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CHARACTERISTICS OF THE AUTONOMIC NERVOUS SYSTEM STATE, ASSESSED BY THE HEART RATE VARIABILITY STUDY IN CIRRHOTIC PATIENTS WITH SYNTROPIC CARDIOMYOPATHY AND ITS FEATURES DEPENDING ON THE QT INTERVAL DURATION

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Abstract.

Background: The patients with liver cirrhosis (LC) have autonomic nervous system (ANS) imbalance that can be evaluated by the heart rate variability (HRV) study. ANS imbalance results into cirrhotic cardiomyopathy (CCMP) and the most easily diagnosed feature of CCMP is the prolonged QT interval. Usually, in the literature not all HRV parameters are characterized, or their assessment period is short, not allowing covering all the important moments and therefore needing further study.

Material and Methods: In a randomized way with the preliminary stratification by the presence of LC 33 patients after signing the informed consent were examined. In addition to routine screening methods, all patients underwent 24-hour ECG monitoring.

Results: Patients with LC and syntropic CCMP have the ANS disorders with a HRV decrease, predominance of the sympathetic over the parasympathetic system, heart rate regulation at the humoral-metabolic level. The ANS disorders severity depend on the LC severity according to C. G. Child-R. N. Pugh criteria.

During the analysis of the received results the significant positive correlation between the SDNN index and maxQT, avg QT, positive correlation between HF and max QTc, avg QTc were found. The diagnostic sensitivity of SDNN index and HF was high in the patients with LC and CCMP.

Conclusions: The ANS imbalance can be regarded as syntropic comorbid disorder in the cirrhotic patients. The diagnostic sensitivity of SDNN index and HF was found to be high in the patients with LC and CCMP, serving as diagnostic markers of CCMP.

Key words. Liver cirrhosis, QT interval, autonomic nervous system, syntropic diseases, cirrhotic cardiomyopathy.

Introduction.

Liver cirrhosis (LC) is a leading cause of mortality and morbidity across the world. It is the 11th leading cause of death and 15th leading cause of morbidity, accounting for 2.2% of deaths and 1.5% of disability-adjusted life years worldwide in 2016 [1]. Also, it is known that patients with LC have a significant autonomic nervous system (ANS) imbalance [2,3], being one of the pathogenetic mechanisms of LC severity increase and an important component of unfavorable prognosis [2,4-8]. One of the ultimate pathogenetic mechanisms of this is the potassium channels membrane dysfunction and hyperreactivity of the sympathetic system, which causes β-adrenergic receptors regulation to be decreased [9-11] and so-called transition to the humoral-metabolic level of ANS regulation [1-3,10]. It may be accompanied by the decrease of ANS influence, prolongation of the QT interval, which does not depend on heart rate [12] and modulation of ventricular repolarization [13-17].

The results of studies based on 24-hour HRV recording [4-6] show impaired cardiac autonomic function in cirrhotic patients with decreased vagal tone and impaired sympathetic regulation of the heart [18]. Imbalance of the ANS regulation in the cirrhotic patients leads to the development of the cirrhotic cardiomyopathy (CCMP) [20,21,22]. And the most common and easily diagnosed feature of CCMP is the previously mentioned prolonged QT interval and its modifications [23].

We hypothesized that some HRV parameters can be reliable indices for the diagnostics of cirrhotic cardiomyopathy. Usually, in the literature not all indicators of HRV in patients with CCMP are characterized, or their assessment only for the five-minute period is carried out and that does not allow covering all the important moments of its analysis [24]. So, it is necessary to clarify the patterns of QT interval and its relationship with temporal and spectral HRV as integral characteristics of the ANS state in patients with syntropic CCMP, which would provide the important independent information that is beyond the traditional approach to understanding the pathogenesis of CCMP.

Objectives. To characterise the ANS state, assessed by the HRV study in cirrhotic patients with syntropic CCMP and its features depending on the QT interval duration.

Research Methods.

All the participants obtained the written consent to take part in the study in accordance with the principles of the Helsinki Declaration of Human Rights, the Council of Europe Convention on Human Rights and Biomedicine and relevant laws of Ukraine. In a randomized way (by assigning the random numbers from random number tables) with the preliminary stratification by the presence of LC 33 patients (13 females (39.4%), 20 males (60.6%), aged 48.0 ± 12.0 years) were included to the study during 2018-2019 years. All of them were hospitalized and treated at Lviv Regional Hepatology Center created on the base of the Department of Internal Medicine N 1 of Danylo Halytsky Lviv National Medical University and Gastroenterology Department of the Municipal Non-profit Enterprise of Lviv Regional Council "Lviv Regional Clinical Hospital" for the period 2018-2019.

