Cardiovascular risk assessment by electrocardiographic Holter monitoring in patients with chronic hepatitis C

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Abstract

Introduction: Cardiovascular diseases are ranked as the third cause of mortality among people infected with hepatitis C virus (HCV), but the relationship of infection with cardiovascular risk remains disputable. We have focused on the comprehensive use of parameters obtainable during long-term electrocardiographic (ECG) Holter monitoring.

Material and methods: Heart rate variability and turbulence (HRV and HRT), deceleration/acceleration capacity (DC/AC), corrected QT interval (QTc) and late potential (LP) were used. 36 persons were included, and 30 healthy subjects formed a control group. All were submitted to 24-hour Holter ECG-monitoring.

Results: The studied groups were not statistically significantly different with regards to basic anthropometric parameters. Statistically significantly higher medium and maximum heart rhythm and aminotransferase activities were recorded in patients with hepatitis C. The HRV parameters r-MSSD, p50NN, HF, and absolute DC/AC values were significantly lower in the subjects with hepatitis C than those in the control group. The QTc interval, measured for nocturnal hours, was also significantly longer in that group. There were no differences in the albumin level or basic echocardiographic parameters, including left ventricle ejection fraction. Nor was there any difference in the HRT parameters, or LP. The most interesting observation was the positive correlation among the number of viral RNA copies and DC, and LF.

Conclusions: We confirmed the presence of autonomic disorders with prevalence of sympathetic system activity and prolonged QTc interval in patients with chronic hepatitis C. Those parameters significantly correlated with infection intensity. Our results suggest that HCV infection could be an independent cardiovascular risk factor, not associated with the lipid profile. Further prospective studies are needed.

Key words: chronic C hepatitis, cardiovascular risk, ECG Holter.

Introduction

It is estimated that the incidence rate of anti-hepatitis C virus (HCV) antibodies, which indicate HCV infection, is 2.8% in the entire world population, which corresponds to more than 185 million infected subjects [1].

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Every year, 3–4 million people are infected with this virus. The majority of newly infected persons may remain totally unaware of the fact, as the course of HCV infection is usually asymptomatic [2]. Unfavourable consequences of HCV infection lead to rather high annual mortality figures of more than 350 thousand fatalities in the world [1]. So far, more than 30 diseases and medical conditions have been identified as secondary to chronic HCV infection; however, the cause-and-result mechanisms of these relationships are sometimes far from clear [3]. Cardiovascular diseases are ranked the third, regarding the structured incidence of mortality, causes among patients with chronic hepatitis C [4, 5]. The relationship of HCV infection with cardiovascular risk remains disputable. Some reports also mention either an increased risk of coronary disease [6] or no increase of the risk for cardiac infarction [7]. In addition, it seems that HCV infection may be associated with disorders of systolic and diastolic functionality of the left ventricle, an increased risk for arrhythmia, elongation of the QTc interval and disturbed autonomic control [8–12]. Regarding metabolic changes, increased resistance to insulin and endothelial lesions have been confirmed [13, 14]. It is suspected that these changes may be supported by specific activity of the hepatitis C virus, triggering a cascade of immunological processes.

An evaluation of the cause-and-effect relationship between hepatitis C and cardiovascular risk is especially important as the majority of cardiovascular conditions are identified randomly and incidentally, after an unknown time from infection. Therefore, it is rather difficult to estimate how long the virus has been active in the body.

In our research, we focused primarily on the complex use of the parameters which are available in the course of long-term Holter monitoring, especially of those parameters which correspond to the autonomic system balance. They are more and more commonly used for prediction of cardiovascular risks, including the risk of sudden cardiac death. They are also considered to be prognostically significant after cardiac infarction in dilated cardiomyopathy. Disorders of these parameters have also been demonstrated in a number of other conditions, including hepatic cirrhosis, autoimmune diseases or the testosterone deficiency syndrome [15–22]. The study made use of such parameters as the heart rate variability (HRV) and heart rate turbulence (HRT), deceleration capacity/acceleration capacity (DC/AC), the corrected QT interval (QTc) and late ventricular potentials (LP). The obtained parameters were then compared with those from a healthy population. They were also correlated with the marker parameters of hepatic cell damage and the HCV RNA levels.

