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Use of the Method of Heart Rate Variability Analysis for the Assessment of Functional-Clinical State of Patients with Chronic HF, its Prognosis and the Effectiveness of the Standard Treatment.

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In this review, data about the heart rate variability (HRV) assessment in patients with chronic HF and the prognostic value of spectral and time analysis indicators are presented. The effect of the main drugs used for the treatment of HF on the HRV is described.

Key words: chronic heart failure, heart rate variability, prognosis.

Currently, the world incidence of chronic HF is 1-3% in the population under 70 years old, and 10% among those above 70 years old. About 1 million new HF cases are diagnosed annually (1). Studies of the incidence of such disease in the different countries indicate: 6.5 million diseased people in Europe, 5 millions in the United States, and 2.4 millions in Japan (2). In Russia, no less than 3-3.5 million patients suffer the impairment of their ventricular function and decompensated HF symptoms (3).

According to statistical data, 35-40% of HF patients die within the first year of diagnosis. Within 5 years, mortality reaches 75%. In spite of the new treatment methods, chronic HF remains widespread, worsening the socio-economic aspects of patients' life, their physical capacity and life quality in general. For these reasons, the development of more effective diagnosis, treatment and prognosis methods is one of the important issues in current cardiology (4).

The present pathophysiological chronic HF model is neurohormonal. It is considered that, the impairment of the ventricular function and the decrease of ejection fraction (EF) lead to the descent of BP and the activation of the sympathetic nervous system (SNS), which causes tachycardia and peripheral vasoconstriction (5). Initially, the SNS activation is counterbalancing, since it improves EF and redistributes peripheral circulation to the heart and muscles. Renal vasoconstriction, at this moment, produces sodium and water retention, which improves the perfusion of important organs. Nevertheless, the continuous increase of the SNS tone stimulates

the adverse effect chain, as increase of oxygen consumption, worsening of ischemias and arrhythmias. It also produces direct effects on the myocardium (remodeling, hypertrophy, apoptosis, and cardiomyocyte necrosis) (6).

The simplest indicator reflecting the effect of the autonomous nervous system (ANS), is HR during 24 hours. For the assessment of the circadian dynamics the circadian index is used (the relationship between the mean day HR and the mean night HR) (7). In the Molgnart H. and Staessen J. (8) studies, which included 140 and 6975 patients respectively, the circadian indexes were 1.24 and 1.42. For patients with cardiovascular pathology, the decrease of the circadian index is typical, especially for patients with chronic HF. According to Casolo G. et al (9) data, such index, in patients in FC III, who died because of their HF decompensation, it was 1.03, in comparison to 1.09 in the patients who survived. In a similar study by Ilio T. et al, indexes were 1.05 and 1.19, respectively. The data obtained show the damage in the intracardiac nervous system and the progression of autonomous heart denervation (7).

Heart rate variability (HRV) provides the most complete view about the influence of ANS on heart activity. The term *"heart rate variability"* refers to changes in the duration of normal RR intervals (10). There are different levels of HR regulation. The first level (intrasystemic) guarantees homeostasis of the cardiorespiratory system (the circulatory and the respiratory systems may be considered as the only functional system). The vasomotor and respiratory centers develop an important role at this level: they stimulate or inhibit heart activity through the sympathetic and parasympathetic nerves. Precisely, at this level, the regulation of the RR interval duration is carried out, related to breathing (respiratory arrhythmia) (11). The second level (intersystemic) guarantees the balance between the different organism systems, through the hypothalamus and the hypophysis. The third (central) one supervises the interaction between the organism and the environment (organism adaptation). This level is located in the central nervous system, including the cerebral cortex. On the second and third level, the non-respiratory sinus arrhythmia regulation is carried out, which consists in the variation of HR in the larger periods of 6-7 sec. The slow non-respiratory waves of 1º, 2º and higher degrees are differentiated. The slow 1º-degree waves correlate to the similar waves of blood pressure (BP). The purpose of the non-respiratory waves of the highest degrees is not yet defined (12).