According to the results of the examinations, all patients were evaluated in accordance with the severity class of LC according to the criteria of C. G. Child-R. N. Pugh: class A – 8, class B – 14, class C - 11 people.

In addition to routine screening methods, all patients underwent 24-hour ECG monitoring using a 12-channel Holter

ECG system HEACO VI6600, UK (software version V3.1/12, recorder version № VI/TFCE-11-10) and processed the received parameters, in particular minimum, maximum and average daily heart rate; average QT (avg QT), average corrected QT (avg QTc), maximum QT (max QT) and maximum corrected QT (max QTc); time (the standard deviation of NN intervals - SDNN), the mean standard deviation of NN intervals (for each 5 min interval of a 24-h HRV recording - SDNN index), the square root of the mean squared differences of successive NN intervals (rMSDD), the proportion of the number of intervals between adjacent NN intervals greater than 50.0 ms to the total NN-intervals in the HRV record (which introduced the NN50 count, defined as the mean number of times an hour in which the change in successive normal sinus NN intervals exceeds 50.0 ms - pNN50.0%)) and spectral (general spectral characteristics (number of total NN intervals/number of NN intervals in the modal bin - RR triangle), high-frequency (HF) spectrum - 0.15-0.40 Hz - reflects the influence of the parasympathetic ANS on heart rate, low frequency (LF) spectrum - 0.04-0.15 Hz - which reflects mainly the influence of the sympathetic nervous system on heart rate, very low frequency (VLF) - spectrum 0.003-0.04 Hz - reflects the humoral effects on heart rate) HRV characteristics recommended by the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.

The duration of ECG monitoring was 24 hours. The information obtained was statistically processed in the program "Jupyter" using the programming language "Python". The values of the studied parameters were presented as M ± m, where M is the arithmetic mean, m - the standard deviation. The t-test was used in the analysis of the obtained parameters (statistically significant indicators were considered if $p < 0.05$) and K. Pearson's correlation coefficient (r) - to assess the reliability and density of the linear relationship, the parameters of the regression equation were determined by the method of least quadrants. Diagnostic sensitivity (DS) was assessed by the percentage of true positive test results in patients with CCMP.

Results.

The values of the temporal characteristics of HRV during 24-hour Holter ECG monitoring in patients with LC and syntropic cardiomyopathy are shown in table 1.

The SDNN index of the cirrhotic patients decreases by 24.7%, the SDNN index - by 29.3%, rMSSSD - by 11.5% compared with the reference values. There is an increase of pNN50.0% in 2.8 times compared to the reference values.

Analysis of the temporal characteristics of HRV revealed the significant difference between the SDNN index ($p < 0.05$, $t = 2.62$), and its absence between rMSDD ($p > 0.05$, $t = 0.34$), pNN50.0% ($p > 0.05$, $t = 0.55$) and reference values.

The values of the HRV spectral characteristics during 24-hour Holter ECG monitoring in patients with LC and syntropic CCMP are shown in table 2.

The RR triangle decreases more than four times, VLF decreases almost six times, HF - twice, LF - more than three times, LF/HF ratio - increases by 10.8% compared to the reference values.

Analysis of the spectral characteristics of HRV indicates a significant difference between the reference values and LF ($p < 0.01$, $t = 5.74$), VLF ($p < 0.05$, $t = 2.26$). The HF value was unreliable ($p < 0.05$, $t = 0.02$). No statistically significant difference for the LF/HF ratio and reference values ($p > 0.05$, $t = 0.57$) was found. However, the value of the LF/HF ratio, calculated using the ratio of low and high waves of the spectral HRV, was 3.14 ± 2.44, showing an imbalance of the ANS in patients with LC.

Table 1. *Time characteristics of heart rate variability during 24-hour Holter electrocardiogram monitoring in patients with liver cirrhosis and syntropic cardiomyopathy (M ± m, g).*

Parameters, reference values	Values	p
SDNN, 126.62 ± 20.64 ms	95.39±38.42	p>0.05
SDNN index, 52.0 ± 15.0 ms	36.79±18.83	p<0.05
rMSDD, 25.0 ± 9.0 ms	22.12±16.17	p>0.05
pNN 50.0 %, 6.0 ± 6.0 %	17.06±7.74	p>0.05

Table 2. *Spectral characteristics of heart rate variability during 24-hour Holter electrocardiogram monitoring in patients with liver cirrhosis and syntropic cardiomyopathy (M ± m, p).*