Material and methods

Fifty-four subjects with newly identified HCV infection were qualified to a preliminary inclusion assessment. Those patients were then submitted to a further qualification process to specific antiviral therapy. All of them were hospitalised at the Department of Infectious and Liver Diseases of the Medical University in Lodz. The suspicion of HCV infection was based on the presence of anti-HCV antibodies, identified in screening tests or incidentally, in the course of other diagnostic tests. In order to confirm the presence of HCV virus, the levels of HCV RNA were assayed and liver biopsy examinations were performed. The COBAS TaqMAN HCV RNA, v 2.0 (Roche) test was applied to assess viremia levels. The test employs real-time PCR technology for HCV RNA detection and quantitative analysis. The HCV RNA detection threshold in the test is 25 IU/ml.

The study was performed in agreement with the ethical guidelines of the 1975 Declaration of Helsinki with later amendments and was approved by the local Bioethics Committee. Written informed consent was obtained from all the included subjects.

Prior to inclusion into the study, the genotype and subgenotype of the HCV virus were evaluated, using the VERSANT HCV genotype 2.0 assay (LiPA 2.0), based on the sequence of regions: 5'NCR (the non-coding region of HCV RNA region) and of the core coding region. In doubtful situations, an NS5B fragment was submitted to direct sequencing. Each of the study participants underwent detailed medical examinations and laboratory tests, including albumin, alanine transaminase (ALT), aspartate transaminase (AST) and bilirubin levels, lipid profile, thyroid-stimulating hormone (TSH), echocardiography and rest electrocardiography (ECG). The presence of HCV RNA was the inclusion criterion. In compliance with the goal of the study, attempts were undertaken to eliminate all the factors which could have disturbed the especially sensitive parameters, obtained during Holter monitoring. Therefore, the exclusion criteria included acute coronary syndrome, cerebral stroke or intracranial bleeding in history, pregnancy and lactation, thyroid function disorders (hyper- or hypothyroidism), hypertension, a rhythm other than sinus, cardiac failure – class II and higher according to NYHA, neoplastic disease – persons after 5 years from therapy closure were treated as cured, nicotinism, alcohol abuse and other addictions, acute inflammation or an infection, identified within the last 2 weeks, systemic diseases, kidney failure (GFR < 60 ml/min/1.72 m^2), diabetes mellitus and the intake of drugs which affect the autonomous system functions, such as β-blockers, etc. Based on the above-mentioned

criteria, 36 persons were included in the final phase of the study. Thirty healthy subjects, matched with respect to sex, age and basic anthropometric parameters, formed a control group.

The included subjects were submitted to 24-hour Holter ECG monitoring in a domestic environment.

Twenty-four hour Holter monitoring and further analyses

All the persons participating in the study underwent 24-hour Holter monitoring by means of a DMS 300-3A device and a CardioScan 12 analyser of DM Software Inc. USA. The obtained recorded data were then interpreted and verified by an experienced cardiologist, performing non-invasive cardiological examinations as part of daily clinical routine. All of the obtained records were characterised by satisfactory length and quality. They were then submitted to a computer analysis to obtain necessary parameters. Having detected QRS complexes and QT intervals, the following parameters were calculated:

