HEART RATE VARIABILITY ANALYSIS AND DYSFUNCTION OF SINOATRIAL HEART NODE IN PATIENTS WITH CORONARY ARTERY DISEASE

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Abstract: The purpose of research was an evaluation of the particularities autonomic deregulations in the sinus heart node (SN) by mean of the heart rate variability (HRV) analyses in 362 patients with the coronary artery disease (CAD) and sinus atrial node dysfunction (SND). Except the standard cardiological investigation, there was high-resolution rhythmocardiography, applied for HRV analysis and evaluation of the peripheral autonomic deregulation in SN. Data of the HRV and results of standard cardiological investigations were compared. There were defined differential symptoms of the SND and sick sinus syndrome (SSS), signs of hemodynamic significance in the each arrhythmic episode, and also arrhythmogenic autonomic background of the SND. By electronic microscopy there were defined symptoms of the SN destruction in deceased pts with autonomic cardioneuropathy in life.

Key words: sinoatrial heart node dysfunction, high-resolution analysis of heart rate variability, peripheral autonomic regulation, clinical rhythmography

1. Introduction

Purpose of these researches was substantiated by the insufficiency investigations of the pathogenesis of cardioarrhythmias at the sinus node (SN) dysfunction (SND), absence of the information about pathological influence of the peripheral autonomic system (PAS) on formation of the SND or sick sinus syndrome (SSS). This arrhythmia is polyetiologic pathology, but near 50% of it connects with the chronic ischemic process, and in 49% of SND cases cause by regulative breaches in SN [1]. The participation of the PAS in the SND formation isn’t studied enough, though suggestions on the autonomic SN deregulation is motivated in a number articles and publications [2, 3, 4] but without data on peripheral autonomic regulation in SN. The estimation of the particularities autonomic dysregulation in the SN was carried out by mean of the high-resolution analysis of the heart rate variability (HRV) in patients (pts) with SND and SSS. In the presented information have showed the part of the clinical approbation results of the high-resolution method rhythmocardiography (RCG) and HRV analysis. Some pathogenic and diagnostic autonomic particularities were determined in pts with CAD and ischemic SND and SSS.

2. Material and methods

During 5-8 years 362 pts with CAD and SND were studied some times by standard cardiological methods (ECG, bicycle ECG, EchoCG, Holter monitoring, blood pressure monitoring, coronarography in 137 pts and others). Diagnosis of CAD was verified. In all 362 pts were syncopes and presyncope paroxysms. As specific investigation for evaluation of the peripheral autonomic system was used method of high-resolution rhythmocardiography diagnosis by apparatus-program complex CAP-RC-01-“Micor” (electrocardiosignal exactitude of 1000 Hz, the HRV data presented with accuracy till 1 millisecond) [5, 6]. There were a consequent registration of the RR-intervals between systoles and evaluation of the wave structure HRV by statistical analysis in Time-Domain and spectral nonparametric analysis in Frequency-Domain with Fast Fourier Transformation and Hamming and Parsen spectral windows [6]. HRV data of pts were compared with HRV –indices of healthy control group (48 persons) (Fig. 1). Synchronously with RCG was registered ECG. The cardioarrhythmia episodes were analyzed by software program. RCG was registered in posture lying down (Ph) and in 4 tests - Valsalva-Burker manoeuvre (Vm), Ashner (pA), the active orthostatic test (Aop) and in PWC120 with exercise. In HRV statistical analysis defined next indices: average RR-interval, standard quadratic deviation of all intervals (SDNN), average amplitude respiratory arrhythmia (ARA), quadratic dispersion of the HRV waves of short period, stimulated mainly parasympathetic influences in the SN (rs), waves of long period, connected with sympathetic regulative factors (rm) and humoral-metabolic waves of very long period (el), which are influencing on slow potentials of action in the SN . In the spectral analysis the shares of different frequencies fluctuations to the total spectral density were evaluated the correlation of regulative factors in the SN: VLF% - very low frequency humoral waves of 0, 0033-0,04 Hz, LF% - low frequency sympathetic HRV waves >0,04-0,15 Hz, and HF% - high frequency vagal fluctuations >0,15-0,4 Hz, accordingly [1, 3, 4, 5, 6]. Records were short-term on 260-300 intervals in each test position. 1500-1800 intervals registered the whole under RCG-investigation. The special program "Stat" was used in statistical evaluation of RCG-material for verification of the hypothesis equality of variable rows on criterion Student. Normalcy of the distribution was checked on the N. Colmogorov factor with approximation on Yu. Tyurin. For correlative analysis between HRV data and other data of the standard cardiological investigation was used nonparametric Spremen method with program SPSS 12.0. Correlation was considered significant at level 0.01-0.05.
3. Results and interpretation