Parameters, reference values	Values	p
RR triangle, 13.1±5.0 CU	3.14±2.44	p>0.05
VLF, 2912.0±2675.0 ms	494.97±355.31	p<0.05
HF, 318.0±251.0 ms	156.10±120.53	p>0.05
LF, 788.0±397.0 ms	250.85±168.11	p<0.01
LF/HF, 2.8±2.6	3.14±2.44	p>0.05

Table 3. *Indicators of QT interval duration during 24-hour Holter monitoring of the electrocardiogram in patients with liver cirrhosis and syntropic cardiomyopathy (M ± m,g).*

Parameters, reference values	Values	p
max QT, 373.0 ±25.0 ms	405.52±38.81	p<0.01
max QTc, 395.0±16.0 ms	459.52±23.03	p<0.01
avg QT, 365.0±25.0 ms	334.00±26.25	p<0.05
avg QTc, 387.0±16.0 ms	393.70±6.06	p<0.05

Table 4. *Correlation between time characteristics of heart rate variability and QT interval in patients with liver cirrhosis and syntropic cardiomyopathy (r, p).*

Parameters	SDNN	SDNN index	rMSSD	pNN 50.0%
max QT	0.55**	0.60**	0.49	0.38**
max QTc	0.37	0.36	0.22**	0.16**
avg QT	0.48**	0.57**	0.58*	0.43**
avg QTc	0.27**	0.20*	0.19**	0.12**

*Note: * – p<0.05, ** – p<0.01.*

Parameters of the QT interval duration during 24-hour Holter ECG monitoring in patients with LC and syntropic CCMP are shown in table 3.

Analysis of the QT interval duration revealed a statistically significant difference between max QT ($p < 0.01$, $t = 4.90$), max QTc ($p < 0.01$, $t = 3.09$), avg QT ($p < 0.05$, $t = 2.19$), avg QTc ($p < 0.05$, $t = 2.02$) and reference values.

Correlations between the HRV frequency characteristics and the QT interval in the cirrhotic patients with syntropic CCMP are shown in table 4.

According to the results of our research, we found a significant positive correlation between the values of avgQTc, avg QT and all time HRV parameters. In particular, such correlation was

Table 5. *Correlation between spectral characteristics of heart rate variability and QT interval in patients with liver cirrhosis and syntropic cardiomyopathy (r, p).*

Parameters	HF	LF	VLF
max QT	0.36	0.57	0.63
max QTc	0.18**	0.35	0.34
avg QT	0.40	0.52	0.66
avg QTc	0.13**	0.15	0.28

*Note: * – p<0.05, ** – p<0.01.*

found between the avg QT and SDNN (p <0.01) and pNN50.0% (p <0.01), SDNN index values (r> +0.5, p < 0.01) and rMSSD (r> +0.5, p <0.05). The correlation between avg QTc and all frequencies was significant (r> +0.1). Max QTc significantly correlated with rMSSD and pNN 50.0% (p<0.01), its correlation with frequency parameters was positive. Max QTc significantly correlated with SDNN and SDNN index values (r> +0.5, p <0.01).

Correlation relationships between the spectral characteristics of HRV and the QT interval in patients with LC and syntropic CCMP are given in table 5.

The calculation of the HRV spectral characteristics revealed a significant (p <0.01) correlation between maxQTc, avgQTc and HF (r <+0.5, p <0.01). For other HRV spectral parameters, the relationship was insignificant (p> 0.05). Although between maxQT and LF, VLF, as well as between avgQT and LF, VLF there was found the significant direct correlation (r> +0.5).

The DS for time and spectral parameters of HRV in patients with LC and syntropic CCMP, for which there is a correlation with the duration of QT interval was calculated as following: SDNN index - 72.7%, HF - 67.7%, VLF - 24.2%. Similar results were obtained during the calculation using the software. This indicates the diagnostic sensitivity of HRV indicators such as SDNN index and HF - 67.7% in patients with CCMP.

Discussion.

To understand the significance of the study it is important to mention some facts. In 1958, J. H. Lunset et al. [14] reported myocardial thickening observed at autopsy in patients with LC who had no history of any heart disease. Histological examination revealed hypertrophied pigmented cardiomyocytes with nuclear vacuolation, edema and fibrosis [1,9]. Soon it was investigated that the typical for LC increase of nitric oxide level with concomitant elevation of the sodium content and fluid retention leading to myocardial hypertrophy [25] can lead to pathological left ventricular relaxation with the formation of diastolic dysfunction [17,20,26].