1. The heart rhythm variability parameters, both time domain – SDNN (ms) – standard deviation of NN intervals; SDNN index (SDNNI) – the average of the standard deviations of successive intervals NN from the 5-minute test periods; SDANN (ms) – standard deviation of averaged NN intervals; r-MSSD – root mean square successive differences (ms); p50NN – percentage of differences between adjacent NN intervals that are greater than 50 ms (%) – and frequency domain – TP – total power of frequency domain (ms^2); HF – high frequency domain (ms^2) (0.15–0.4 Hz); HF – high frequency domain (ms^2) (0.04–0.15 Hz); VLF - very low frequency domain (ms^2) (0.003–0.04 Hz); ULF – ultra low frequency domain (ms^2) (< 0.003 Hz); LF/HF – LF/HF ratio. Out of the studied parameters, SDANN is assumed to be the best in describing the activity of the sympathetic system, while r-MSSD and p50NN are assumed to be the best in describing the activity of the parasympathetic system. In turn, the value of the HF domain is treated as the marker of the vagus nerve, LF evaluates the efficacy of the entire vegetative system, while the LF/HF ratio assesses the balance between its sympathetic and parasympathetic parts [15].
2. Deceleration/acceleration capacity (DC/AC). Both parameters correlate with the activity of the sympathetic and parasympathetic system. In the case of parasympathetic activity, a higher correlation was demonstrated for DC. These values also correlate with the cardiovascular risk [23, 24].
3. Heart rhythm turbulence (HRT). Two main parameters – turbulence onset (To) and turbulence slope (Ts) – were used. Records with at least 5 premature ventricular stimulations and those with, at least, 20% prematurity degree were regarded appropriate for interpretation [25, 26].
4. Late ventricular potentials (LP – late potentials). In order to identify late ventricular potentials, the classical Simson and Denes criteria were applied, taking into account the total QRS duration > 120 ms; RMS 40 ms < 25 μV and LAS 40 μV > 30 ms [27, 28].
5. Corrected QT interval (QTc) according to Bazett's formula. It was employed in our study with division into the day hours activity (6:00 a.m. – 10:00 p.m.) and night hours rest (10:00 p.m. – 6:00 a.m.). QT interval elongation is an independent risk factor of rapid arrhythmic death and dangerous ventricular rhythm disorders [29].

Statistical analysis

The Statistica 9 PL program of StatSoft Inc. was used to perform statistical calculations. The distribution of variables within the study population was verified using the Shapiro-Wilk W test. Student's t parametric test as well as Wilcoxon and Mann-Whitney non-parametric tests were used to assess the significance of differences between the study groups. The value of $p < 0.05$ was defined as the level of statistical significance. The results are shown as mean and standard deviation and median and max/min values. Spearman's test was used to determine the correlation between the groups of variables.

Results

The studied groups were not statistically different with regards to basic anthropometric parameters (Table I). There were 15 women, both in the study group with hepatitis C and in the control group. It was impossible to reliably assess disease duration since none of the study participants had been able to provide the time period when the symptoms occurred and which symptoms could have been associated with an early phase of HCV infection. No differences were found in maximum heart rhythm rates, while a statistically significantly higher medium and maximum heart rhythm was recorded in patients with hepatitis C. The time period from detection of the anti-HCV antibodies to the date of inclusion in our study was below 1 year.

Regarding biochemical and morphological parameters, the subjects with hepatitis C were characterised by significantly higher aminotransferase activities, while there was no such difference for the other parameters, including the albumin level (Table II). Liver biopsy results indicated grade G0 or G1 and stage S1 or S2 in the majority of patients.

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Table I. Comparison of basic parameters in the study groups. The results are presented as mean values ± standard deviation

Feature	Hepatitis C ($n = 36$)	Control ($n = 30$)	*P*-value
Age [years]	34.08 ±13.73	30.53 ±7.65	0.797
Weight [kg]	75.83 ±14.63	69.70 ±16.63	0.166
Height [cm]	172.78 ±11.85	170.10 ±11.25	0.337
BMI [kg/m²]	25.32 ±3.81	23.80 ±4.06	0.166
Max HR [beats/min]	141.78 ±18.37	144.90 ±13.45	0.503
Min HR [beats/min]	47.58 ±9.58	43.20 ±4.28	0.033
Mean HR [beats/min]	77.64 ±9.37	72.30 ±7.91	0.033

BMI – body mass index, HR – heart rate.

