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Interrelation of plasma haemostasis and heart rate variability in patients with chronic coronary syndrome in combination with COVID-19

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Abstract. The aim of the study was to identify the relationship between activated partial thromboplastin time, prothrombin time, fibrinogen, D-dimer and indicators of N-N interval deviations, heart rate, on the one hand, and to identify the relationship between parasympathetic and sympathetic heart rate activity and dynamic blood viscosity, on the other hand. The COVID-19 pathogen affects the functioning of the parasympathetic and sympathetic nervous systems, which also changes the heart rate. To study this process, a group of 10 patients with chronic coronary syndrome in combination with COVID-19 without comorbidities aged 35-48 years was observed in a hospital. To study this relationship, plasma haemostasis parameters (activated partial thromboplastin time, prothrombin time, fibrinogen, D-dimer) and heart rate variability were taken at the time of admission to the hospital and after discharge from the hospital. A direct correlation between the indicators was found: in patients 1 and 4, at the time of admission to the hospital, there was an increase in activated partial thromboplastin time, prothrombin time, D-dimer and a decrease in fibrinogen, which coincides with an increase in heart rate, 5-10 minute and long-term deviation of the N-N segments. That is, changes in blood plasma affect the rhythm of the heart already at the onset of COVID-19 in combination with chronic coronary syndrome. Patients 1 and 4 had an increase in D-dimer at the time of discharge from the hospital, which coincided with an increase in heart rate. Patients require further follow-up, as these are signs of a cautious prognosis. All other plasma haemostasis parameters are normal in all patients, with minor changes. It is necessary to monitor plasma haemostasis and heart rate variability to adjust treatment during hospitalization of patients with chronic coronary syndrome in combination with COVID-19 and after discharge from hospital

Keywords: activated partial thromboplastin time; prothrombin time; fibrinogen; D-dimer; N-N interval; parasympathetic-sympathetic activity

INTRODUCTION

Almost immediately after studying the pathogenesis of COVID-19, it became clear that it is more complex than just viral pneumonia and acute respiratory distress syndrome [1-3]. The relevance of studying the impact of this infection on the cardiovascular system is based on the fact that the "cytokine storm" caused by uncontrolled Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection and the release of pro-inflammatory cytokines causes damage to many organs, including the heart. Another mechanism that causes cardiovascular manifestations is discoagulation and thromboembolic circumstances. The most common comorbidities were found in critically ill patients treated in intensive care units. The mechanism of chronic coronary syndrome (CCS) in patients with COVID-19 is not known for certain. It is assumed that it can be a spasm of the coronary arteries, the formation of microthrombi on the background of systemic inflammation or rupture of an atherosclerotic plaque.

That is, coronary thrombosis caused by endothelial dysfunction is a common process in COVID-19. This is not

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a theory, but a scientific axiom, and is an urgent problem of modern COVID-19 therapy. L. Chen *et al.* [4] documented cases where people who did not have cardiovascular disease at all (or had it latently) went to the hospital because of cardiovascular symptoms and were later diagnosed with COVID-19.

Thrombosis in COVID-19 has two possible origins. The first is that the virus damages the endothelium (the inner surface of blood vessels). In response to the invasion of the virus, pro-inflammatory proteins are produced on the endothelium, and the process of thrombosis begins. The second version of thrombus formation is associated with the effect of the virus on the immune system. A distinctive feature of SARS-CoV-2 is that it provokes a strong immune response. If the body cannot cope with the virus quickly, a so-called cytokine storm occurs. This is a complete "disorientation" of the immune system, when macrophages, the cells that protect the body, give a hyperresponse – they increase the synthesis of cytokines. This is followed by a whole cascade of reactions that leads to the production of substances that activate platelet and plasma haemostasis, and pathological thrombosis can begin even in intact vessels. Despite the possibility of developing CCS in SARS-CoV-2 infected individuals, the number of hospitalised patients with CCS has significantly decreased during the COVID-19 outbreak. According to M. Chung *et al.* [5] and E. Driggin *et al.* [6], it decreased by 40-50% in some countries.

