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ARRHYTHMIAS INCLUDING ATRIAL FIBRILLATION CLINICAL COURSE AFTER CORONAVIRUS INFECTION

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This study aimed to determine how coronavirus infection provoked arrhythmias. Fifteen patients with arrhythmias who had coronavirus infection (group C +) and 10 patients who had the same arrhythmias but did not pass through COVID-19 (group C-) were examined. In most cases, atrial fibrillation or atrial flutter dominated in patients of both examined groups – 86.6 % and 80 % appropriately. Age and overweight are risk factors for arrhythmia onset after coronavirus infection. The frequency of paroxysms increased by 88.9 % in patients with AF who underwent coronavirus infection, p<0.005.

Key words: COVID-19, cardiac arrhythmias, atrial fibrillation, echocardiography.

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КЛІНІЧНИЙ ПЕРЕБІГ АРИТМІЙ, ВКЛЮЧАЮЧИ ФІБРИЛЯЦІЮ ПЕРЕДСЕРДЬ ПІСЛЯ КОРОНАВІРУСНОЇ ІНФЕКЦІЇ

Метою цього дослідження було визначення того, як коронавірусна інфекція провокувала аритмії. Було обстежено 15 хворих з аритміями, що перенесли коронавірусну інфекцію (група С+), та 10 хворих, що мали такі ж аритмії, і не хворіли на COVID-19 (група С-). В більшості випадків у хворих обстежених груп домінували фібриляція чи тріпотіння передсердь – відповідно у 86,6 % та 80 %. Вік та надлишкова маса тіла є факторами ризику появи аритмії після короновірусної інфекції. У хворих на ФП, що перенесли короновірусну інфекцію частота пароксизмів збільшилась на 88,9 % пацієнтів, p<0.005.

Ключові слова: COVID-19, порушення ритму серця, фібриляція передсердь, ехокардіографія.

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Coronavirus disease 2019 (COVID-19) is a new, highly contagious and severe disease caused by a strain that has spread rapidly around the world. So far, almost 11 million cases have been diagnosed and more than 500,000 people have died [10]. However, the true prevalence is probably much higher, as many people have the asymptomatic disease and therefore have never been tested. Some reports show that up to 80 % of infected people have mild or moderate symptoms and, in theory, represent a group that may not seek medical care and therefore the true prevalence rate of infection is artificially lowered [6, 8].

Although electrophysiology, calcium level, and structural remodelling play a key role in the pathophysiology of atrial fibrillation (AF) [13, 14], the clinical course of AF is diverse, and the exact mechanisms of AF remain unclear in many patients [2]. There are no specific reports of AF during COVID-19 infection. According to the available literature, among patients with COVID-19 AF was detected in 19 % to 21 % of all cases [3, 4]. The main causes of AF in patients with COVID-19 are mostly unknown. In a small report, up to 75 % of hospitalized geriatric patients with COVID-19 had a history of AF [10]. Based on case reports [9, 11] and small clinical trials [12], new AF ranges from 3.6 % to 6.7 % in patients with COVID-19.

The pathophysiology of COVID-19-related AF is poorly understood, and probable mechanisms include decreased angiotensin-converting enzyme 2 (ACE2) receptor availability, CD147 protein and sialic acid interactions, enhanced inflammatory signaling, and ultimately inflammatory cytokine induction, electrolyte disorders and acid-base balance in the acute phase of severe disease and increased adrenergic activation [15]. On the contrary, many virologists and health experts made a conclusion that an effective vaccine will help us to achieve a certain level of immunity, so treatment and therapy will continue to reduce suffering, but the virus is likely to continue circulation. In addition, for those who are vulnerable, it is prognosed to be a serious danger.

One common problem with both COVID and AF is that each disease increases the risk of thrombosis and stroke [10]. Such serious medical problems as obesity, hypertension, heart failure, diabetes and vascular diseases increase risk of both these clinical situations. Unfortunately, when COVID and AF are combined, there is a possibility of a synergetic risk effect, which makes the risk of stroke even higher.

The purpose of the study was to determine how often the coronavirus infection provoked arrhythmias including atrial fibrillation, how their clinical course has changed compared to cases without coronavirus history.

Materials and methods. All included patients were consulted in the Expert Consultive-Diagnostic and Treatment Center of Life-threatening Arrhythmias of National Scientific Centre "M. D. Strazhesko Institute of Cardiology" National Academy of Medical Sciences of Ukraine from May to June 2021.

Fifteen patients with arrhythmias who had coronavirus infection (CI) (group C +) and 10 patients who had the same arrhythmias and did not have COVID-19 (group C-) were examined. A comparative analysis of these groups of patients with cardiac arrhythmias depending on the CI was provided.