The 24-year experience of using HRV analysis in the practical cardiology and the database more, than in 68 700 of RCG examinations of patients with different cardiovascular pathology proved that SN deregulations are registered on RCG, pathologically connected with the majority of cardioarrhythmias clinical forms, including SND. 25-minute RCG-monitoring is suitable and has a row advantages, not realized under ECG and under Holter monitoring with sampling rate ECS less 1000 Hz. SND has differentiated RCG-symptoms, which may be defined in particular estimation on frequency, clinical forms and their correlation between they self. First of all, RCG has possibilities for the different diagnostics between SND and SSS. In condition of the broad popularization of the cardiosurgical methods of the CAD treatment question about installation electrocardiostimulation (ECS) is very important in pts with SND of ischemic genesis, because ECS installation the cardinal change of patient life and requires the considered decisions. In spite of possibility of the complications under ECS – the thrombosis, under constant ventricle ECS, paroxysmal form of the atrial fibrillation and etc., motivations for ECS installation more frequent in pts with SSS, than with SND. The choice of therapy must be taken at estimation of a number of the clinical and instrumental data. RCG, as additional method, useful and allows to solve many questions.

For presented RCG-study 270 and 92 patients with SND and SSS of 2 degrees 1 and 2 types were selected. In the anamnesis of all patients there were presyncoes and syncoes. On the ECG there were registered changes the value and the forms of P and R cogs and PQ intervals, as predictors of the pacemaker migration in SN and atrium of the heart. On RCG in pts with SND and SSS the Wenckebach periodicity (360 pts) registered more frequently, as sinoatrial blockade of 2 degree on the background of different symptoms of the SN deregulation. The Wenckebach periodicity on the RCG was shown by long P-P blocked interval, the following intervals were lengthened too, but gradually it’s had shorten with following reduction of the blocked interval, the following intervals were lengthened too, its amplitudes and the forms, different value of the PQ, as well as R were registered. Sometimes these symptoms were absent on ECG with a low sensitivity. ECG-symptoms of rhythm pacemaker migration were in 49, 2% pts with SND and in 100% pts with SSS (p< 0.001). Wenkechab periodicity was more often in the selected pts, than Mobitz’s blockades (only in 2 pts). They were accompanied by other arrhythmias, often there were the atrial arrhythmias (on the RCG they had no the compensation postectopic pause), supraventricular arrhythmia, paroxysms of the atrial fibrillation (AF) and others. In pts with SSS, than M obitz’s blockades (only in 2 pts). They were accompanied by other arrhythmias, often there were the atrial arrhythmias (on the RCG they had no the compensation postectopic pause), supraventricular arrhythmia, paroxysms of the atrial fibrillation (AF) and others. In pts with SSS was formed gradual in these pts. The clinical form of cardioarrhythmias. To example, extrasyntoles can move over to the allorhythmia or may be changed to the atrial fibrillation (in 58 pts), Fig. 3.

3. SSS more often, than SND, is accompanied by the autonomic cardiomegaly (ACM), with the HRV stabilization and significant reduction its reaction on stimuli in tests, in 74 (27%) and 38 (41%) patients, accordingly (p<0.05), Fig. 1, Fig. 2, Fig. 3. Atropine test is usually negative in pts with SSS. That is to say, after the atropine introduction arrhythmias did not disappear at the SSS, but they can become rare in dependency on dose of the atropine (in 72 pts). In both groups of pts with SND and SSS HRV changed in atropine test (0,01-0,02/kg). There are decreased average values of RR, σs, amplitude respiratory arrhythmia - ARA, decreased the number of arrhythmia episodes. However, in pts with SSS arrhythmias never disappeared totally.