In its turn the existing in the cirrhotic patients comorbid ANS regulation imbalance (with sympathetic branch predominance over the parasympathetic as it was also confirmed in our study) [4-6] is characterized by the increased cardiac output and decreased blood pressure [1]. Increased resting heart rate as a marker of autonomic neuropathy and chronotropic incompetence is often observed in decompensated cirrhotic patients and along with increased ejection fraction and decreased blood pressure are the signs of hyperdynamic circulation [19,24]. Thus, the combination of weakened myocardial contractility with systolic and diastolic dysfunction, as well as electrophysiological disorders that occur in patients with LC, is interpreted as CCMP [20,21]. It is known that the cirrhotic patients often have the prolongation of QT interval, fluctuating during the day, which may be associated with an increased risk of ventricular arrhythmias, tachycardias and even sudden death [8,25,27-30]. Thus, the prolonged QT interval and its modifications become the most common and easily diagnosed feature of CCMP [23]. And the best way to evaluate it correctly is not the simple ECG as it is used commonly but the ECG Holter monitoring that let us avoid the inaccuracies that may occur and characterize the picture completely as we proposed in our study.

In the work of S. Genovesi et al. [4] it is stated that the cirrhotic patients have reduced overall HRV, and the degree of its reduction directly correlates with the LC severity [18]. However, usually, not all HRV parameters in the patients with CCMP are evaluated, or their assessment period is short [24]. Therefore, the best way to avoid this is also to use HRV monitoring for 24 or 48 hours what we did in our study.

Analyzing the temporal characteristics of HRV in our study we revealed the significant difference between the SDNN index (p <0.05), and its absence between rMSDD, pNN50.0% (p> 0.05) and reference values. In its turn the analysis of the HRV spectral characteristics indicates a significant difference between the reference values and LF (p <0.01), VLF (p <0.05). However, the value of the LF/HF ratio shows an imbalance of the ANS in the cirrhotic patients. The QT interval duration in the cirrhotic patients as one of the most important marker for prognosing the sudden death in such category revealed a statistically significant difference between max QT, max QTc (p <0.01), avg QT, avg QTc (p <0.05) and reference values. Also in our research, the significant positive correlation between the values of avg QTc, avg QT and all time HRV parameters was found. HRV spectral characteristics analysis revealed the significant correlation between max QTc, avg QTc and HF (p <0.01). Although between max QT and LF, VLF, as well as between avg QT and LF, VLF there was found the significant direct correlation.

Therefore, analyzing the results of Holter monitoring of HRV and ECG it was firstly found the significant positive correlation between the SDNN index and maxQT, avg QT, positive correlation between HF and max QTc, avg QTc. The diagnostic sensitivity of SDNN index and HF are significant, which can serve as diagnostic markers for CCMP.

Conclusion.

In the HRV structure in the cirrhotic patients the sympathetic branch of the ANS predominates over the parasympathetic that can be regarded as syntropic comorbid disorder. Between the SDNN index and max QT, avg QT there is a significant positive correlation, between HF and max QTc, avg QTc - positive correlation. The diagnostic sensitivity of SDNN index and HF are high. So, taking into account the fact that QTc serves as a reliable marker of CCMP, these parameters can serve as diagnostic markers for CCMP.

Conflict of interest.

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Характеристика состояния вегетативной нервной системы по данным исследования вариабельности сердечного ритма у больных циррозом печени с синтропической кардиомиопатией и ее особенности в зависимости от продолжительности интервала QT

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Введение. У пациентов с циррозом печени (ЦП) имеется дисбаланс вегетативной нервной системы (ВНС), который можно оценить с помощью исследования вариабельности

сердечного ритма (ВСР). Дисбаланс ВНС приводит к цирротической кардиомиопатии (ЦКМП), и наиболее легко диагностируемым признаком ЦКМП является удлинение интервала QT. Обычно в литературе охарактеризованы не все параметры ВСР, либо период их оценки короток, что не позволяет охватить все важные моменты и поэтому требует дальнейшего изучения.

Материал и методы. Рандомизированным способом с предварительной стратификацией по наличию ЦП обследовано 33 пациента после подписания ими информированного согласия. Помимо рутинных методов скрининга, всем больным проводили суточное мониторирование ЭКГ.

Результаты. У больных ЦП и синтропической ЦКМП выявлены нарушения ВНС со снижением ВСР, преобладанием симпатической системы над парасимпатической, регуляцией сердечного ритма на гуморально-метаболическом уровне. Тяжесть нарушений ВНС зависит от тяжести ЦП по критериям C. G. Child-R. N. Pugh.