Analyzing clinical data body mass index (BMI), coronary heart disease (CHD) and hypertension (AH) history, systolic (SBP) and diastolic (DBP) blood pressure level, heart failure (HF) class and oxygen saturation were considered. Daily ECG monitoring was performed using Solvay recorders (Ukraine). Evaluated: mean heart rate (HR) per minute, both on sinus rhythm and during AF, the total number of supraventricular extrasystoles (SE) and ventricular extrasystoles (VE) per day, the presence of supraventricular tachycardia (SVT) paroxysms and unstable ventricular tachycardia (UVT), AF, cardiac conduction disorders. Frequency and spectral parameters were used to estimate heart rate variability (HRV) parameters. HRV frequency characteristics: SDNN (ms) **–** standard deviation of all RR-intervals and its index – iSDNN; SDANN5 (ms) **–** standard deviations of the mean values of RR-intervals, calculated at 5-minute intervals throughout the recording; RMSSD (ms) is the square root of the mean sum of the squares of the differences between adjacent RR intervals. Spectral characteristics of HRV: LF (ms^2) **–** low-frequency (slow-wave) part of the spectrum of oscillations in the frequency range from 0.04 to 0.15 Hz; HF (ms^2) – high-frequency component of the spectrum of oscillations in the frequency range 0.15**–**0.5 Hz and sympatho-vagus balance **–** LF/HF ratio.

Transthoracic echocardiography (EchoCG) using the ultrasound system "Philips HD 11 XE" and "MEDISON 9900" was used to assess the structural, functional and hemodynamic parameters of the heart at rest. In B-mode, the end-diastolic volume (EDV) of the LV, the end-systolic volume (ESV) of the LV, and the LV EF were calculated using the biplane method of disks (modified Simpson's formula) [11].

Statistical processing of the results was performed using Excel XP software (Microsoft Office, USA) and statistical program Statistica 10.0 Portable (Statsoft, USA). Calculated the mean value (M), the error of the mean value (m), the criterion of reliability (t) and the value of reliability (p), at $p<0.05$ differences were considered significant. The relationship between the variables was determined using parametric correlation analysis.

Results of the study and their discussion. Fifteen patients with arrhythmias who had coronavirus infection (group C +) and 10 patients who had the same arrhythmias and had no COVID-19 (group C-) were examined aged 63.7±1.8 years against 60.8±0.7.

Patients in the (C +) group had 11 cases of AF (73.3 %), 2 cases of AFl (13.3 %), 1 **–** SVT (6.7 %), 9 **–** VE (60.0 %), 10 **–** SVE (66.7 %). In addition, among the examined patients with atrial fibrillation in the group (C+) paroxysmal form of AF occurred in 6 pts out of 11 (45.4 %), persistent form of AF in 3/11 (27.3 %), permanent form of AF 3/11 (27.3 %). In contrast, in patients of group (C -) AF occurred in 7 out of 10 hospitalized patients (70 %), 1 had AFl (10 %), 1 had SVT (10 %), 7 **–** VE 70 %), 6 **–** SVE (60 %). Accordingly, among patients with AF in the group (C -): 4/7 **–** a paroxysmal form of AF (57.1 %), 1/7 – a persistent form of AF (14.3 %), 2/7 **–** a permanent form of AF (28.6 %). Thus, in the presence of the most frequent arrhythmias, the examined groups did not differ significantly. In most cases, patients AF dominated, respectively, in 73.3 % and 70 %. Thus, our data coincide with the literature data that among patients with COVID-19, AF is one of the most common forms of arrhythmias.

As one can see from comparative table 1, the groups by the condition of comorbidities were completely comparable. However, a number of issues arise regarding the age, physique of patients and HR on SR.

Patients with coronavirus infection were older and had a higher BMI and heart rate on SR in rest than patients without a coronavirus infection history. The CHD and AH experience, the level of systolic SBP and DBP, as well as the level of blood oxygen saturation significantly had no difference. That is, it can be argued that age and overweight are risk factors for arrhythmia onset after coronavirus infection. A high HR at the time of study inclusion was the evidence of readiness for the paroxysmal tachyarrhythmias development.

It should be noted that during groups formation not only clinical and anthropometric data were mentioned, but also the presence of certain arrhythmias.

As can be seen from the table above, comparing the presence of the most frequent arrhythmia the examined groups of patients had no significant difference.