Thus, HRV reflects the numerous regulatory effects on the circulatory system with the interference of the periodic components of different frequency and amplitude, with the non-linear interaction character of the different levels of regulation (13). For the quantitative assessment of

RR intervals, the time and spectral HRV analysis is performed. The base of the time method is the statistical calculus of a certain amount of RRs with the following physiological and clinical interpretation of the data obtained. The standard deviation of the SDNN and SDANN indicators is used for the analysis of consecutive RR intervals (10).

The rMSSD and pNN50 indicators evaluate the degree of difference between the contiguous RR intervals. In the case of absence of variability ("fixed" rhythm, typical of autonomous denervation), these indicators approach to zero. These indicators reflect the vagal effect. The increase of HRV time parameters indicates an increase of the parasympathetic effects and a decrease of the sympathetic influences (13).

According to the data by Umetani K., Singer K. et al (14), who studied 102 healthy people, between 30 and 60 years old, the SDNN indicator turned out to be 120-150 ms in average, SDANN – 115-140 ms, rMSSD - 25-40 ms, pNN50 7-18%. The superior and inferior limits of HRV time indicators in healthy 30-year-old people from the same study were: SDNN 86-237 ms, SDANN 73-223 ms, rMSSD 18-74 ms, pNN50 2-68%.

For diseased people with chronic HF, decrease in time indicators is characteristic (7). In the UK – Heart (15) study 443 FC I-III patients with chronic HF were included, with a mean age of 62 ± 96 years old and EF of 41 ± 17%. A decrease in SDNN was found, depending on HF severity level, and besides, concomitantly with the decrease of SDNN, an increase in the death risk and progression of disease were observed. Among patients with SDNN < 100 ms, during the first year of study 5.5% died; out of those with SDNN between 50-100 ms and less than 50 ms, 12.7% and 51.4% died respectively. The SDNN of the patients who survived was 116.6 ± 39.3 ms and for those who died was 93.4 ± 48.1 ms. The rMSSD value in those who survived was 22 ± 12 ms, and in those who died, 19 ± 8 ms, which indicates the vagal tone decrease adjusted to chronic HF progression.

In the study by Galiner M. et al (16), survival of 190 patients with FC II-IV chronic HF (EF < 45%) was analyzed. Mortality 3 years later among sick people presenting SDNN < 67 ms, and among those who had SDNN > 67 ms was 55.9% and 30.6% respectively.

The mathematical analysis of the heart rate not only enables evaluating the statistical indicators of HRV, but also presenting them graphically. This is the base of the geometrical methods of heart rate analysis, which is included in the time analysis method (12).

The main technique of geometrical analysis is the preparation and analysis of heart rate histograms. The idea of this method is the unification of similar RR intervals in separate polygons and the presentation of the obtained data, graphically. In the graphic of the histogram it is possible to assess the most frequent RR duration (mode), the maximum and minimum values of RR and their difference (7). In Russian literature, the difference between the maximum and minimum values is called "*вариационный размах*" and it correlates to vagal activity (12). In foreign literature, the term *"triangular interpolation of NN intervals"* (TINN) is used. With the histogram graphic the triangular index is calculated (HRVti), which is the relationship between the total quantity of RR intervals and the modal polygon intervals (17).

According to Farell T. et al data (18), the triangular index of HRV correlates to the SDNN indicator (r = 0.84) and it characterizes the general HRV; on the other side, the TINN correlates to rMSSD and pNN50 (r = 0.76) and determines the parasympathetic activity.