При анализе полученных результатов были обнаружены значимая положительная корреляция между индексом SDNN и maxQT, avg QT, положительная корреляция между HF и max QTc, avg QTc. Диагностические чувствительности индекса SDNN и HF были высокими у больных ЦП и ЦКМП.

Выводы. Дисбаланс ВНС можно рассматривать как синтропическое коморбидное расстройство у больных ЦП. Установлено, что диагностическая чувствительность индекса SDNN и HF высока у больных ЦП и ЦКМП, выступаючи в качестве диагностических маркеров ЦКМП.

Ключевые слова: цирроз печени, интервал QT, вегетативная нервная система, синтропические заболевания, цирротическая кардиомиопатия.

ვეგეტატიური ნერვული სისტემის მდგომარეობის დახასიათება გულის რითმის ვარიაბელობის კვლევის მონაცემების მიხედვით პაციენტებში ღვიძლის ციროზით და სინტროპული კარდიომიოპათიით და მისი, QT ინტერვალის ხანგრძლივობასთან დაკავშირებული, თავისებურებები

ზ. ბილოუს, ო. აბრაგამოვიჩ, მ. აბრაგამოვიჩ, ო. ფაიურა, ა. ფედეც.

შესავალი. ღვიძლის ციროზით (ღც) დაავადებულ პაციენტებს აქვთ ვეგეტატიური ნერვული სისტემის (ვნს) დისბალანსი, რომელიც შეიძლება შეფასდეს გულის რითმის ვარიაბელობის (გრვ) კვლევის გამოყენებით. ვნს-ის დისბალანსი იწვევს ციროზულ კარდიომიოპათიას (ცკმპ) და ცკმპ-ის ყველაზე ადვილად დიაგნოსტირებადი ნიშანი არის QT ინტერვალის გახანგრძლივება. ჩვეულებრივ, ლიტერატურაში არ არის დახასიათებული გრვ–ის ყველა პარამეტრი, ან ხანმოკლეა მათი შეფასების პერიოდი, რაც არ იძლევა ყველა მნიშვნელოვანი მომენტის გაშუქების საშუალებას, და ამიტომ საჭიროებს შემდგომ შესწავლას.

მასალა და მეთოდები. 33 პაციენტი გამოკვლეულია რანდომიზებული წესით ღც–ის არსებობაზე წინასწარი სტრატიფიკაციის და ინფორმირებული თანხმობის ხელმოწერის შემდეგ. სკრინინგის რუტინული მეთოდების გარდა, ყველა პაციენტს ჩაუტარდა ოცდაოთხსაათიანი ეკგ მონიტორირება.

შედეგები. პაციენტებში ღც–ით და სინტროპული ცკმპ-ით გამოვლინდა ვნს-ის დარღვევები გრვ-ის დაქვეითებით, სიმპათიკური სისტემის ჭარბობით პარასიმპათიკურ სისტემაზე, გულის რითმის რეგულირებით ჰუმორალურ-მეტაბოლურ დონეზე. C. G. Child-R. N. Pugh კრიტერიუმებით ვნს-ის დარღვევების სიმძიმე დამოკიდებულია ღც–ის სიმძიმეზე.

მიღებული შედეგების გაანალიზებისას, აღმოჩნდა მნიშვნელოვანი პირდაპირი ძლიერი კორელაცია SDNN ინდექსსა და maxQT, avg QT-ს შორის, ძლიერი კორელაცია HF და max QTc, avg QTc-ს შორის. HF–ს და SDNN ინდექსის დიაგნოსტიკური მგრძნობელობა მაღალი იყო ღც–ით და ცკმპ-ით დაავადებულ პაციენტებში.

დასკვნები. ვნს-ის დისბალანსი შეიძლება მიჩნეული იქნას როგორც სინტროპიული კომორბიდული აშლილობა ღც–ით დაავადებულ პაციენტებში. დადგენილია, რომ HF–ს და SDNN ინდექსის დიაგნოსტიკური მგრძნობელობა მაღალი იყო ღც–ით და ცკმპ-ით დაავადებულ პაციენტებში, რომლებიც მოქმედებენ როგორც ცკმპ-ის დიაგნოსტიკური მარკერები.

საკვანძო სიტყვები: ღვიძლის ციროზი, QT ინტერვალი, ვეგეტატიური ნერვული სისტემა, სინტროპული დაავადებები, ციროზული კარდიომიოპათია.