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# HEART RATE VARIABILITY AFTER CORONAVIRUS DISEASE

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**ABSTRACT**
During the Covid-19 pandemic different research teams report that certain patterns of heart rate variability (HRV) predicted the deterioration of patients. Similar dependencies have been observed in other respiratory infections, too. We present several related clinical cases of patients without evidence of diabetes mellitus suffering from covid pneumonia with low HRV (a sign of sympathicotonia) and an increase in blood glucose levels during the disease and in the recovery phase. Monitoring the changes in HRV is important for both coronavirus and convalescent patients. Therefore, it can be included in the standard protocols for their treatment and rehabilitation.

**Key words**: heart rate variability, covid-pneumonia, sympathicotonia, blood glucose

## INTRODUCTION

### Coronavirus pandemia - general issues

The Coronavirus disease due to SARS-CoV-2 was identified at the end of 2019 in Wuhan, China. Its pandemic evolution developed into a global health crisis, which changed the lifestyle, industry and even the psyche of the majority of the earth's population. (1)

There are different strategies for prevention of COVID infection on a global, national and individual level. These strategies are based on early identification, diagnosis and isolation of the infected person, the classic anti-epidemic measures to limit the concentration of many people in one place and prevent closer contact between them and from the beginning of 2021 - vaccine prophylaxis. (2)

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However, the coronavirus pandemic remains a major health and economic problem. This is due to the high virulence of SARS-CoV-2, asymptomatic carrier and relapse in some patients with very mild symptoms, as well as underestimation of the risk. The COVID infection is dangerous with its complications, the most common of which is the COVID pneumonia, which occurs with respiratory failure as well as an increased risk of thrombosis and thromboembolism. In addition, in the course of this disease, other organs and systems are also affected. An example of this is the cardiovascular system, which is in close anatomical and functional connection with the respiratory system. (3)

### COVID-19 and the heart - why is the problem so important?

The heart diseases are of particular interest in the context of the coronavirus pandemic for two reasons. On the one hand, in the course of each epidemic, patients with serious comorbidities are more likely to develop complications or die as a

result of the infection. For example, the mortality rate for patients with existing cardiovascular disease is 10% in comparison to 6,9% overall global mortality rate in SARS-CoV-2 according to COVID-19 Map of Johns Hopkins Coronavirus Resource Center. (4)

SARS-CoV-2 like other respiratory viral infections could exacerbate an extant heart failure due to different mechanisms, for example, increased metabolic demand, direct myocardial injury or myocardial injury from cytokine storm, increased risk of thrombotic events and septic shock. (5)

On the other hand, however, there are many cases of new onset heart failure. According to Bader et al. „new " cardiovascular involvement develops quarter of hospitalized COVID-19 patients. And in intensive care units this part is even bigger, because one-third of the patients in it developed heart failure without a previous history of cardio-vascular disease. (6)

Different mechanisms such as an acute myocarditis (SARS-CoV-2 have direct cytotoxic effect, but also could be the initial factor that unlocks immune-mediated injury.), pulmonary embolism with acute right ventricular failure, stress cardiomyopathy owing to generalized inflammatory response and sympathetic activation are discussed as a reason for new onset heart failure in the context of the SARS-CoV-2 infection. (7, 8)

Another reason for the cardiovascular involvement in COVID-19 patients is the interaction with the renin angiotensin aldosterone system. An important role in it has the membrane-bound angiotensin-converting enzyme (ACE) 2, because it is used by the virus as a gateway. This receptor is expressed on the surface of the endothelial cells mainly in the lungs, intestines, kidneys, and choroid plexus. Its activation by the virus leads to fibrosis formation. (9) And the follow of the pulmonary fibrosis is pulmonary restriction with pulmonary hypertension and right heart failure. This is the mechanism of chronic pulmonary heart disease - a disabling complication that is difficult to treat because the fibrotic process is irreversible. (10, 11)

If we have to summarize, sequelae of SARS-CoV-2 are diagnosed in patients who developed severe acute COVID-19, but also in patients who experienced only mild or asymptomatic cases. The COVID infection affects the cardiovascular system both by general and by specific mechanisms. The most important of them are hypercoagulation, direct and indirect myocardial damage, incised metabolic demand, septic shock, cytokine storm, renin-angiotensin-aldosterone-system involvement. In all of these conditions, as well as in the condition of respiratory failure or heart failure the activation of the sympathetic nervous system has an important role.