One of the most appropriate geometric methods to evaluate HRV is correlational rhythmography (scattergram). According to the data from the de Ramaekers D. et al (19) study, which included 276 healthy people between 30 and 60 years old, the "comet"-shaped scattergram was in 96% of cases and was considered normal. In the study by Bonaduce D., Petretta M. et al (20), 97 patients with EF < 40% and mean age 55 ± 13 years old were included. Fifty-six (58%) patients presented as their HF etiology, ischemic disease, and 40 (41%) – idiopathic dilated cardiomyopathy. Fifty-six (58%) patients were in FC II, and forty-one (42%), in FC III-IV. Among patients with FC II, mean values of SDNN, rMSSD and pNN50 were 124±38 ms, 65±31 ms, and 14±13 ms, respectively, and in the 75% of cases, scattergrams presented pathological forms (*complex*). In FC III-IV patients, mean values of SDNN, rMSSD and pNN50 turned out to be 98±38 ms, 45±27 ms, and 10±4 ms, respectively, and the pathological form of the scattergram was present in 80% of cases. Among the patients who died (33%), the pathologic scattergram was observed in 81% of cases and among the surviving people – in 55%.

In the Woo J. et al (21) study, with 21 FC III patients, a correlation between the plasmatic level of noradrenalin and the amount of pathologic forms (*complex*) of scattergrams was found (r = 0.67). The data obtained indicate that the form of the scattergram depends on the sympathetic activity.

Presently, spectral analysis methods of HRV are widely used. The analysis of spectral density of oscillation power provides information about power redistribution, according to the

oscillation frequency. The use of spectral analysis allows the quantitative assessment of the different frequencies that constitute heart rate oscillation, and the graphic visualization of the relationships between the different components of heart rate, which reflect the activity of certain regulatory components (11). The high frequency component (respiratory) - HF - reflects the parasympathetic activity of the ANS. During vagal tests, the power of this sampling increases (7).

The base of the low frequency components (vasomotor) - LF - is the activity of the vasomotor center and the sympathetic system. The power of such spectrum increases in healthy people, during physical or mental activity (12).

In the study by Bonaduce D., Petretta M. et al (20), which included 97 patients in FC II – IV, ECG monitoring was carried out with assessment of HRV for 24 hours. The correlation between the indicators of time and spectral analysis was estimated. The correlation between high frequencies and rMSSD was 0.72, between high frequencies and pNN50 – 0.68, and for low frequencies and SDNN – 0.85 ($p < 0.01$).

The balance between the sympathetic and parasympathetic activity is assessed as the relationship between high and low spectrum components (LF/HF) (10).

The physiological importance of oscillations in the very low frequency sampling (VLF) has not yet been studied. Some authors consider that the base of VLF is the sympathetic activity; however, in this case, it is about the most complex influences of the suprasegmentary regulatory level, since the VLF amplitude is closely related to the state of psychic tension and cerebral cortex (17). In the Fleishman A.N. et al (22) study, during the performance of functional tests (hyperventilation, calculations without pronouncing numbers, etc.) the change of power in the VLF sampling was recorded, which according to the author's opinion, is a sensitive indicator of the state of the organism energetic deficit (hypoxia, metabolic disorders) and reflects the relationship between the autonomic level (segmentary) of the circulatory regulation with the suprasegmentary level, which includes hypothalamus, hypophysis, and cerebral cortex. In a study by Mortara A., Sleight P. and coauthors (23) of FC II - IV patients, the relationship between VLF and the degree of dyspnea was found.

In the study by Saul J.P. et al, 25 patients with FC III-IV and 21 healthy people were included as a control group. In the FC III – IV patients, a decrease in all spectral parameters was observed, especially in the diapason < 0.04 Hz (VLF), until the disappearance of such spectral component, which was explained as the decrease of ANS influence in this category of patients. In