The treatment of ST-segment elevation CCS in patients with COVID-19 should not differ from uninfected patients, and testing for SARS-CoV-2 should not delay revascularization. In turn, the management of patients with non-ST-segment elevation CCS should be based on risk stratification (very high, high, moderate, and low). Thus, patients with very high risk (criteria – unstable haemodynamics or cardiogenic shock; chest pain resistant to drug therapy; cardiac arrest or life-threatening rhythm disturbances; mechanical complications; acute heart failure and ST-segment elevation) should receive urgent invasive care. The exact mechanism of discoagulation in COVID-19 patients is not known. One hypothesis is that a severe inflammatory response and endothelial damage may have a prothrombotic effect. Also, blood stasis and immobilization of critically ill patients contribute to thrombosis. It is also worth noting the interaction of many drugs used to treat patients with COVID-19. For example, the combination of antiviral drugs lopinavir-ritonavir is metabolised through cytochrome P-450 3A4, which is also used to metabolise anticoagulants and antiplatelet agents. Consequently, the use of these drugs in the treatment may reduce the effectiveness of antithrombotic therapy. Finally, the amount of viral load in SARS-CoV-2 infection correlates with the severity of the disease, with higher viral loads at presentation correlating with the worst outcomes. The effect of SARS-CoV-2 on the heart has many manifestations, which are generally manifested by endothelial cell dysfunction. This causes changes in blood density, the formation, or destruction of blood clots, narrowing of the vessel span (including coronary vessels) and even destruction of the vessel structure.

Cardiovascular disease can occur in a healthy person in the post-COVID period, chronic, or mild cardiovascular disease becomes more severe during inpatient treatment for COVID-19, and the presence of any cardiovascular disease is a negative element in predicting the course of COVID-19. All of these theses are presented in the scientific articles by O. Golubovska [1] and M. Ackermann *et al.* [2].

R. Esmel-Vilomara *et al.* [7] and S.C. Fang *et al.* [8] point out the potential importance of direct viral toxicity in the pathogenesis of COVID-19 infections. The pathogenic effect of COVID-19 on the lungs causes an ischaemic effect, and in combination with the effect on the coronary vessels (compilation with ACE2), it increases the likelihood of myocardial infarction.

The complex interrelationships of the simultaneous effects of SARS-CoV-2 on the nervous system (which affects heart rate), the respiratory system (which also affects heart rate and plasma haemostasis), blood plasma levels (which changes the functioning of coronary vessels) and the vascular system (which affects plasma haemostasis). That is, plasma haemostasis and heart rate form the basis of this pathogenic effect. Thus, the aim of the study was to prove the direct mutual influence of changes in the two most important elements of the cardiovascular system: plasma haemostasis and heart rate. Thus, the tasks for achieving this goal are to study the theoretical basis of the problem under study; to identify the relationship between heart rate (HR), mean daily heart rate variability (SDANN), mean heart rate variability index (SDNN-i) and activated partial thromboplastin time (APTT), prothrombin time (PT), fibrinoge, D-dimer; to identify the relationship between the low-frequency component of heart rate variability (LF), the power of heart rate oscillations in the high-frequency range (HF) and dynamic blood viscosity.

LITERATURE REVIEW

A number of studies have closely linked coronary pathophysiological phenomena to the course of COVID-19. For example, M. Ackermann *et al.* [2] noted direct damage to the vascular endothelium by the COVID-19 virus in the deceased; Z. Varga *et al.* [9] describe a series of cases of 3 patients with SARS-CoV-2 infection, where they demonstrated damage to the capillary endothelium by the virus with the development of endotheliitis in organs such as the intestines, lungs, and kidneys; O. Golubovska [1] studied post-COVID syndrome. According to her, endotheliitis explains systemic microcirculatory disorders and their clinical consequences in patients with COVID-19. Obviously, similar processes can occur in coronary vessels.

L. Chen *et al.* [4] and M. Hoffmann *et al.* [10] went even further in their studies when they examined the importance of angiotensin-converting enzyme 2 (ACE2). These studies are interesting because they proposed and confirmed the mechanism of pathogenesis by which it contributes to SARS-CoV-2-associated myocarditis, SARS-CoV-2 infects myocardial cells that express ACE2. These two pathological links (ACE2 expression and myocardial damage) mutually influence each other and create a pathophysiological vicious circle. Studying the mechanism of SARS-CoV-2 impact, M. Vaduganathan *et al.* [11] noted the importance of ACE2 penetration and its expression inhibition in the pathogenesis of SARS-CoV-2-associated myocarditis. This leads to a decrease in angiotensin absorption.

The impact of SARS-CoV-2 on heart rhythm has been observed since the first days of studying this pathology. D. Wang *et al.* [12] note that one of the first reports on

COVID-19 infected patients in Wuhan indicated that 46% of patients had some kind of comorbidity. The most common were hypertension (31%), cardiovascular disease (15%), and diabetes mellitus (10%). The trend was confirmed by further studies. COVID-19 infection can cause acute coronary syndrome. Thus, in a series of 18 patients with COVID-19 with ST-segment elevation on electrocardiography and suspected myocardial infarction, 5 patients required percutaneous coronary intervention. Observations by G.G. Stefanini *et al.* [13] showed that about 60% of patients infected with SARS-CoV-2 and ST-segment elevation had obstructive coronary disease and indications for revascularization. In 24 out of 28 patients in this series, the primary diagnosis was acute coronary syndrome, thus being the main manifestation of COVID-19. The problem is exacerbated by the fact that the development of ST-segment elevation and non-ST-segment elevation heart disease with the onset of heart pain may seem insignificant to a patient compared to the risk of going to the hospital during a pandemic, even if they already have undiagnosed COVID-19. This has led, for example, to the mandatory testing for COVID-19 for all patients with signs of SARS-CoV-2-associated myocarditis in Hong Kong.

