hypertrophy and progression of renal failure [3]. However, the data evaluating HRV are often contradictory [4].

The outcome of cardiovascular disease is chronic heart failure (CHF) accompanied by an increase in SNS activity and a decrease in the parasympathetic nervous system (PNS) tone. Initially, increased activity of the SNS is a compensatory mechanism that serves to maintain cardiac output. However, as the systolic function of the left ventricle decreases, increased activity of the SNS leads to the progression of CHF. In CHF, there is a decrease in baroreflex and an increase in cardiac afferent and chemoreceptor reflexes [5]. Developing decompensation of CHF is accompanied by a decrease in HRV, and effective treatment leads to an improvement in HRV to the values of compensated patients [6]. Although HRV cannot be attributed to standard cardiovascular risk factors [7], the tool that allows to evaluate the activity of the autonomic nervous system (ANS) should not be disregarded [8].

In recent times, HRV analysis has been carried out using the time domain, the frequency domain (spectral analysis), geometric and nonlinear analysis [9]. Mostly, time domain analysis of HRV is used, which is based on the analysis of changes in successive RR (NN) intervals with an estimate of the duration and the difference in the duration of adjacent NN intervals. The integral indicator, which reflects the entire period of HRV observation, depending on SNS and PNS activity, is the standard deviation from the average duration of all sinus intervals. Spectral methods of HRV assessment allow

to analyze the frequency components of rhythm oscillations quantitatively [10]. The respiratory component of the spectrum shows the activity of the PNS, and the activity of the vasomotor center and SNS underlies the vasomotor component of the spectrum.

Literature that describes HRV is more often devoted to patients with hypertension and coronary heart disease, which are the main causes of CHF. There are few works related to the follow-up monitoring of patients with chronic rheumatic heart disease (CRHD) [11] and the assessment of HRV impairment in heart failure associated with acquired heart disease.

The objective was to evaluate HRV in patients with heart failure associated with CRHD.

Materials and Methods

The study enrolled 230 patients. All of the patients signed informed consent and underwent examination at the regional cardiology clinic. One hundred and fifty-six patients with Echo signs of mitral stenosis were selected in the CRHD group (determined by the area of the mitral valve orifice and the average pressure gradient on the mitral valve). CRHD was diagnosed taking into account the data of outpatient and discharge records, medical history, and history of acute rheumatic fever. Patients with congenital heart disease, connective tissue disease and possible non-rheumatic causes of mitral stenosis were excluded from the study. The average age was (55.35 ± 0.69) years; 132 women (84.6%) and 24 men (15.4%). The two comparison groups included patients without a history of acute rheumatic fever: with mitral valve regurgitation (MVR), determined via Doppler echocardiography according to the regurgitation flow (average age (52.13 ± 9.67) years; 28 women (77.8%) and 8 men (22.2%)) and with acquired aortic stenosis (AS) determined according to the pressure gradient across the valve (average age (55.54 ± 9.05) years; 15 women (39.5%) and 23 men (60.5%)). NYHA functional class (FC) of CHF was determined using a 6-minute walk test according to the

standard method [12]; patients with FC IV were not enrolled because they had atrial fibrillation. HRV values were obtained using Kardiotekhnika-04-3R (M) cardiorespiratory monitor, Inkart. The time and frequency domains were also evaluated; the recording time was reduced to 24 hours. The time domain was estimated using the following indicators: standard deviation of NN intervals for the considered period (SDNN, ms); standard deviation of the average NN intervals for all 5-minute sections (SDANN, ms); average standard deviations for all 5-minute sections (SDNNidx, ms). The difference in the duration of the NN intervals was assessed by the percentage of NN50 of the total number of successive pairs of NN intervals (pNN50, %); the root mean square of successive NN intervals (RMSSD, ms) [13]. The frequency domain was evaluated by: low-frequency band with power from 0.04 to 0.15 Hz (LF); very-low-frequency band with power below 0.04 Hz (VLF); high-frequency band with power from 0.15 to 0.40 Hz (HF). HRV re-assessment was carried out after 5 years of follow-up. Statistical data were processed using IBM SPSS Statistics 23.0. Verification of distribution normality for quantitative indicators was carried out using the Kolmogorov — Smirnov test. In the normal distribution, M (mean), m (standard error), CI (95%

confidence interval for the mean), and p (achieved significance level) were calculated. The differences were considered statistically significant at $p < 0.05$. Quantitative indicators in the groups were compared using Student's t-test; ANOVA was used for multiple comparison.