recent years, great attention has been paid to the prognostic value of HRV. In a study by Galinier M., Pathak A. et al (16) 190 patients with chronic HF were included, mean age 61±12 years old, of which 109 (57.4%) were in FC II and 81 (42.6%) in FC III – IV. ECG monitoring during 24 hours was carried out in all the patients, with HRV assessment. During the 3-year follow-up, 55 patients died, of which 22 presented sudden cardiac death. Mortality along 3 years was 38.9%. Comparing HRV among the surviving patients and those who died, a marked decrease of SDNN was observed in the dead patients, from 91.3±36.1 ms to 69.3±31.7 ms; the decrease of SDANN was from 81.1±33.9 ms to 61±27 ms ($p<0.001$); the decrease of the general power of the spectrum, especially during the night period, from 6.3±1.2 to 5.7±1.3 ($p < 0.0015$) and, also the decrease of LF, especially at night, which varied from 4.1±1.2 to 3.7±1.2 ($p < 0.0016$). The most revealing indicators were SDNN, SDANN, TP and night LF. For example, mortality 3 years later among patients with SDNN < 67 ms was 55.9%, in comparison to 30.6% in the group with SDNN > 67 ms ($p < 0.0001$); besides, the decrease of SDNN was related to the risk of sudden death. Among patients with night LF <3.3 ($p<0.007$), mortality 3 years later was 3%, in comparison to 14.6% of patients with LF >3.3 ($p<0.007$). Night decrease of LF was related to the increase of death risk because of HF progression, and according to the authors, it indicated the decrease of the vagal effect on cardiac regulation.

The prognostic value of SDNN was confirmed in the study by Ponikowski P. et al (24), which included 102 patients with heart disease and HF. The decrease of SDNN < 100 ms was an independent predictor of mortality because of HF progression.

In a study by Bonaduce D., Petretta M. who analyzed HRV in 32 patients, dead due to HF progression, in comparison to 65 surviving patients, a significant decrease of all spectral parameters was noticed, especially LF/HF, from 1.85±0.53 to 1.3±0.2 ($p < 0.01$), which was explained as the decrease of sympathetic influence on heart activity. Besides, the relationship LF/HF with end diastolic volume (EDV) of LV ($r = 0.52$; $p < 0.0001$) was observed.

In recent years, the relationship between HRV and the types of death in HF was studied. There were 330 patients with HF, mean age 54±5, who were included in a study by Guzzeti St., La Rovere M.T. (25). During the 3-year follow-up 108 patients died, of which 79 (24%) died due to progression of their HF and 29 (9%) due to sudden cardiac death. The decrease of VLF power in the night sampling < 509 ms was related to the decrease in EF < 24% and to an increase of pulmonary artery pressure (PAP) (> 18 mmHg), and also, it was a prognostic indicator for mortality because of HF progression. During the 3 years, mortality among patients without risk factors was

7%, with 1 risk factor it was 20%, with 2 factors 32%, and with 3 factors it increased to 44%. Night decrease in LF diapason < 20 ms was related to increase of EDV LV >61 mm and it was a prognostic indicator, regarding sudden death. During the 3 years, mortality among patients with 2 risk factors was 21%, in comparison to 8% among the sick ones without risk factors. The data obtained showed the decrease of sympathetic activity in advanced stages of HF.

In recent years, the relationship between the different medications, including beta-blockers, and HRV indicators was evaluated in many studies.

In a work by Belencov Y.N. and Mareev V.Y et al (26), the significant increase of SDNN was observed, from 98.3±39.1 to 119±51.6 ms in FC II - III patients who received carvedilol for 6 months. The 40% raise of SDNN, according to the authors, indicates the positive effect of the drug on HRV. Another study by Keeley E.C. et al (27) included 43 patients post AMI, of which 28 received metoprolol for 1 year. In the metoprolol group, a significant increase of rMSSD from 20±1 to 24±9 ms and pNN50 from 3.6±6 to 5.5±6% was observed, and that reflects the increase of vagal tone under treatment with metoprolol. The data regarding the influence of ACEIs on HRV are contradictory. In the study by Zhang Y.H. et al (28), in 12 patients with moderate HF, treated with enalapril during 6 months, an increase of SDNN was observed, from 119±13 to148±15 ms, rMSSD from 17±8 to 21±8 ms and pNN50 from 1.1±2.1 to 2.8±2.9%. According to the authors, enalapril influences in a positive way on HRV, activating the parasympathetic tone.

However, in the work by Belencov Y.N. and Mareev V.Y and coauthors (26), in patients with FC II - III, being treated with enalapril for 6 months, SDNN and SDANN virtually did not vary. The increase of SDNN towards the end of the treatment was 3.5%, and, regarding their initial level, SDANN values did not change.