4. SSS more often, than SND, was accompanied ECG-symptoms of the migration of rhythm pacemaker on atrium with the change of cog R (in 92 vs 132 pts with SSS and SND, p<0,001). The level of HRV record may be high, accordingly to bradycardia, on this background there are single irregular lengthening of the intervals between systoles. 5. At the differential RCG-diagnostics between SND and SSS is found, that the HRV wave structure in pts with dysfunction was more preserved, than in pts with SSS Fig. 3. The prospective observation of 18 pts showed, that in case with preserved HRV structure after atropine test, the medical intervention can be minimal and may be limited by the choice of drug and its dose.

At the SN blockade 1 dg. RCG bradycardia registered, and average value RR-interval was more 1 second, changed HRV wave structure in the manner of reduction SDNN (σRR) and breached of the normal correlation of the spectral densities in the different frequency diapasons. SN blockade 2 dg. was on the background of more expressing HRV reductions, than under SN blockade 1 dg., or even on the background of HRV stabilization (in 112 pts). There are ECG-changes of the P, different its amplitudes and the forms, different value of the PQ, as well as R were registered. Sometimes these symptoms were absent on ECG with a low sensitivity. ECG-symptoms of rhythm pacemaker migration were in 49, 2% pts with SND and in 100% pts with SSS (p< 0.001). Wenkechab periodicity was more often in the selected pts, than Mobitz’s blockades (only in 2 pts). They were accompanied by other arrhythmias, often there were the atrial arrhythmias (on the RCG they had no the compensation postectopic pause), supraventricular allorhythmia, paroxysms of the atrial fibrillation (AF) and others. In pts with SSS the AF registered more often, in 33 cases (35.8%) vs 48 (17.7%) at SN, p<0.01. The AF paroxysms were longer in pts with SSS, than at SND -8,3±4,1 vs 4,5±1,2 sec. (p<0.002), accordingly.

In 74 pts with clinical expressed SSS significant the HRV stabilization was registered Fig. 3. Also there were absence or reduction of the HRV reactions on stimulus tests, which was corresponded to ACM. All HRV indices in these 74 pts were reduced at the criteria p<0,01-0,001, that is high reliability. 28 pts were studied by HRV analysis some times during prospecitive observation. ACM was formed gradually in these pts. The first symptoms were the loss of the normal parasympathetic predominance in SN, then the share of the very low frequency diapason (VLF%), connected with the humoral-metabolic influence in SN, increased at the expense of the spectral density reduction of the low frequency sympathetic and high frequency parasympathetic diapasons of the total spectrum, LF% and HF%, in accordance with decreased autonomic influences in SN. The reactions on stimuli in tests were decreased, too gradually. At the angina pectoris the reaction on transition in Aop from initial rest to active ortostase had decreased earlier whole [4, 5].
Fig. 1. Rhythmocardiograms and spectrograms of the healthy man. On the all RCG here is predominance of the parasympathetic, high frequency HRV waves. In Vm, pA, Aop and PWC exercise periods of stimulations are marked by the vertical needles. On the spectrograms dark part corresponds to very low frequency (VLF) diapason of the HRV fluctuations. It connects with the humoral-metabolic influences in the SN. Middle spectral diapason (LF) connects with the sympathetic influences on the pacemaker cells in the SN. And high-frequency part (HF) of the spectral density corresponds to the parasympathetic regulation in the SN. Reactions on the test-stimuli here are sufficient.

Electron microscopy morphological studies of the materials of 2 deceased pts with ACN on the RCG at the life, showed the reveal the signs of structure breaches in the SN pacemaker cells, Fig. 4. That affords ground expect that ACN is the complex of signs not only of the autonomic denervation in the SN, but also it is syndrome of the morphological and functional changes in the SN pacemaker cells. After publication by D. Ewing et al., (1978) and the other authors [1, 3, 4] about HRV stabilization in pts with CAD, ACN is recognized, as the predictor of the high risk of lethal outcome [4, 8, 9, 10].