CCS becomes acute after contracting COVID-19. Myocardial damage, defined as an increase in cardiac biomarkers or changes in electrocardiography, is observed in 5-20% of patients. Myocardial damage was most commonly observed in patients with severe disease treated in intensive care units and was associated with poorer outcomes and mortality. Another mechanism that causes cardiovascular manifestations is discoagulation and thromboembolic circumstances.

In their works, E. Driggin *et al.* [6] and N. Tang *et al.* [14] note a number of pathophysiological phenomena in patients with SARS-CoV-2 infection that sometimes act together and contradict each other according to pathophysiological logic: endothelial inflammation, increased coagulation and disseminated intravascular coagulation (DIC), thrombosis, and ischaemia. The mechanism of myocardial damage caused by SARS-CoV-2 is not fully understood, but it may be caused by systemic inflammation or direct infection of cardiomyocytes.

Deep vein thrombosis and pulmonary embolism are common complications in critically ill patients with COVID-19. Thus, according to autopsy data, deep vein thrombosis was detected in 58% and pulmonary embolism in 33% of patients who were not diagnosed with venous thrombosis during life. According to Y.D. Gao *et al.* [15] and J.M. Grégoire *et al.* [16], arterial thrombosis is also common in SARS-CoV-2 infected patients.

In addition, the presence of coronary artery disease, heart failure, arrhythmias, chronic obstructive pulmonary disease, age over 65 years and smoking in patients with COVID-19 are independent risk factors for in-hospital mortality. The impact of SARS-CoV-2 on the hypothalamus-pituitary-adrenal axis and the autonomic nervous system (ANS) should be considered separately, as its disorders are clinically manifested by changes in heart rate variability (HRV) and pathophysiologically contribute to cardiac death. This is stated in the works of K. Lundstrom *et al.* [17], S. Mandal *et al.* [18], and C. Minguito-Carazo *et al.* [19].

X. Yang *et al.* [20], X.W. He *et al.* [21], and Y.Y. Zheng *et al.* [22] note in their works that nine reports reported the association of acute heart injury with death, as well as dynamic changes in cardiac biomarkers during hospitalization. Scientists have noted a link between clinical symptoms of heart disease at the onset of the disease and the course of COVID-19. S.L. Harrison *et al.* [23], G. Hindricks *et al.* [24], and Q. Husain *et al.* [25] pointed out that heart disease progresses during the disease and can even occur in people who did not have heart disease before the disease. Thus, the review concluded that endotheliitis is the cause of cardiac pathologies in COVID-19, which causes the deterioration of both healthy hearts and hearts with chronic heart failure.

MATERIALS AND METHODS

The study was conducted at Bogomolets National Medical University. To confirm the claim that cardiovascular functioning is directly related to the course of COVID-19, 10 patients with CCS in combination with COVID-19 were monitored throughout their hospital treatment. The study continued during the patients' hospital stay. Comparative statistical analysis was used without the use of methods to assess the significance of changes.

Patients with mild disease who are not at risk of developing complications of COVID-19 are recommended to be treated on an outpatient basis (at home), but the selected patients had CCS and therefore received inpatient treatment. As can be seen from Table 1, the patients did not have all the factors that could affect the outcome of COVID-19: overweight, comorbidities (except for CCS), bad habits (except for patients 1, 4, 6), age (the oldest patient was 7-48 years old). Thus, a homogeneous group of 10 people with CCS diagnosed before COVID-19 infection was obtained.

Table 1. Personal data of patients

Patient	Age	Sex	Weight, kg	Height, cm
1	40	Female	85	178
2	35	Female	70	169
3	38	Male	69	160
4	32	Male	74	168
5	39	Female	73	162
6	35	Male	70	163
7	48	Male	69	162
8	45	Female	80	170
9	37	Male	74	175
10	35	Male	71	174

Source: compiled by the author

All parameters for the study were obtained twice: on the first day of hospitalization and before discharge. The most informative indicators of plasma haemostasis are APTT, PT, fibrinogen, and D-dimer. To study the changes in these parameters in patients with CCS in combination with COVID-19, the values at baseline, at the onset of the disease, and after recovery (or death) were taken. Before taking venous blood for the study, the patients were asked about the use of anticoagulants. None of the patients were taking such drugs. All parameters were determined using an automatic blood coagulation analyser Coagulometer K 3002 OPTIS (KSELMED, Poland). The data on physiological correlates of HRV parameters presented in Table 2 can be used to interpret the results of HRV analysis.