Data in some studies show the absence of a significant effect of thiazide diuretics and ASA and also, digitalis, on the time and spectral indicators of HRV.

Studies in recent years revealed metabolic disorders of cardiomyocytes in HF. For the optimization of metabolic processes and prevention of adverse effects on cardiomyocyte function, cytoprotectors like trimethazidine (preductal MB) are used. Its action on HRV in patients with HF has not been studied enough. In a study by Ulgen M.S. et al (29), 31 post-AMI patients, treated with preductal MB were assessed. An increase of parasympathetic activity indicators (rMSSD, pNN50) and a reduction of LF / HF were observed. In another work by Davitashvili Y, Cobalava

Z.D., the effect of preductal MB was evaluated on HRV parameters in patients with AMI. An increase in the group indicators was observed, treated with such drug. Especially, SDNN and HRVti values increased, reflecting the general HRV and rMSSD, pNN50, HF values, showing vagal influence. Also, LF/HF diminished, expressing the decrease of sympathetic activity. Changes in the mentioned parameters correlate to the reduction of sudden death and complex arrhythmias probabilities. Also, among the groups receiving preductal MB, differences in the evolution of HF were observed. In the preductal MB group, 2% of patients died, in comparison to 12% from the control group. In the set of patients treated with preductal MB, 16% developed complex arrhythmias and needed urgent treatment, in comparison to 32% from the control group. The authors concluded that the inclusion of preductal MB in the treatment scheme of patients with AMI improves HRV parameters, and decreases significantly mortality and the probability of complex arrhythmias appearing.

To summarize the mentioned data, we came to the conclusion that there is a relationship between chronic HF and HRV. FC I - II patients are characterized by a moderate decrease in general HRV, due to inhibition of parasympathetic activity and increase of sympathetic activity. In FC III - IV patients, a significant decrease of general HRV is observed due to autonomous denervation, manifested as a significant decrease of all HRV indicators and the normalization of vagal-sympathetic balance. Disorders of ANS are confirmed by the decrease of the circadian index and absence of HRV for 24 hours. Nevertheless, the significance of circadian variations of HRV time and spectral indicators, its prognostic value in the evaluation of the course of the disease and the different causes of mortality in chronic HF, are not studied enough. Data of different studies show a positive effect of beta-blockers and the myocardial cytoprotector preductal MB on general HRV, due to the increase of vagal tone. The effect of other drugs used for chronic HF treatment, like ACEIs, ARAs II, digoxin, are not yet studied enough.

Bibliography:

1. Breithardt G. Foreword// Eur. Heart J.-2002.-№4.-C.1-2
2. McMurray J.J.V., Stewart S. Epidemiology, aetiology and prognosis of heart failure// Heart.-2000.-№83.-C.596-602
3. Беленков Ю.Н., Агеев Ф.Т. и соавт. Эпидемиология и прогноз хронической сердечной недостаточности// Русский медицинский журнал.-1999.-№2.-С.51-56
4. Беленков Ю.Н. Классификация хронической сердечной недостаточности// Сердечная недостаточность.-2001.-№6.-С.249-251