Results

Comparison of HRV assessment results in the groups with various valve disease (Table 1) shows an increase in the general tone of the ANS (SDNN — 140.10 ms), the activity of the central regulatory mechanisms (VLF — 2,830.47 ms²) and sympathetic tone in both the time domain (SDANN — 123.10 ms) and the frequency domain (LF — 1,374.93 ms²) in the group of mitral valve regurgitation. The lowest general tone of both ANS and SNS was observed in patients with CRHD, and those with AS had intermediate values of HRV. The PNS tone assessed via time indicators did not significantly differ, although it was highest in the groups with MVR (RMSSD — 35.00 ms) and AS (RMSSD — 35.70 ms). In the frequency domain of the PNS assessment, the situation was similar to the general tone of the ANS and SNS: HF was highest in the group with MVR — 436.17 ms², and lowest in the CRHD group — 323.48 ms².

Table 1. Heart rate variability in rheumatic heart disease, mitral valve regurgitation and aortic stenosis groups

HRV indicators	CRHD M (CI 95%)	MVR M (CI 95%)	AS M (CI 95%)	p
SDNN (ms)	126.38 (121.84; 130.92)	140.10 (134.75; 145.45)	131.81 (125.18; 138.44)	0.001
pNN50 (%)	7.62 (6.81; 8.43)	7.90 (6.37; 9.43)	7.86 (6.63; 9.10)	0.888
RMSSD (ms)	32.79 (30.81; 34.77)	35.00 (31.83; 38.17)	35.70 (32.54; 38.87)	0.522
SDNNidx (ms)	46.60 (44.77; 48.42)	54.30 (51.69; 56.91)	50.65 (48.01; 53.29)	0.001
SDANN (ms)	112.07 (107.68; 116.46)	123.10 (117.93; 128.27)	116.89 (110.35; 123.43)	0.002
VLF (ms ²)	2,098.59 (1,847.04; 2,350.15)	2,830.47 (2,437.10; 3,223.83)	2,331.16 (2,059.70; 2,602.63)	0.001
LF (ms ²)	865.39 (743.98; 986.80)	1,374.93 (1,152.97; 1,596.90)	1,010.57 (881.78; 1,139.35)	0.001
HF (ms ²)	323.48 (283.83; 363.12)	436.17 (328.51; 543.83)	356.65 (304.17; 409.12)	0.021

Note. AS is aortic stenosis, HRV is heart rate variability, CI is confidence interval, MVR is mitral valve regurgitation, CRHD is chronic rheumatic heart disease.

Table 2. *The effect of combined mitral-aortic stenosis on heart rate variability in rheumatic heart disease*

HRV indicators	CRHD without AS M (CI 95%), n = 114	CRHD with AS M (CI 95%), n = 42	p
SDNN (ms)	127.83 (122.45; 133.20)	120.75 (113.28; 128.22)	0.301
pNN50 (%)	7.28 (6.39; 8.17)	8.94 (6.96; 10.91)	0.186
RMSSD (ms)	31.18 (29.33; 33.03)	39.06 (32.67; 45.46)	0.028
SDNNidx (ms)	47.17 (45.14 ; 49.20)	44.38 (40.15; 48.60)	0.238
SDANN (ms)	113.45 (108.25; 118.65)	106.69 (99.41; 113.96)	0.469
VLF (ms ²)	2,159.86 (1,862.84; 2,456.87)	1,860.25 (1,429.58; 2,290.92)	0.227
LF (ms ²)	799.33 (695.77; 902.89)	1,122.38 (682.02; 1,562.73)	0.926
HF (ms ²)	286.36 (252.83; 319.89)	467.88 (326.86; 608.89)	0.027

Note. AS is aortic stenosis, HRV is heart rate variability, CI is confidence interval, CRHD is chronic rheumatic heart disease.

Table 3. *Heart rate variability change in survivors with rheumatic heart disease, 5-year follow-up*

HRV indicators	Initial M ± m, n = 135	After 5-year follow-up M ± m, n = 135	p
SDNN (ms)	122.91 ± 3.44	119.41 ± 3.25	0.170
pNN50 (%)	7.55 ± 0.58	6.42 ± 0.57	0.078
RMSSD (ms)	33.29 ± 1.69	30.91 ± 1.14	0.145
SDNNidx (ms)	46.55 ± 1.28	43.73 ± 1.19	0.002
SDANN (ms)	108.24 ± 3.25	106.00 ± 3.09	0.376
VLF (ms ²)	1,882.73 ± 119.48	1,603.54 ± 99.22	0.015
LF (ms ²)	819.48 ± 94.41	647.01 ± 42.50	0.072
HF (ms ²)	334.34 ± 33.13	252.87 ± 17.84	0.011

Note. HRV is heart rate variability.