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Clinical and anthropometric data and Holter ECG results of the examined patients

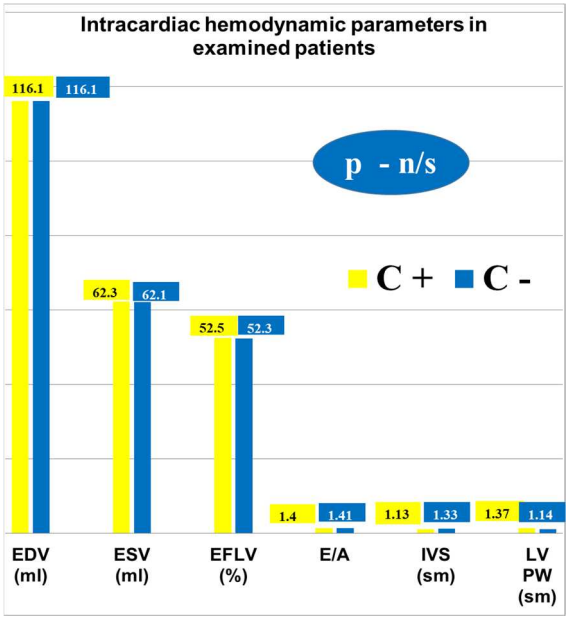
Parameter	Group C+	Group C-	p
Number	15	10	-
Age (years)	63.7±1.1	60.8±0.7	<0.05
BMI (kg/m2)	27.0±0.6	25.5±04	<0.05
CHD (number and %)	9/15 (60 %)	6/10 (60 %)	n/s
NYHA HF class	1.5±0.2	1.6±0.2	n/s
AH (number and %)	9/15 (60 %)	6/10 (60 %)	n/s
SBP (mm Hg)	132.7±2.7	137.2±2.9	n/s
DBP (mm Hg)	80.7±3.6	87.6±3.4	n/s
HR (bpm)	97.9±2.9	80,1±0.9	<0.001
SpO2 (%)	97.5±0.6	97.2±0.4	n/s
AF (number and %)	11/15 (73.3 %)	7/10 (70.0 %)	n/s
Paroxysmal AF (number and %)	6/11 (54.4 %)	4/7 (57.1 %)	n/s
Persistent AF (number and %)	3/11 (27.3 %)	1/7 (14.3 %)	n/s
Permanent AF (number and %)	3/11 (27.3 %)	2/7 (28.6 %)	n/s
Atrial flutter (number and %)	2/15 (13.3 %)	1/10 (10.0 %)	n/s
AV tachycardia (number and %)	1/15 (6.7 %)	1/10 (10.0 %)	n/s

Notes: n/s – not significant, heart rate min. – the minimum heart rate

It should be noted that among 15 patients in group C + before coronavirus disease 6 (40 %) had no cardiac arrhythmias that could disturb them. It can be argued that there is a direct relationship between coronavirus infection and arrhythmias.

It should be also mentioned that first reports from China noted that hypertension was one of the most common comorbidities in 20–30 % of cases. This analysis did not consider age, which is important because hypertension is very common in the elderly (~ 50 % of people over 60 years old are hypertensive), and the prevalence of hypertension increases sharply in very old people. Older age is also the most important risk factor for serious complications and death due to COVID-19, therefore, older patients with severe infection due to older age can expect a high incidence of hypertension. To date, there is no evidence that hypertension itself is an independent risk factor for severe complications or death from COVID-19 infection.

As it is depicted in this table, patients in group C + had higher mean and maximum heart rate. Heart rate, as well as a clearly reduced temporal rate of heart rate variability, such as SDNN – standard deviation of mean RR intervals at electrocardiogram, indicate certain denervation of the heart due to coronavirus infection.



Note: EDV – End-diastolic volume, ESV – End-systolic volume, EFLV – Left ventricular ejection fraction, E/A – Peak ratio of transtricuspid flow, IVS – interventricular septum, LV PW –Left ventricular posterior wall

During Holter's ECG monitoring assessment we found out that patients in the group (C+) experienced a higher average HR 78.3±2.4 bpm, which is higher than this figure in patients in the group (C-) – 68.4±2.1 (p<0.05). The maximum heart rate also had a significant difference: in the surveyed group (C+) it is 117.9±3.5 vs. 109.8±2.6 in patients in the group (C-), where the reliability rate is p<0.05. As for the indicators of the minimum heart rate in patients who had a rhythm disturbance before the coronavirus infection (C+), it was 50.8±1.9 vs. 109.8±2.6 in patients in whom arrhythmia appeared after coronavirus infection. These indicators had no reliable difference. We noticed a clearly reduced time rate of heart rate variability, such as SDNN – the standard deviation of average R-R intervals on an electrocardiogram, which indicates a certain denervation of the heart due to coronavirus infection, and therefore readiness for the development of cardiac arrhythmias. Other indicators of heart rate variability, such as SDANN – standard deviation of

average SDNN values of 5 (10) – minute segments for average duration, hours or 24-hour records and RMSSD – the standard (average quadractic) deviation of the difference in consecutive RR intervals in patients of both groups had no reliable difference. SDANN in group (C+) was 116.8±4.2 against 128.3±4.5 in group (C-). The same applies to RMSSD in group (C+) of 73.6±2.2 versus 76.8±2.2 in group (C-). According to the results of the study, the indicators of maximum pause did not exceed 2.5 on the sinus rhythm and 3.0 s with atrial fibrillation. We recorded such indicators in the group (C+) they amounted to 1.79±0.4 against 1.82±0.5 in group (C-).