Table II. Comparison of basic biochemical and morphological parameters. The results are presented as mean values ± standard deviation

Feature	Hepatitis C ($n = 36$)	Control ($n = 30$)	*P*-value
ALT [U/l]	55.56 ±31.00	16.57 ±6.11	< 0.001
AST [U/l]	40.00 ±20.36	19.27 ±4.47	< 0.001
WBC [thousand/ml]	6.12 ±1.35	6.51 ±1.19	0.322
PLT [thousand/ml]	198.22 ±64.52	218.53 ±46.32	0.169
TSH [mU/l]	2.44 ±1.60	1.99 ±0.82	0.543
TC [mg/dl]	166.75 ±31.35	165.77 ±25.01	0.865
HDL [mg/dl]	60.04 ±13.84	53.45 ±9.68	0.143
TGL [mg/dl]	96.45 ±35.97	100.23 ±35.48	0.562
Tbil [mg/dl]	0.798 ±0.85	0.55 ±0.24	0.250
Albumin [g/l]	45.63 ±4.66	46.08 ±3.08	0.835

The HCV RNA levels demonstrated a distribution pattern different from its normal configuration – with the median value of 2229204 copies (min. 6800; max. 10469614). Only the presence of the viral genotype (1 and 3) was identified in the study group. Subtype 1a was found in 16 subjects, 1b in 18, while genotype 3 was identified in 3 persons only.

No statistically significant differences were noted in the basic echocardiographic parameters, including left ventricle ejection fraction. None of the examined patients demonstrated disorders in left ventricular muscle contractility.

The results, obtained from 24-hour Holter monitoring, are presented in Table III. The heart rhythm variability parameters, r-MSSD and p50NN, as well as HF, were significantly lower in the subjects with hepatitis C vs. those in the control group. The other parameters did not demonstrate any statistically significant differences. The absolute DC and AC values were also significantly lower in the sick persons. The QTc interval, measured for nocturnal hours, was also significantly longer in

that group, unlike the QTc, measured during day active hours, which did not show any statistically significant differences. Also there was no difference for the heart rhythm turbulence parameters, or for late ventricular potentials. One subject of the study group demonstrated abnormal values of both To and Ts, while another subject presented To abnormalities only. The other patients in the study group had both parameters normal. LPS was identified in 7 subjects with hepatitis C and in 6 controls. None of the studied parameters showed any statistically significant differences with regards to viral genotype.

Numerous correlations were identified among the studied parameters. One of the most interesting ones was the positive correlation among the number of viral RNA copies and DC ($R = 0.598$; $p < 0.05$) and LF ($R = 0.394$; $p < 0.05$). Also notable was the negative correlation with AC ($R = -0.515$; $p < 0.05$), QTc day ($R = -0.431$; $p < 0.05$), QTc night ($R = -0.505$; $p < 0.05$) and with the HDL cholesterol level ($R = -0.661$; $p < 0.05$). Numerous correlations were similarly demonstrated for the albumin level (Figure 1), which positive-

Table III. Comparison of parameters from 24-hour Holter monitoring. The results are presented as the median, maximum and minimum values