Table 2. Interpretation of HRV analysis results

Indicator	Definition	Nature
Temporal indicators		
SDANN	Standard deviation of SDNN averages from 5 (10) minute segments for medium duration, multi-hour or 24-hour recordings	Humoral regulation, activity of central oscillators
SDNN-i	Standard deviation of N-N intervals	Sympatho-parasympathetic modulation
Spectral characteristics		
LF	Power in the very low frequency range (0.04-0.15 Hz)	Sympatho-parasympathetic modulation of baroreflex nature
HF	Power in the very low frequency range (0.04-0.15 Hz)	Parasympathetic activity

Source: created by the author based on [23]

HRV and plasma haemostasis parameters were compared twice during the course of the disease: at the beginning of the disease and after its completion. HRV was studied using appropriate software (ECG-pro®Holter, IMESS, Ukraine). The study of plasma haemostasis parameters was performed on the first day of hospital stay. A coagulometer K 3002 OPTIC (KSELMED, Poland) was used to determine the dynamic blood viscosity. All patients received full information about the study, test results, and conclusions and prognoses in accordance with the World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects [26]. This does not affect the results of the study and does not contradict the 2008 Declaration.

RESULTS AND DISCUSSION

The criteria for selecting patients for the study resulted in a fairly homogeneous group of patients. This is confirmed by the number of days of treatment (Table 3).

Table 3. Number of days of treatment

Patient	Number of days of treatment
1	15
2	10
3	11
4	15
5	10
6	11
7	11
8	12
9	12
10	11

Source: compiled by the author

All of the above leads to the conclusion that the average treatment duration was 13 days, which corresponds to the duration of treatment for mild COVID-19. The presence of a diagnosis of COVID-19 to affect plasma haemostasis on the first day of inpatient treatment meant that patients had passed the first (direct infection with the virus, the beginning of a pathophysiological chain reaction manifested by infection of immunocompetent cells of non-specific immune defence), second (excessive production of proinflammatory cytokines) and third (vascular endothelial damage, first in the lungs, then in other vessels, endotheliitis) stages of COVID-19 pathogenesis.

The third stage is of greatest importance for plasma haemostasis parameters because it was at this stage that patients were admitted to the hospital. It is at this stage (depending on the severity of the disease) that changes occur that lead, against the background of the depletion of the anticoagulation system due to endothelial destruction, to a sharp change in plasma haemostasis due to the entry of tissue thromboplastin into the bloodstream. At the same time, the natural fibrinolysis system could not cope with such a load. These two factors (decreased fibrinolysis and anticoagulation function) could lead (in the long run) to thrombosis of the heart's microvasculature. As a consequence, the impaired blood supply to the heart should certainly lead to changes in the heart rhythm. It should be noted that clinical manifestations of COVID-19 usually appear five days after infection. Thus, at the time of the COVID-19 diagnosis, plasma haemostasis parameters are presented in Table 4.

Table 4. Plasma haemostasis parameters on admission to the hospital

Patient	APTT		PT		Fibrinogen		D-dimer	
		Norm		Norm		Norm		Norm
1	42 s	30-40 s	19 s	11-18 s	1.9 g/L	2-4 g/L	0.6 mcg FEU/mL	0-0.55 mcg FEU/mL
2	40 s		18 s		2 g/L		0.5 mcg FEU/mL	
3	40 s		18 s		2 g/L		0.5 mcg FEU/mL	
4	42 s		19 s		1.9 g/L		0.6 mcg FEU/mL	
5	40 s		18 s		2.2 g/L		0.5 mcg FEU/mL	
6	40 s		18 s		3 g/L		0.5 mcg FEU/mL	
7	40 s		18 s		3 g/L		0.5 mcg FEU/mL	
8	40 s		18 s		2.2 g/L		0.5 mcg FEU/mL	
9	40 s		18 s		3 g/L		0.5 mcg FEU/mL	
10	40 s		18 s		2.4 g/L		0.5 mcg FEU/mL	

Source: compiled by the author

In severe cases of COVID-19, the massive entry of tissue thromboplastin into the vascular bed and the formation of a pro-convertin leads to significant changes in plasma haemostasis at the onset of the disease. In addition, the very concept of "onset of COVID-19" was subjective, as patients (voluntarily) might not immediately be admitted to the hospital, so the first day of inpatient treatment could differ in terms of plasma haemostasis due to a different number of days after infection. The table shows that patients do not differ significantly in terms of plasma haemostasis, so patients 1-10 were admitted to the hospital at approximately the same time of infection. In addition, it is worth not forgetting about the coagulation cascade that occurs as a result of the pathophysiological link due to the entry of tissue thromboplastin into the vessels and the activation of the Hagemann factor. According to Table 4, it can be concluded that at this stage, patients do not have severe pathological changes in plasma haemostasis.