To evaluate the intracardiac hemodynamic influence on the cardiac arrhythmias occurrence and according to the protocol of examinations, all patients underwent echocardiography.

As it is depicted on the graphic, in patients who were examined main indicators of intracardiac hemodynamics were comparable in both groups. So, myocarditis, following coronavirus infection (based on inflammation of the heart muscle) and cardiac arrhythmias, especially paroxysmal, may develop as a result of fibrotic changes due to COVID-19 disease, are likely to be considered.

A treadmill test to determine exercise tolerance, diagnose coronary heart disease and arrhythmias occurrence was performed. The data obtained are shown in table 2.

Table 2

Treadmill test results in examined patients

Parameter	Group C+	Group C -	p
Exercise value (ME)	5.6±1.2	7.1±0.2	<0.05
Exercise duration (min.)	3.9±0.8	14.3±0.7	<0.001
HR on exercise peak (bpm)	120.2±5.3	136.0±4.0	<0.05
SBP on exercise peak (mm Hg)	178.0±6.3	185.0±5.0	n/s
DBP on exercise peak (mm Hg)	95.0±4.1	102.0±2.0	<0.05
Double product (c.u.)	226.2±8.5	251.8±4.2	n/s
IHD Positive test (%)	66.7	50.0	n/s
Provoked arrhythmia (%)	66.7	50.0	n/s

As it is shown patients with coronavirus infection had lower exercise tolerance, significantly lower heart rate and BP on exercise peak. In patients of this group the test was also positive for coronary heart disease and more often various arrhythmias were provoked, which may indicate microcirculation system damage due to COVID-19 infection.

Our results demonstrate that the coronavirus infection is a predictor of new arrhythmia episodes development and is also the cause of the existing arrhythmia deterioration [1]. The most common type of arrhythmias was atrial fibrillation, which accounted for 73.3 % of the remaining rhythm disturbances [6, 8]. The number of patients with COVID-19 AF is by 2–4 times higher than in the general population. Recall that every 3–4 patients out of 10 who have fallen ill with coronavirus have AF [4]. In particular, the frequency of new episodes of AF increased by 2.7 times ($p<0.001$). It should be noted that not only the frequency of paroxysms increases, but also their duration, on average from 7.5±1.2 to 20.8±1.5 days, that is, by 2.8 times longer than in patients who had no coronavirus infection ($p<0.001$). As COVID-19 is an acute disease with an incubation period of 14 days on average, we understand that this is a short time for fibrosis [3, 5]. Although structural remodellinging of the atria is an important component for providing a substrate that supports AF, the onset of AF and its paroxysms are often associated with acute COVID-19 infections. It is possible that these changes in the arrhythmia course are associated not only with the fibrosis formation in the myocardium, but also with the development of acute sytem inflammation [3]. Probably, some patients with COVID-19 with newly diagnosed AF may have an existing substrate for AF, and acute COVID-19 infection may be a trigger for initiating AF, which is consistent with the temporary relationship between the new phenomenon of AF and COVID-19 infection [2].

It should be noted that patients with COVID-19 who developed arrhythmias were older, and most of them had at least one existing risk factor, including hypertension [13, 14]. In particular, those patients who had a coronavirus infection and arrhythmias were older than 63.7±1.1 against those who had no history of arrhythmias 60.8±0.7 (<0.05). As for the other cohorts of patients, we have similar results. Patients who had coronavirus infection and had arrhythmia were older than those who had arrhythmia, but did not suffer from COVID-19, namely 61.8±0.9 against 66.2±1.2 (<0.05).

Changes in heart rate variability, namely SDNN before and after Covid-19 infection, allow you to suspect the risk of potentially life-threatening arrhythmias and needs further study.

Conclusions

1) Cardiac arrhythmias after COVID-19 infection occurred in 40 % of patients (AF in 33.3 % and 6.7 % – AFl).

2) Coronavirus infection significantly worsens the course of arrhythmias and often provokes new arrhythmias onset, mainly atrial fibrillation and atrial flutter.

3) Patients with COVID-19 had higher mean and maximum heart rates, as well as decreased SDNN, indicating a violation of the autonomic balance of the heart nervous system due to coronavirus infection.

4) Decreased exercise tolerance and more frequent provocation of arrhythmias in patients with coronavirus infection may indicate microcirculation system damage due to COVID-19.

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