RCG-studies consists the possibilities of the estimation multiversion, diagnostic and therapeutic great importance peripheral autonomic arrhythmogenic background in pts with SND. This is one of the main advantage the estimation of the autonomic deregulation in the SN, as obligatory pathogenic factor, that is very significant in the diagnosis of ischemic SND. Recently high-resolution HRV analysis is the single method, which allows defining this.

RCG with HRV analysis is the noninvasive method, and it’s more careful for pts, than unnatural electrophysiological investigation (EPHI) [7]. It is may be recommend, as preliminary investigation before discomfort EPHI for pts. The high-resolution RCG presents itself the short controlled monitoring, which allows to value main chronotropic heart activity during 20-25 min. record, define the direction of the diagnostic searching, form and particularities of the SN deregulation, clinical form of the cardioarrhythmias, it’s autonomic background and also the hemodynamic value of every arrhythmic episode, also define risk of the lethal outcome. Information about that will be in the front.

The CAD is connected with chronic ischemic pathology, which accompanied by the reduction of HRV and reactions of the sinus rhythm (SR) on stimuli in tests. The deregulation in the SN is one of the pathogenical links of forming cardioarrhythmias in pts with CAD and it’s the autonomic background. In Aop reduction of the rhythm reaction on the transition from rest to orthostase correlated to degree of the coronary reserve (r=0,377), that was confirmed by data D. Zemaytite [8]. There was HRV stabilization during the ischemic episode of the angina pectoris, synchronous with clinical signs and ST-depression on ECG in pts with the angina pectoris [3, 4, 9]. Probably it was connected with the reduction of SN blood perfusion in moment of the ischemic coronary occlusion, and hibernation of the pacemaker SN cells in response to this breach. After all the often coronary occlusions provoked irreversible remodeling of the heart tissue, including SN.

The arrhythmic episodes at the SND correlated (r=0,383-0,456) to increase the frequency and length episodes of HRV stabilizations, especially in the heavy cases.
Fig. 2. RCGs of patient with the sinus atrial dysfunction and synapses in the anamnesis. Here is Wenckebach periodicity, which become frequent in Ph, Vm, pA, and it disappears in Aop during sympathetic stimulation. HRV wave structure is changed pathologically.

For example, the increase of frequency and lengthening of the episodes of HRV stabilizations was typical of negative beginning of the acute coronary syndrome (34 pts), as predictor of myocardial infarction. The increase of the cardioarrhythmias frequency may be predictor of the myocardial electric instability. The heart failure in pts with CAD corresponded to the progressive HRV reduction till stabilization, with slow and insufficient, inadequate rhythm reactions to stimulant tests. It must be perceived, that the pharmacotherapy considerably changes all HRV structure and causes the difficulties in the high-resolution HRV analysis.

There is very important achievement of the RCG – possibility to value influences of the each arrhythmia on the hemodynamics in pts with SND. The relationship SND with the hemodynamic breaches was proved by the next HRV-symptoms: 1. Reduction or change of HRV- wave structure after the arrhythmic episode, connected with the SN cells hibernation and perfusion breach. 2. Sometimes ischemic HRV- stabilization proceeded to arrhythmia (in 80 pts with SND and 32 pts with SSS -29 and 35.2%, p<0.05). These cases proved the pathogenic connection of the arrhythmia with ischemia. The provocation of the cardioarrhythmias was also conditioned by the ischemia of the myocardium, it was accompanied by the ST depression and HRV reduction. 3. In pts with angina pectoris after paroxysm of the stenocardia arrhythmias were rarely during 30-60 min. (in 18 pts with SND, 0, 66 %), but only at the 1 functional class of the angina pectoris. It was connection with phenomenon of the precondition. 4. Electric instability of the myocardium accompanied by the extrasystoles with the super compensative postectopic interval on the background HRV sympathetic waves. The increase of the sympathetic periodicity, then change of the level RCG and/or HRV structures, were indicative of the increasing risk of death and correlative of the cardioarrhythmias with hemodynamic breach [10, 11].