5. Лопатин Ю.М. Симпатико-адреналовая система при сердечной недостаточности: роль в патогенезе, возможности коррекции// Сердечная недостаточность.-2002.-№1.-С.20-21
6. Ferrari R., Ceconi C. Neuroendocrine activation in left ventricular dysfunction// Eur.Heart J.-1998.-№19.-С.1423-1424
7. Макаров Л.М. Холтеровское мониторирование.- Москва: Медпрактика-М, 2003.-С.65-115
8. Staessen L., Bieniaszewski L. Nosturnal blood pressure fall on ambulatory monitoring in a large international database// Hypertension.-1997.-№1.-С.30-39
9. Casolo G., Balli E., Taddei T. Decreased spontaneous heart rate variability in congestive heart failure// Amer. J.Cardiol.-1989.-№15.-С.1162-1167
10. Дабровски А., Дабровски Б., Пиотрович П. Суточное мониторирование ЭКГ.- Москва: Медпрактика, 1998.-208с.
11. Иванов Г.Г. Вариабельность сердечного ритма// «Современная электрокардиография: новые возможности и области применения в клинике» Сб. науч. трудов.-Москва.-2000.-С.24-27
12. Баевский Р.М. Анализ вариабельности сердечного ритма при использовании различных электрокардиографических систем: Метод. рек.- Москва, 2002.-С.487-513
13. Михайлов В.М. Вариабельность сердечного ритма. Опыт практического применения.-Иваново,2000.-200с.
14. Umetani K., Singer D. 24 hour time domain heart rate variability and heart rate: relation to age and gender over nine decades// JACC.-1999.-№31.-С.593-601
15. Nolan J., Batin P.D., Andrews R. Prospective study of heart rate variability and mortality in chronic heart failure// Circulation.-1998.-№98.-С.1510-1516
16. Galinier M., Pathak A., Fourcade J. Depressed low frequency power of heart rate variability as an independent predictor of sudden death in chronic heart failure// Eur.Heart J.-2000.-№6.-С.475-482
17. Bigger T.J., Fleiss J.L., Steinman R.C. Heart rate variability in healthy middle-aged persons compared with patients with chronic coronary heart disease or recent acute myocardial infarction// Circulation.-1995.-№21.-С.245-311
18. Goldberg J., Kadish A. Influence of sympathetic and parasympathetic maneuvers on heart rate variability. In: Noninvasive Electrocardiology. Clinical Aspects of Holter Monitoring. Moss A., Stern S.-1997.-С.207-223
19. Ramaekers D., Ector H., Aubert A. Heart rate variability and heart rate in healthy volunteers// Eur. Heart J.-1998.-№19.-С.1334-1341
20. Bonaduce D., Petretta M., Marciano F. Independent and incremental prognostic value of heart rate variability in patients with heart failure// Amer. Heart J.-1999.-№8.-С.138-145

21. Woo M.A., Stevenson W.G. Patterns of beat-to-beat heart rate variability in advanced heart failure// Amer. J. Cardiol.-1992.-№123.-C.704-710
22. Флейшман А.Н. Медленные колебания гемодинамики.-Новосибирск,1999.-С.264
23. Mortara A., Sleight P., Pinna G.D. Abnormal awake respiratory patterns are common in chronic heart failure and may prevent evaluation of autonomic tone by measures of heart rate variability// Circulation.-1997.-№96.-C.246-252
24. Ponikowski P., Anker S.D., Chua T.P. Depressed heart rate variability as an independent predictor of death in chronic congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy// JACC.-1997.-№79.-C.1645-1650
25. Guzzetti S., La Rovere M.T., Pinna G.D. Different spectral components of 24 h heart rate variability are related to different modes of death in chronic heart failure// Eur.Heart J.-2004.-№26.-C.357-362
26. Беленков Ю.Н., Мареев В.Ю., Скворцов А.А. Эналаприл против карведилола. Сравнительное рандомизированное исследование у больных с хронической сердечной недостаточностью (ЭКСТАЗ)// Сердечная недостаточность.-2001.-№2.-С.23-25
27. Keeley E.C., Page R.L., Lange R.A. Influence of metoprolol on heart rate variability in survivors of remote myocardial infarction// Am.J.Cardiol.-1996.-№77.-C.557-560
28. Zhang Y.H., Song Y.C., Zhu J. Effects of enalapril on heart rate variability in patients with congestive heart failure// Am.J.Cardiol.-1995.-№76.-C.1045-1048
29. Ulgen M.S., Akdemir O., Toprac N. The effects of trimetazidine on heart rate variability and signal average electrocardiography in early period of acute myocardial infarction// Int. J. Cardiol.-2001.-№7.-C.255-262
30. Давиташвили И.М., Кобалава Ж.Д., Климиашвили А. Действие препарата предуктал на параметры вариабельности ритма сердца у больных с инфарктом миокарда// Материалы Всероссийского научно-практического семинара «Современные возможности холтеровского мониторирования» .- Санкт-Петербург , 25-29 мая 2000 г.-С.12