Variable	Hepatitis C (*n* = 36)	Control (*n* = 30)	*P*-value
SDNN [ms]	159.50 (62.00; 254.00)	161.50 (121.00; 256.00)	0.619886
SDNN-ix [ms]	64.50 (20.00; 115.00)	69.00 (43.00; 124.00)	0.177933
SDANN [ms]	144.00 (33.00; 224.00)	140.0 (81.00; 211.00)	0.928136
r-MSSD [ms]	29.50 (9.00; 81.00)	38.00 (22.00; 74.00)	0.022897
p50NN (%)	7.50 (0.00; 42.00)	15.50 (3.00; 43.00)	0.010250
TP [ms^2]	3667.35 (436.80; 12,093.00)	4530.60 (1826.70; 13725.00)	0.090240
HF [ms^2]	265.20 (21.90; 1570.60)	393.70 (166.70; 1182.80)	0.034067
LF [ms^2]	937.10 (53.60; 1913.60)	1003.55 (441.00; 2033.60)	0.204445
VLF [ms^2]	2452.75 (343.60; 8521,00)	3138.75 (1209.40; 10416.70)	0.076489
ULF [ms^2]	15.65 (2.70; 121.10)	21.75 (9.70; 90.80)	0.154506
LF/HF	3.15 (1.20; 16.90)	2.40 (1.70; 4.70)	0.093615
AC	−9.00 (−10.00; −2.63)	−9.96 (−10.00; −6.55)	0.024673
DC	7.81 (2.67; 10.00)	8.66 (6.02; 10.00)	0.033858
To	−5.07 (−9.17; 10.71)	−3.15 (−9.62; −0.06)	0.808508
Ts	20.30 (2.40; 36.70)	15.20 (9.70; 61.60)	0.823298
QTc day	443.50 (397.00; 490.00)	438.00 (414.00; 476.00)	0.273066
QTc night	448.00 (413.00; 486.00)	434.00 (417.00; 473.00)	0.022867
Total QRS	113.50 (72.00; 212,00)	101.00 (94.00; 178,00)	0.233021
LAS < 40 ms	29.00 (9.00; 79,00)	30.50 (15.00; 55,00)	0.170336
RMS voltage	100.00 (4.00; 477.00)	48.00 (11.00; 395.00)	0.633518

SDNN – standard deviation of NN intervals, SDNN-ix – the average of the standard deviations of successive intervals NN from the 5-minute test periods, SDANN – standard deviation of averaged NN intervals, r-MSSD – root mean square successive differences, p50NN – percentage of differences between adjacent NN intervals that are greater than 50 ms, TP – total power, HF – high frequency, LF – low frequency, VLF – very low frequency, ULF – ultra low frequency, AC – acceleration capacity, DC – deceleration capacity, To – turbulence onset, Ts – turbulence slope, LAS < 40 – amount of time that the QRS complex remains below 40 µV, RMS 40 – root mean square voltage of the terminal 40 ms of the QRS complex.

ly correlated with SDNN-ix (*R* = 0.483; *p* < 0.05), r-MSSD (*R* = 0.488; *p* < 0.05), p50NN (*R* = 0.453; *p* < 0.05), DC (*R* = 0.513; *p* < 0.05), TP (*R* = 0.496; *p* < 0.05), HF (*R* = 0.555; *p* < 0.05), LF (*R* = 0.541; *p* < 0.05), VLF (*R* = 0.450; *p* < 0.05), ULF (*R* = 0.390; *p* < 0.05) and Ts (*R* = 0.812; *p* < 0.05). In contrast, a negative correlation for the albumin level was demonstrated with the minimum and medium HR (*R* = –0.445 and –0.432; *p* < 0.05), AC (*R* = –0.515; *p* < 0.05), QTc day and night (*R* = –0576 and –0.386; *p* < 0.05) and To (*R* = 0.812; *p* < 0.05). AC correlated positively and DC correlated negatively with the total cholesterol level (*R* = 0.542; *p* < 0.5 and *R* = –0.481; *p* < 0.05), and the correlations with HDL were similar (*R* = 0.760; *p* < 0.05 and *R* = –0.688; *p* < 0.05) (Figure 1).

Discussion

Studies to date do not provide any unequivocal answer to the issue of possible HCV infection effects on cardiovascular risk. The actual data are largely inconsistent, although it seems that hepatitis C may be approached as a modifiable non-lipid cardiovascular risk factor, which can be eliminated, such as e.g. vitamin D deficiency [30, 31]. The determination of infection duration is another issue. Following the earlier reports, demonstrating a lack of significant differences or even a more favourable lipid profile in patients with chronic hepatitis C, we did not observe any statistically significant differences in our study in the levels of particular lipid fractions, either [6, 13]. It may indicate other mechanisms involved in cardiovascular risk increase in this group of patients; also such mechanisms may cause accelerated sclerosis progression.