The correlation between cardioarrhythmias and hemodynamic breaches revealed itself change HRV level and its wave structure - the reduction, or even HRV stabilization, reduction or absence of reactions to stimuli in tests, appearance or increase in frequency of the arrhythmia paroxysms. Also their clinical form can be changed, the fixed ischemic threshold changed on the variable, the period of the rehabilitation after action stimuli in test increased and others. In 118 pts arrhythmias were provoked by the ischemic episodes, in 112 they preceded to ischemia, manifesting its hemodynamic value. In other cases of the correlation SND and angina pectoris had an individual mixed nature. In pts with SSS ACN transformed to the AF Fig. 4. In the beginning there were the AF paroxysms, and then AF gradually changed to permanent form, demonstrating the organic breaches in SN at these cases – in 38 pts (39%) for period of the observations. Every clinical variant of the SND has the peculiarities of HRV breaches, connecting with pathogenesis of the disease and its form [3, 10, 12, 13]. The most heavy cases accompanied by the high influence of humoral-metabolic factor (VLF %) on the activity of pacemaker SN function and autonomic sympathetic and parasympathetic significant depression (LF %, HF %).

Thus, in pts with CAD and SND, SSS the breaches of the peripheral autonomic regulation in the SN are accompanied by the ischemic chronic process, as the obligate syndrome [4, 13]. SND arrhythmic episodes dependent on the functional or organic pathology of SN and the peripheral autonomic influences on the pacemaker cells in SN. These particularities were registered by high-resolution rhythmocardiography. Also, the analysis of HRV wave structure, recorded in the stimulant tests, allows recognizing a number detail of the cardioarrhythmias. The most important RCG preferences are related to definition the arrhythmogenic autonomic background, hemodynamic value of each arrhythmic episode and connection with ischemic pathology. Besides, there are appointed HRV distinctions between SND and SSS.
Fig. 3. RCG, spectrograms and HRV-indices of patient with the coronary artery disease and sick sinus syndrome. There were syncope\ness in the anamnesis. Here are HRV stabilization (corresponds to the autonomic cardioneuropathy), atrial fibrillation in Ph and Vm, bigeminy in the Vm end. In Aop, during sympathetic stimulation all cardioarrhythmias are disappeared. HRV-indices shows predominance of the humoral influence in SN – VLF% is the largest in all positions.

Fig. 4. Electronic microscopy of the pacemaker cells of the SN in patient with autonomic cardioneuropathy under life. Here are necrobiotic changes – hypertrophy of the mitochondrias, calcifications, vacuoles, lipid dystrophy, as the signs of the decomposition.
4. Conclusions

1. The sinus node dysfunction and sick sinus syndrome in patients with coronary artery disease are accompanied by the obligatory different multivariate peripheral autonomic deregulation of the pacemaker activity in sinoatrial node.

2. High resolution RCG examination of patients with chronic coronary artery disease allows registering the majority of the cardioarrhythmias at the sinoatrial dysfunction, to define the background of the autonomic deregulation and hemodynamic value of the each arrhythmic episode.

3. Analysis of the HRV-wave structure and the high-resolution rhythmocardiography contain the additional markers for the differential diagnostics between the sinus nodal dysfunction and sick sinus syndrome. Appearing of the arrhythmic episodes in patients with SND dependent on the prevalence that or other factor of the regulation in the SN. Cardioarrhythmias at the sick sinus syndrome are more independent from the autonomic regulation of the SN pacemaker activity, particularly at the syndrome of autonomic cardiomegaly.

4. The extreme sympathetic and parasympathetic oppression in SN, corresponding to the autonomic cardiomegaly, accompanies to the destructive changes in the pacemaker cells of the sinus node.

5. References


Abbreviation

ACN –autonomic cardioneuropathy
AF – atrial fibrillation
CAD- coronary artery disease
EchoCG - Echocardiography
ECG - electrocardiography
ECS - electrocardiosignal
HRV – heart rate variability
PAS -peripheral autonomic system
RCG - rhythmocardiography
SAD – sinoatrial dysfunction
SN – sinoatrial node of the heart
SR- sinus rhythm
SSS- sick sinus syndrome
EPHI