Low APTT is a symptom of hypercoagulation. In this case, in patients 1 and 4, an elevated APTT may occur due to the initial stage of DIC syndrome. In most cases, anticoagulants are prescribed during the treatment of patients with COVID-19. Monitoring of such parameters as APTT, PT and fibrinogen allows for a prompt response to changes in the blood condition during inpatient treatment of COVID-19, and these tests are ordered immediately upon admission to the hospital. In this case, none of the patients received anticoagulants for both prophylactic and therapeutic purposes. It is recommended not to prescribe them due to low values, and to monitor the dynamics after discharge.

The PT indicates how long it takes for a fibrin clot to form in the blood serum. Fibrinogen (plasma fibrin) – its elevated level indicates inflammation in the body, a fibrin precursor protein that forms an insoluble clot. In the study, fibrin is at the lower end of the normal range, except for patients 1 and 4, who have lower levels.

The reasons for the decrease in fibrinogen can be severe liver damage (the organ where it is synthesised), test errors (when fibrin breakdown products in the blood plasma give a false result) or the DIC syndrome. In fact, there are more causes, including severe conditions of blood loss or shock, hereditary and gynaecological diseases, and cancer. All these causes were eliminated during the history taking. And the presence of elevated D-dimer in conjunction with a decrease in fibrinogen in patients 1 and 4 allows us to confidently conclude that the decrease in fibrinogen is associated with DIC. The etiopathogenesis of DIC syndrome is a generalised activation of blood coagulation, which can occur in parallel with the activation or inhibition of the fibrinolytic system. Microthrombi disrupt the blood supply to the coronary vessels, causing functional failure, which leads to changes in heart rate (especially in the context of pulmonary pathogenesis in COVID-19).

It is still unclear how SARS-CoV-2 activates the coagulation cascade. These questions have not been finally resolved in the 2020-2023 studies. M. Parohan *et al.* [27], and A.A. Rabaan *et al*. [28] note that mild COVID-19, the absence of bacterial sepsis and DIC syndrome result in a lower degree of prolongation of APTT and PT, and the presence of severe COVID-19 and other components on the contrary.

It should also be noted that the study by A. Silverio *et al.* [29] suggest that the coagulopathy observed in patients with severe COVID-19 is a mixture of localised pulmonary thrombotic microangiopathy and low-grade DIC. Assessment of the prognostic ability of haematological parameters yields mixed results. Significantly and prolonged elevated PT and APTT are independent predictors of mortality. H. Keski [31] notes that the frequency of abnormal haematological coagulation parameters increased with the severity of COVID-19. The D-dimer is directly correlated with COVID-19 mortality: the higher the D-dimer, the higher the likelihood of death. H. Keski [31] noted an increase in D-dimer in groups with acute respiratory distress syndrome and in a subgroup of patients with mortality. The increase in D-dimer concentration is primarily associated with the formation of blood clots of various sizes and health risks. Thrombi formed in the coronary and nervous system vessels pose the greatest threat. Thus, at the time of admission to the hospital, patients with CCS in combination with COVID-19 had an increase in APTT, PT and D-dimer in patients 1 and 4. In other patients, plasma haemostasis parameters were higher than normal. These data indicate the presence of inflammatory processes in all patients, processes at risk of a "red thrombus".

The increase in D-dimer and the presence of a smoking habit in patients 1 and 4 allows us to make a cautious prognosis. In general, according to the data obtained, no more than 25% of patients with an elevated D-dimer by 0.1-0.5 μm, an increase in APTT by no more than 5 seconds and PT by 3, and fibrinogen at the lower limit of normal in most cases correspond to a mild form of COVID-19.

In viral infections, the coagulation system is activated to protect the host, namely, to limit the spread of pathogens. Initially, an adaptive plasma haemostasis response occurs, which is associated with a systemic inflammatory response. As a result of increased inflammatory activity, the fibrinogen content increases significantly, and thrombin is produced. The studies on fibrinogen contradict this, so they were conducted after this adaptive reaction, when the body's plasma resource is reduced (Table 5).