Beside a cardio-metabolic evaluation, we used a broad range of non-invasive parameters, available during the analysis of the long-term ECG recording
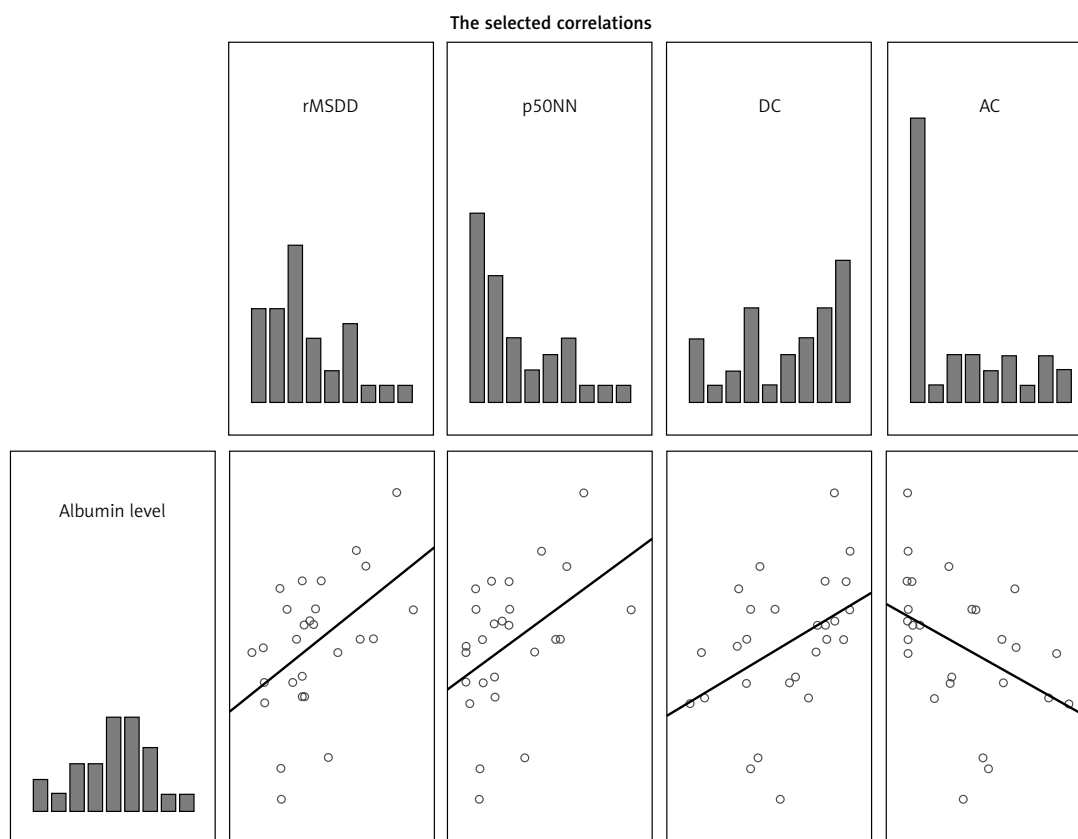
The selected correlations