Since HRV values differed in patients with CRHD and AS, we decided to divide the patients with mitral stenosis into two groups: with combined mitral-aortic stenosis (CRHD with AS) and without combined mitral-aortic stenosis (CRHD without AS), and to compare HRV values in these groups (Table 2). It turned out that only PNS indicators significantly differed, and their values were higher in the group of CRHD with AS: in the time and frequency domains: RMSSD — 39.06 ms, HF — 467.88 ms². Differences in general tone and SNS between groups were not obtained. A linear regression analysis showed the dependence of the area of the mitral valve orifice on HRV indicators: HF (p = 0.003), SDANN (p = 0.037), VLF (p = 0.018), LF (p = 0.302), RMSSD (p = 0.001), SDNN (p = 0.022). Five years later, in patients who maintained sinus rhythm, there was a decrease in the indicators of the time domain analysis (Table 3): SDNN by 3.5 ms, RMSSD by 2.38 ms, SDANN by 2.24 ms, and pNN50 by 1.13%. These changes, however,

were not significant, except for a decrease in SDNNidx by 2.82 ms. The values of the spectral analysis indicators reduced significantly: VLF by 279.73 ms² and by HF by 81.47 ms²; a decrease in LF by 172.47 ms² was insignificant. It is important that HRV indicators differed depending on CHF FC, determined by the 6-minute walk test (Table 4). RMSSD and pNN50%, which reflect PNS activity, increased from FC I to FC III. Similarly, the frequency domain index (HF) almost doubled in FC III, in comparison with FC I and FC II CHF. In the time domain, SDANN, which reflects SNS activity, was minimal in the group with FC II CHF, although there was no significant difference between the groups. However, according to the frequency domain in the group with FC II, LF, which also reflects SNS activity, was minimal. Similarly to the SNS tone, the general tone varied: SDNN and VLF, reflecting the function of central regulation mechanisms, which were minimal in FC II CHF. Over a five-year follow-up period, 10 patients died (out of 156) and the initial HRV values in the group

Table 4. Heart rate variability depending on function class of chronic heart failure

HRV indicators	FC I M (CI 95%), n = 21	FC II M (CI 95%), n = 90	FC III M (CI 95%), n = 45	P
SDNN (ms)	138.83 (121.73; 155.93)	122.07 (112.98; 131.15)	139.00 (128.13; 149.87)	0.032
ρNN50 (%)	6.17 (2.79; 9.54)	5.53 (4.40; 6.67)	10.54 (8.51; 12.57)	0.001
RMSSD (ms)	26.67 (20.74; 32.59)	29.06 (26.43; 31.69)	43.69 (36.68; 50.71)	0.001
SDNNidx (ms)	53.51 (44.11; 62.89)	42.79 (39.77; 45.81)	54.69 (49.66; 59.73)	0.001
SDANN (ms)	119.67 (104.58; 134.75)	109.66 (100.73; 118.59)	119.54 (109.04; 130.04)	0.192
VLF (ms ²)	2,743.67 (1,647.82; 3,839.52)	2,219.58 (1,609.45; 2,829.71)	2,678.00 (2,112.18; 3,243.82)	0.001
LF (ms ²)	1,074.50 (634.76; 1,514.24)	777.96 (579.47; 976.46)	1,463.31 (944.10; 1,982.52)	0.001
HF (ms ²)	254.67 (168.44; 340.89)	219.66 (184.75; 254.57)	541.23 (369.85; 712.61)	0.001

Note. HRV is heart rate variability, CI is confidence interval, FC is function class.

Table 5. Heart rate variability in survived and deceased subjects

HRV indicators	Survived M (CI 95%), n = 146	Deceased M (CI 95%), n = 10	P
SDNN (ms)	125.86 (121.62; 130.10)	134.00 (96.73; 171.27)	0.345
ρNN50 (%)	7.74 (6.90; 8.59)	5.80 (2.76; 8.84)	0.153
RMSSD (ms)	33.20 (31.13; 35.27)	26.80 (20.25; 33.35)	0.107
SDNNidx (ms)	46.98 (45.17; 48.79)	41.00 (29.69; 52.31)	0.004
SDANN (ms)	111.31 (107.21; 115.41)	123.20 (87.15; 159.25)	0.613
VLF (ms ²)	2,108.81 (1,852.38; 2,365.23)	1,949.00 (663.51; 3,234.49)	0.003
LF (ms ²)	894.67 (766.23; 1,023.10)	436.40 (234.20; 638.60)	0.001
HF (ms ²)	333.45 (291.62; 375.28)	177.40 (97.55; 257.25)	0.014

Note. HRV is heart rate variability, CI is confidence interval.

of the deceased and those who survived were compared. Comparison of time domain HRV values in patients with CRHD (Table 5) showed a decrease in PNS (ρNN50, RMSSD) and an increase in general ANS tone (SDNN) and SNS tone (SDANN), but the differences between the groups were insignificant. Only a decrease in SDNNidx was significant. However, all frequency domain indicators (VLF, LF, HF) in deceased patients were significantly reduced.