Table 5. HRV in patients with CCS in combination with COVID-19 on admission to hospital

Patient	Indicators											
	HR, bpm		SDNN, ms		SDANN, ms		SDNNi, ms		LF, ms²/Hz		HF, ms²/Hz	
		Norm		Norm		Norm		Norm		Norm		Norm
1	102	60-90	89	51.6±1.7	58	77.5±3.8	60	51.1±1.8	2,500	710-770	2,670	386-411
2	85		75		50		51		1,060		1,106	
3	85		67		44		50		1,060		1,800	
4	102		89		58		60		2,500		2,670	
5	89		80		50		52		2,100		2,200	
6	90		80		44		51		2,200		2,400	
7	89		77		50		52		2,200		2,000	
8	90		78		50		50		1,500		2,200	
9	90		80		44		51		1,500		2,300	
10	90		80		48		50		1,500		2,340	

Source: compiled by the author

In fact, the HRV assessment also evaluates the functioning of the ANS. Currently, with mild COVID-19 on the first day of hospital treatment, the impact of the virus on the ANS was minimal. However, after treatment of the acute stage of COVID-19, nervous disorders of the ANS may develop due to hypoxic injury from the direct impact of the coronavirus on the respiratory and cardiovascular centres of the medulla oblongata and, as a result, HRV disorders. Conversely, high HRV stability indicates an overstrain of the ANS. HRV is an indicator of cardiovascular homeostasis and a very convenient tool for assessing stress resistance.

HR always responds to the needs of the body and a decrease in HR at the onset of the disease is a negative prognostic factor for the course of COVID-19, especially if patients already have CCS. At the same time, heart rate at the beginning of the disease is not informative. In practice, individual health characteristics have proven that a person can have a heart rate of less than 60 beats per minute or more than 100 beats per minute throughout their life, but they will feel fine [22]. More valuable information can be obtained by comparing the heart rate on the first day of inpatient treatment and after discharge. Then changes were visible for each individual patient. A similar principle exists in the analysis of HRV temporal and spectral parameters.

Despite the known negative impact of COVID-19 on the prognosis of patients with cardiovascular disease, there is currently a need to supplement the understanding of the pathophysiology of cardiovascular damage in SARS-CoV-2 infection, in particular, by studying changes and interrelationships in plasma haemostasis and HRV in patients with concomitant CCS (Table 6).

Table 6. Indicators of plasma haemostasis after discharge from hospital

Patient	APTT		PT		Fibrinogen		D-dimer	
		Norm		Norm		Norm		Norm
1	40 s	30-40 s	18 s	11-18 s	2 g/L	2-4 g/L	1 mcg FEU/mL	0-0.55 mcg FEU/mL
2	38 s		18 s		2 g/L		0.5 mcg FEU/mL	
3	37 s		18 s		2 g/L		0.5 mcg FEU/mL	
4	40 s		16 s		2 g/L		1 mcg FEU/mL	
5	38 s		18 s		2.2 g/L		0.5 mcg FEU/mL	
6	38 s		18 s		3 g/L		0.5 mcg FEU/mL	
7	37 s		18 s		3 g/L		0.5 mcg FEU/mL	
8	36 s		18 s		2.2 g/L		0.5 mcg FEU/mL	
9	38 s		18 s		3 g/L		0.5 mcg FEU/mL	
10	37 s		18 s		2.4 g/L		0.5 mcg FEU/mL	

Source: compiled by the author

Post-acute symptoms can occur in almost half of patients with COVID-19, so the study of HRV in the range of dynamic changes during the treatment of patients with CCS in combination with COVID-19 has a number of goals: diagnosis of heart disease, analysis of the activity of the ANS, and implementation of the stress response. Thus, the most pronounced increase in HRV was observed in patients 1 and 4 at the time of admission to the hospital. In patients 1 and 4, at the time of admission to the hospital, there was an increase in APTT, PT, D-dimer and a decrease in fibrinogen, which coincided with an increase in heart rate, 5-10 minute and long-term deviation of the N-N

segments. That is, changes in blood plasma affect the rhythm of the heart already at the onset of COVID-19 in combination with CCS. Other patients have normal plasma haemostasis and increased HRV compared to the norm. However, the increased HRV values can be explained by the fact that patients with CCS and normal HRV values are not relevant for them.

Among the patients, an increase in D-dimer of more than two norms (1 ng/mL) was determined in 24% of cases. The level of fibrinogen and other plasma haemostatic parameters did not exceed the normal range. Analysis of haemostatic parameters showed neither hypercoagulable tendencies nor signs of consumption. Indicators that are commonly observed in coronavirus infection, such as fibrinogen levels (hyper- or hypofibrinogenemia), reached normal values. During the acute phase of coronavirus, microthrombi with viral particles are formed. And when the body begins to fight these blood clots and dissolve them, the virus is released and provokes inflammation again. There is little information in scientific sources about blood counts in patients after discharge. S. Mandal *et al.* [18] noted an increase in D-dimer in one-third of patients (Table 7).