**Heart rate variability as a sign of the involvement of the cardiovascular and autonomic nervous system in the infectious process**

The heart rate variability is an easy to perform, non-invasive methodology for assessing the effect of the autonomic nervous system on cardiac function. Acceleration of the heart rate under the influence of various stressors (including fever, shock, respiratory disorders) has been known since the time of Hippocrates. But fundamental to HRV is the momentary variation in the interbeat interval (R-R interval) of the electrocardiogram due to the momentary interplay between both divisions of the vegetative nervous systems. (12)

For example, the sympathetic activity leads to an increase in the heart rate (HR). In this way it makes the RR-interval shorter. The parasympathetic activity induces a lower HR and longer RR-interva, respectively. In normal condition thereares rapid changes between the sympathetic and parasympathetic activity and the myocardial electrical and contractile activity is able to response to these changes. (13)

It is important that the vagus nerve maintains tonic inhibitory control of proinflammatory cytokines via acetylcholine release into the organs of the reticuloendothelial system. Therefore, the changes in the HRV can be used not only for indication of autonomic nerve system branches interaction, but also as a mark of healthy heart and immune activity. For example, the reduced heart rate variability is a predictor of the

increased risk for cardiovascular mortality and morbidity. (14)

The idea to use HRV to monitor the condition of patients with viral infections, sepsis and disorders of the respiratory system is not new. In support of this, I will cite several studies from the time before the covid pandemic.

Various factors that influence the autonomic nerve system lead to changes in HRV. They can be both exogenic and endogenic.

For instance, according Gold et al. ambient air pollution can reduce the HRV due to decreased vagal tone. (15)

Mittal et al. report about depression in the heart rate variability in patients with AIDS and HIV-seropositive individuals. The selected patients do not suffer from heart disease or autonomic dysfunction. The conclusion of the study is that the heart rate variability as an early marker of future global sympatho-vagal imbalance can serve as a predictor of acute infection before its clinical-laboratory marker becomes positive.(16) Another example given by Lin et al. study in children with encephalomyelitis due to enterovirus infection is that HRV parameters are extremely low in infected patient again before the clinical manifestation due to autonomic dysfunction. (17)

According Günther et al. a reduction of very low frequency (VLF) and low frequency to hight frequency ratio may predict sub-acute infection in the first days after acute stroke. The changes in HRV pattern precede clinical and laboratory signs of infection. (18)

Different investigations (Ahmad et al., Bravi et al.) show that changes of VLF in patients with iatrogenic neutropenia preparing for bone marrow transplant antecede onset of sepsis according to Bravi et al within about 60 hours. (19, 20)

All of these studies conducted in different patients concluded that the heart rate variability depression and reduction of very low frequency are not only a sign of autonomic dysfunction, but also a marker of the cardiovascular and autonomic nervous system involvement in the infectious process.

Experience with the use of the heart rate variability in patient with COVID infection Kaliyaperumal et al. observe in case control study with 63 COVID-19 infected patients significantly decreased high frequency powers and low frequency powers in COVID-19 subjects compared to controls. The infected patients have also significantly increased standard deviation of RR intervals (SDNN). (21)

Hasty et al. also observe that decreases in HRV of greater than 40% significantly preceded a 50% increase in CRP during the ensuing 72 hours (90.9% positive predictive value). Therefore, they suggest short-segment, intermittent heart rate variability analysis to be used in triage. (22)

Adler et al. studied post-covid patients in the third and sixth month after discharge and found out that the SARS-CoV-2 infection is associated with persistent impairment of parasympathetic heart rate variability modulation through 6 months after dehospitalisation. They also suspect that this autonomic balance may indicate increased cardiovascular risk among survivors of severe COVID-19 infection. (23)

## CLINICAL CASES

We will present 3 clinical cases of patients with COVID 19, that have viral pneumonia imposed hospital treatment, cardiovascular problems during the viral infection and also after it, impared HRV and increased fasting blood glucose. We begin our observation after the dehospitalization and we continue it until the normalization of the studied indicators.

In our clinical case we use HRV indices representing time-domain: SDNN - standard deviation of the NN id est R-R or beat to beat interval), RMSSD - root mean squared value of successive differences of NN, pNN50 (number of interval differences of successive NN intervals greater than 50 ms are divided by the total number of NN intervals . (24)

### Clinical case 1

We present a 41-year man with complaints of persistent shortness of breath (more pronounced

in the supine position) and easy fatigue in medium physical effort a week after the cure of the covid pneumonia. Fatigue does not allow him to work efficiently, because he is professionally engaged mainly in physical work.

The Covid pneumonia was treated in a hospital with colchicine, ivermectin, antibiotic (azithromycin), subcutaneous anticoagulant, melatonin, low doses of vitamin D and other symptomatic and supportive care.