Discussion

A comparison of patients with CRHD, AS and MVR in terms of time domain indicators shows a lower general ANS tone and SNS tone in the CRHD

group. Frequency domain indicators showed a similar pattern: the lowest values of SNS and PNS tone and VLF were observed in the CRHD group. The highest HRV values were observed in the group with MVR, and intermediate — in the group with AS. Since valve regurgitation, as a rule, is asymptomatic for a long time, and decompensation occurs late, it is clear why HRV values reflecting the exertion of regulatory systems were the best in the group with MVR. In the literature, the decrease in the variability values in AS is described in patients with asymptomatic AS and even a connection between the reduced indicators and mortality is indicated [14]. But does the combination of MS and AS have an additional effect on HRV? It turned out that HRV values did not differ in both time

and frequency domains (neither the ANS general tone, nor the SNS tone) in the CRHD group with or without mitral-aortic stenosis. Only the effect of combined mitral-aortic stenosis on the PNS tone with a decrease in time and frequency domains was revealed. Probably, in the case of two-valve stenosis, PNS is activated as a compensatory reaction to hemodynamic cardiac changes. Linear regression analysis showed a relationship between the main indicators of the time and frequency domains of HRV and the area of the mitral valve orifice.

After 5 years, in patients with CRHD, HRV values decreased in both time and frequency domains, but the decrease was not significant in the time domain. This is probably due to the slow progression of CHF and a gradual change in neurohumoral activation, or perhaps no significant changes of the ANS general tone and the SNS tone should be expected in CRHD. Since in CHF the compensatory activation of SNS is associated with impairment of the cardiac pumping function and a decrease of the ejection fraction [40], which are usually absent in CRHD. In the frequency domain, HRV in the group of CRHD decreased significantly: VLF reflecting the action of central ergotropic and humoral-metabolic regulation mechanisms [2], and HF reflecting the activity of the parasympathetic cardioinhibitory center of the medulla oblongata. Apparently, the decrease in these HRV indicators is associated not only with the gradual progression of CHF [13], but also with the possible depletion of the ANS regulatory mechanisms against the background of mitral stenosis with a decrease in the PNS tone. Clarification of emerging issues may require a longer follow-up period for patients with CRHD.

It is believed that there is a significant relationship between the severity of heart failure and HRV: in patients with CHF FC I–II, there is a moderate decrease in total HRV associated with inhibition of PNS and increased activity of the SNS [2]. In CHF FC III–IV, a significant decrease in total HRV already exists against the background of the autonomic denervation of the heart. The latter leads to a significant decrease in all indicators of HRV and normalization of the vagosympathetic balance [40]. However, this is true primarily for patients with heart failure associated with coronary heart disease, cardiomyopathies, and hypertension. In patients with CRHD, an assessment of the

frequency and spectral indicators of HRV showed a significant increase in the PNS tone in the group of CHF FC III. The minimum values of the indicators of total HRV, sympathetic and parasympathetic tone were observed in patients with CHF FC II, which distinguishes patients with CRHD from patients with CHF associated with coronary heart disease and hypertension.

In deceased patients, in terms of the time domain, there was an increase in the general and sympathetic tone of the ANS with a decrease in the tone of the PNS, but the indicators did not reach statistical significance. In patients with coronary heart disease and post-infarction cardiosclerosis, SDNN and SDANN usually decrease [4, 2]. The results are probably associated with a small group of deceased patients, and data collection for a longer follow-up period and in the larger group will show the direction of movement of time domain HRV values. A different situation was observed in patients with CRHD in frequency domain terms. And the slow Mayer second-order waves (VLF) associated with blood plasma renin, angiotensin and aldosterone; and slow Traube — Goering first-order waves (LF); and the values of the high-frequency (respiratory) range (HF²) in the deceased group were significantly lower than in patients who survived. Thus, we can assume a decrease in the activity of the humoral-metabolic regulation mechanisms of both the superior sympathetic thoracic ganglion and the cardioinhibitory center of the medulla oblongata with a decrease in vagus nerve activity in deceased patients with CRHD. The described HRV changes are probably associated with changes in the geometry and structure of the cardiac chambers, since patients did not have data for acute rheumatic fever at the time of HRV assessment.

Conclusion

Therefore, a decrease in the general ANS tone was observed in CRHD patients in comparison with patients with MVR and AS. The minimal values of the general tone of the ANS and SNS were registered in patients with CHF FC II, while PNS activity increased to the maximum in CHF FC III. After five-year follow-up, a decrease in both time and frequency domain indicators of HRV was noted, but significant changes were obtained only for VLF

and HF. The situation was similar in the deceased patients with lower values of the frequency domain indicators in comparison with the patients who survived.

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