Table 7. HRV in patients with CCS in combination with COVID-19 after hospital discharge

Patient	Indicators											
	HR, bpm		SDNN, ms		SDANN, ms		SDNNi, ms		LF, ms²/Hz		HF, ms²/Hz	
		Norm		Norm		Norm		Norm		Norm	Norm	
1	112	60-90	88	51.6±1.7	58	77.5±3.8	38	51.1±1.8	2,500	710-770	2,670	386-411
2	89		75		50		39		1,060		1,106	
3	88		67		44		37		1,060		1,800	
4	112		89		56		38		2,500		2,670	
5	90		80		50		37		2,100		2,200	
6	91		80		44		39		2,200		2,400	
7	90		77		50		38		2,200		2,000	
8	90		78		50		37		1,500		2,200	
9	90		80		44		39		1,500		2,300	
10	92		80		48		38		1,500		2,340	

Source: compiled by the author

Resting heart rate in people with coronavirus was higher than normal. This trend may continue for some time in the post-COVID phase. A decrease in HF gives a poor prognosis for recovery from COVID-19 and the possibility of post-COVID complications. The fact that this indicator has hardly changed in patients provides a positive prognostic argument. HRV can also be assessed after discharge from the hospital. During a seemingly stable period when clinical symptoms of COVID-19 have almost disappeared, autonomic imbalance may occur, which is reflected in a decrease in HRV. This may indicate a higher risk of transitioning to the acute stage of CCS in the first 30 days after COVID-19 infection. The baseline minimum, average daily and maximum HR were 85 ± 1.3, 91.2 ± 8.5 and 102 ± 17.6 min, respectively, without significant dynamics during the repeated study. The baseline values of the temporal indicators were: SDNN – 79.5 ± 9.5 ms, SDNNi – 42.1 ± 17.9 ms, SDANN – 49.6 ± 8.4 ms.

In the dynamics, there was a tendency to decrease SDNNi by 10.7% ($p < 0.1$). Other temporary indicators decreased slightly. At the baseline HRV assessment by the 'short section analysis' method, the number of patients with normal HRV was 5 (33.3%), moderately reduced HRV – 9 (60%), and sharply reduced HRV – 1 (6.7%). In the dynamics, the number of patients with normal HRV did not change, but the number of patients with severely reduced HRV increased by 3 (20%), ($p = 0.1$), 66.7% of patients with CCS in combination with COVID-19 14 days after the development of focal neurological symptoms have moderately and severely reduced HRV. The analysis of the initial state of HRV parameters and their dynamics during the hospital and post-hospital follow-up periods in patients with CCS in both groups revealed statistically significant differences ($p < 0.05$). In patients 1 and 4, at the time of discharge from the hospital, an increase in d-dimer was noted, which coincided with an increase in heart rate. Patients require further follow-up, as these are signs of a cautious prognosis. According to other indicators, plasma haemostasis in all patients is normal, and HRV changes are not significant.

Coronavirus infection initiates activation of the sympathetic nervous system, and therefore the use of β-blockers has a positive effect on the restoration of sympathetic-parasympathetic regulation. In this regard, it is advisable to use higher doses of β-blockers in patients with CCS who have had COVID-19 to restore the sympathetic-parasympathetic balance. Slower recovery and adaptation, on the one hand, and ANS imbalance, on the other hand, may contribute to the development of life-threatening arrhythmias and fatal outcome. In view of these features of the restoration of neurohumoral mechanisms of myocardial regulation, when choosing pharmacotherapy in the hospital and posthospital stages, improving its effectiveness, building rehabilitation programmes and predicting their effectiveness in patients with ACS who have had coronavirus infection, it is necessary to take into account the presence of a longer period of severe sympathicotonia.

An increase in blood and plasma viscosity is associated with a decrease in oxygenation that develops during coronavirus infection. Moreover, rheological parameters change in the subclinical phase of atherosclerosis, that is, HRV changes along with plasma haemostasis parameters already with the development of vascular risk factors. Thus, a slight expression of coronary atherosclerosis, which is simultaneously associated with changes in N-N intervals and a decrease in blood viscosity, is observed. This is particularly evident in patients 1 and 4.