Figure 1. Correlations of root mean square successive differences (rMSDD), percentage of differences between adjacent NN intervals that are greater than 50 ms (p50NN), acceleration capacity (AC) and deceleration capacity (DC) with albumin levels

by the Holter method, including the parameters which determine the functions of the autonomous system. With regards to available knowledge, it has been the first attempt of using HRT parameters for cardiovascular risk evaluation in patients with chronic hepatitis C. HRT is a prognostic method that is more and more broadly used in many cardiovascular diseases, as well as in other clinical conditions. This method has been confirmed, among others, in patients with heart failure, after myocardial infarction and in many other conditions [17, 20, 25]. In our earlier studies, we demonstrated HRT disorders, especially of To in patients with decompensated cirrhosis, regardless of its aetiology [19]. It was an indication of a significantly increased risk of sudden cardiac death in that group of patients. In the case of treatment naive patients with chronic hepatitis C, we did not find any statistically significant differences between the study group and the control group with healthy persons. Nor were abnormal To/Ts values present in more than 2 persons only. On the other hand, the observed strong correlation of HRT with albumin levels was a fairy interesting observation. The causes of that phenomena are, at least so far, rather difficult to explain. It may be evidence of HRT dependence on the degree of liver compe-

tence, as well as on late complications of hepatitis, while it does not occur in early stages of HCV infection, regardless of infection activity, determined by the number of viral RNA copies. So far, there have been no literature data on this issue.

The presence of late ventricular potentials is another parameter used in cardiovascular prediction. They are usually observed in hypoxic or injured cardiac muscle as a result of disturbed intraventricular conduction [27, 28]. In our studies, no significant difference was found in the incidence of LP between the patients with HCV and healthy persons; also no significant difference was found in the particular parameters used to confirm their presence, including the duration of QRS, LAS 40 ms and RMS. These differences may, as in the case of HRT, perhaps appear only in the course of infection or take a longer time to be seen only with growing fibrosis. The latter assumption seems to be possible as fibrosis intensification was demonstrated in that group of patients by MRI scanning. The occurrence and a higher degree of myocardial fibrosis were associated with an increased cardiovascular risk [32]. Hiramatsu *et al.* [33] demonstrated in a group of 22 subjects a transient growth of late potentials and disturbance of their parameters in the course of hepa-

titis C therapy with interferon. However, it did not result in a higher incidence of dangerous ventricular arrhythmia. Also, the disorders disappeared after the therapy was completed.

QT interval prolongation is a proven risk factor of dangerous ventricular arrhythmias [29]. It has been confirmed in studies of liver diseases, including cirrhosis and hepatic failure. Cichoż-Lach *et al.* [34] demonstrated QTc prolongation regardless of cirrhosis cause or its progression. The biggest QTc prolongation was, however, characteristic of patients with cirrhosis, resulting from chronic hepatitis C. Saleh *et al.* [35] similarly observed significant prolongation of QTc in a group of patients with chronic hepatitis C, accompanied by diastolic function disorders in the left ventricle, visualised in a tissue Doppler image, plus by an increased NT-proBNP level. We demonstrated an analogous QTc prolongation in our study, especially during night hours. That prolongation strongly correlated with the number of HCV RNA copies and with the albumin level. It may have indicated a certain dependence of QTc prolongation on the level of infection activity and, contrary to hepatic cirrhosis, on the degree of liver functionality disorders. Its very early occurrence is also possible, already at the stage of viral infection. The report by Nordin *et al.* [9] brings up some interesting data. In their study, QTc prolongation in patients with chronic hepatitis C was significantly greater in cases of concomitant infection with HIV. According to those authors, each of the two viruses, i.e. HCV and HIV, independently elongated QTc, while the coexistence of those two infections significantly increased the risk of dangerous ventricular rhythm disorders.

Disturbed autonomic control is one of the major cardiovascular risk predictors. It is, among others, observed in diabetes mellitus and in heart failure [36, 37]. Moreover, in cases of chronic liver diseases, Hendrickse *et al.* [38] observed that the presence of autonomic neuropathy caused a 4-fold increase in the mortality rate within a 4-year observation period, irrespectively of liver disease severity. Beside HRT, the main elements which determine the sympathetic-parasympathetic balance should include the heart rhythm variability and the acceleration/deceleration capacity. Their significance has been proven in many conditions, including coronary disease, heart failure, hypertension, and liver diseases, including cirrhosis [15, 16, 18, 39–41]. The autonomic balance evaluation is also carried out by means of other methods. Coutinho *et al.* [11] used in their study respiratory sinus arrhythmia (RSA), the tilt test (TT), sustained hand grip (HG) and the Valsalva manoeuvre (VM). Out of all the examined patients, 66.7% of those with chronic hepatitis C present-