Blood viscosity cannot be considered separately. A. Colantuoni *et al.* [32] generally consider fibrinogen to be the main factor in blood viscosity, and therefore all three diagnostic elements under study (coagulogram, blood viscosity, and HRV spectral parameters) are interdependent. According to the literature, an increase in blood viscosity in CCS in combination with COVID-19 is detected from the first day, and the severe form of this disease is associated with a complicated course. Changes in blood viscosity may be a result of an imbalance in neurohumoral regulation. This is confirmed by a number of sources that directly recommend the use of drugs that affect the ANS during the treatment of COVID-19 [27, 28]. Chronic heart failure combined with COVID-19 is more complex and associated with proinflammatory cytokines and neurometabolic imbalances that together affect cardiomyocyte function, but all negative pathogenic manifestations during the acute stage of the disease are still associated with endothelial dysfunction. Under the influence of this imbalance, vascular tone increases and blood moves more slowly through the vessels. This leads to changes in HRV, endothelial damage, and an increased likelihood of pathophysiological causes of blood clots. This was confirmed in a study that found a direct positive correlation between LF and blood viscosity at shear rates from 0.22 to 2.62 seconds. This was especially evident on the first day of hospitalization. The reason for this interaction is the negative effect of increased adrenergic activity with the formation of catecholamines on the dynamic blood viscosity.

CONCLUSIONS

It has been established that plasma haemostasis comprises several indicators that directly affect both heart rate and blood clot formation and the duration of treatment for COVID-19. These are coagulation parameters: APTT, PT, fibrinogen, D-dimer, which generally shows a direct correlation with the results and duration of treatment, and dynamic blood viscosity, which has shown a direct correlation with the sympathetic and parasympathetic components of cardiovascular regulation.

In the studied cases, a mild form of COVID-19 was dealt with, so the correlation of HRV and such indicators as APTT, PT, fibrinogen, and D-dimer was most informative at the onset of the disease. Here, 2 patients (i.e., 20%) of the study had the most pronounced symptoms of autonomic dysfunction in patients with CCS in terms of increased HR, 5-10 minute and long-term N-N segment deviation, and symptoms of plasma haemostasis changes such as increased APTT, PT, D-dimer, and decreased fibrinogen. These 2 patients had the longest number of days of hospital treatment and a 0.5 μg FEU/mL increase in D-dimer from the normal range. Thus, more pronounced pathological changes in HRV parameters and plasma haemostasis are directly related and affect the quality and duration of treatment of CCS in combination with COVID-19. Blood viscosity was particularly informative at the onset of the disease.

This study had a small practical research basis (only 10 patients) because the sample of patients with CCS in combination with COVID-19 without significant comorbidities is very difficult. Therefore, further research is needed because there are very few studies directly related to the treatment of CCS in combination with COVID-19.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Взаємозв'язок показників плазмового гемостазу та варіабельності серцевого ритму у хворих на хронічний коронарний синдром у поєднанні COVID-19

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Анотація. Метою дослідження було виявлення взаємозв'язку між показниками активованого часткового тромбопластинового часу, протромбінового часу, фібриногену, Д-дімеру та показниками відхилень N-N інтервалів, частоти серцевого ритму з одного боку і виявлення взаємозв'язку між показниками парасимпатичної та симпатичної активності серцевого ритму та динамічної в'язкості крові з другого боку. Збудник COVID-19 впливає на роботу парасимпатичної та симпатичної нервової системи, що також змінює серцевий ритм. Для вивчення цього процесу група з 10 пацієнтів із хронічним коронарним синдромом у поєднанні COVID-19 без супутніх захворювань у віці 35-48 років спостерігалась у стаціонарі. Для вивчення цього взаємозв'язку було взято показники плазмового гемостазу (активований частковий тромбопластиновий час, протромбіновий час, фібриноген, Д-дімер) та показники варіабельності серцевого ритму на момент надходження у стаціонар та після виписки зі стаціонару. Виявлений безпосередній зв'язок показників: у пацієнтів 1 та 4 на момент надходження у стаціонар відмічається збільшення активованого часткового тромбопластинового часу, протромбінового часу, Д-дімеру та зменшення фібриногену, це співпадає із підвищенням частоти серцевого ритму, 5-10 хвилинного та багаточасового відхилення сегментів N-N. Тобто зміниу плазмі крові впливають на ритм роботи серця вже на початку розвитку COVID-19 у поєднанні із хронічним коронарним синдромом. У пацієнтів 1 та 4 на момент виписки зі стаціонару відмічається збільшення Д-дімеру, це співпадає із підвищенням частоти серцевого ритму. Пацієнти потребують подальшого спостереження, оскільки це ознаки обережного прогнозу. Усі інші показники плазмового гемостазу у всіх пацієнтів у нормі, зміни незначні. Необхідно відстежувати показники плазмового гемостазу та варіабельності серцевого ритму для корекції лікування під час знаходження у стаціонарі пацієнтів із хронічним коронарним синдромом у поєднанні COVID-19 та після виписки зі стаціонару

Ключові слова: активований частковий тромбопластиновий час; протромбіновий час; фібриноген; Д-дімер; N-N інтервал; парасимпатична-симпатична активність