ed with disturbed autonomic functions. In turn, Osztovits *et al.* [12] making use of HRV analysis, demonstrated a broad range of autonomic balance disorders. They mostly concerned abnormalities of the parasympathetic system and the shift of balance levels towards the sympathetic part. In the authors' research, a significant reduction was found of parameters of the parasympathetic system and vagus nerve activity, including DC, r-MSSD, p50NN and HF. What is even more interesting, they positively correlated with the albumin level. That correlation may be indicative of early autonomic disorders in the course of HCV infection and of increasing parasympathetic insufficiency with growing hepatic function disorders. It is in line with our earlier studies. In those studies, we demonstrated a similar profile of autonomic disorders in patients with cirrhosis decompensation [40]. The parasympathetic system characterising parameters were also significantly lower in that particular case. A shift of the autonomic balance for the benefit of the sympathetic system is a significant factor that may increase cardiovascular risk, including the risk of sudden cardiac death. Such a status is characteristic both for diseases of the cardiovascular system, including heart failure [42], and many other disorders, e.g., testosterone deficit [43]. No causes of autonomic system disorders have yet been identified in the course of hepatitis C. Effects of the virus itself are here fairly realistic or of antibodies which occur in response to infection. According to Glišić *et al.* [44], such a role may be played by the muscarinic receptor of type 3 (M3R), which, via interactions, either directly with NS5A viral protein or with anti-M3R antibodies, induced by the receptor, leads to cardiovagal dysfunction.

In conclusion, we confirmed in our study the presence of a whole range of autonomic disorders in patients with chronic hepatitis C. These disorders are characterised by the prevalence of sympathetic system activity with significantly disturbed parasympathetic activity. The causes of this phenomenon are not fully recognised. Moreover, patients with hepatitis C present other factors of cardiovascular risk, such as prolonged QTc. However, no significant differences were observed with regards to either HRT parameters or LPs. Interestingly, the AC/DC and QTc parameters significantly correlated with infection intensity, expressed as the number of viral RNA copies. In turn, the majority of studied variables correlated with albumin levels. Unfortunately, a complete explanation of this phenomenon is still lacking. This may, among other things, indicate a selective influence of infection on particular studied parameters and, in the case of albumins, it may suggest a correlation between the level of this

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albumin and autonomic system efficiency. Nevertheless, our results suggest that HCV infection could be an independent cardiovascular risk factor, not associated with the lipid profile. Further prospective studies are needed to confirm this hypothesis.

The authors are aware of numerous limitations of the reported study. First, the study involved a relatively small number of subjects. However, we did try in their selection to eliminate any possible disturbing factors of recognised effects on the studied parameters, including medicinal agents and concomitant conditions. As a result, we managed to select a group of patients with chronic HCV infection only. The already mentioned impossibility to precisely quantify the HCV infection duration was another limiting factor. The course of hepatitis C is usually asymptomatic; thus the examined persons learned about their condition purely incidentally. Because of the planned procedure of the research project, i.e. ECG recording in home conditions and in the course of normal activity, neither standardisation nor full control of the study was possible, including, for example, environmental temperature control. The study participants were, however, informed about planned sleep hours and about the requirement to avoid any possible factors disturbing ECG records. As a result, all the obtained electrocardiograms presented appropriate quality, enabling their full interpretation. Despite the mentioned limitations, we assume that the obtained results may contribute to triggering further studies, specifying the mechanisms of HCV infection effects on cardiovascular risk.

Acknowledgments

Conflict of interest

The authors declare no conflict of interest.

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