During the treatment in the hospital, his fasting glucose levels increased several times , but monitoring of blood sugar profile and glycated hemoglobin ruled out diabetes mellitus, therefore, no antidiabetic therapy except diet 9 was initiated. The patient is non-smoker, moderate alcohol consumer. Hereditary burden - father with hypertension and heart failure.

Impressive from the objective state are: hypersthenic habitus, well-defined subcutaneous adipose tissue, BMI 27 - indicative of overweight. Heart rate 78 / min. Blood pressure 135/80 mm Hg. Physical examination and electrocardiographic data rule out pump and coronary heart failure.

Echocardiography is normal - excludes valve dysfunction and pericarditis. Ejection fraction - 69%. The performed biochemical tests showed a normal lipid profile, increased fasting blood glucose - 7 mmol / l, preserved renal function. The liver enzymes AST and ALT was slightly elevated. The study of the heart rate variability shows SDNN 59 ms, RMSSD 39ms and pNN50 14%.

In a differential diagnostic plan we can discuss different conditions as the reason for the shortness of breath such as persistent pneumonia,pericarditis, diastolic dysfunction, dilated cardiomyopathy (postmyocardial and alcoholic). All of them were excluded by echocardiography and radiography.

After consultation with a pulmonologist the patient started an exercises complex to prevent the pulmonary fibrosis. The Colchicine treatment was extended for one month because it is disputable whether AST and ALT raising is due to it, to another drug (eg ivermectin) or to systemic alcohol use.

There is another cause of shortness of breath that is not easy to rule in or rule out and this is the psychogenic shortness of breath.

With regard to the vascular system, there is no indication for drug interventions - the patient has family history of hypertension and heart failure furthermore he is overweight, but he is defined as a patient with low cardio-vascular risk based on data for arterial blood and lipid profile and absence of persistent diabetes with SCORE chart for 10-year risk of fatal cardiovascular disease. Moreover, we supposed that there is not virus induced affecting the myocardium and pericardium.

We decided to monitor the HRV once in every two weeks and within one month the patterns returned to normal (SDNN 78 ms, RMSSD 74ms and pNN50 32%). HRV is improved and pNN50 is doubled. After the same time, he normalized the fasting blood glucose without antidiabetic medicines. The shortness of breath also subsided without additional drug therapy.

**Clinical case 2**

The second patient that we would like to present is a 50-year old woman with complaints of palpitations causing chest discomfort. According to anamnestic data, their appearance is not provoked by physical exertion. She had similar complaints before the covid infection, but their frequency and severity increased during the illness and persisted in the recovery phase.

The patient presented 10 days after discharge from the covid ward a negative PCR test. She was admitted on suspicion of pulmonary thromboembolism, based on the following clinical data: hypotension, dyspnea, increased right ventricular cardiac load on electrocardiogram, varicose veins of the lower legs. D-dimer and fibrinogen were elevated, but contrast-enhanced computed tomography of the lung ruled out the diagnosis of pulmonary thromboembolism, but "saw" the development of viral interstitial pneumonia.

However, the patient was treated for two days with high molecular weight heparin, then with

fractionated heparin subcutaneously until the end of the hospital stay and then she received recommendations to continue anticoagulant therapy with oral agents for one month after discharge. Her medical therapy also included colchicine, antibiotic coating, symptomatic and tonic agents.

On the day of discharge, a blood glucose of 11 mmol / l was registered, explained by dietary error - about 15-20 minutes before taking the blood sample, the patient consumed a bottle (500 ml) of cola in an effort to reduce her complaints of fatigue and general weakness. Concerned about her condition, the patient stopped using not only cola and carbonated drinks, but also all foods containing refined sugar.

Despite the strict diet, she measures high blood glucose levels also two days after dehospitalization. The palpitation and chest discomfort disturb her sleep. Her heart rate rise to 110 b/min. After consultation with a cardiologist, a new pulmonary thromboembolism was found out. She had ventricular extrasystoles Lown II on the ECG, therefore, she added Magnesium 2 x 500mg to her therapy. About a week later, the number of ventricular extrasystoles decreased, so we could calculate the parameter of heart rate variability. The result is SDNN 54 ms, RMSSD 38 ms and pNN50 10%.

On the 20 day after dehospitalisation the HRV is still normalised (SDNN 75 ms, RMSSD 72 ms and pNN50 29%), but the fasting blood glucose is 6,5 mmol/l. On the 23 day after the discharge the patient makes an oral glucose tolerance test to exclude diabetes mellitus although fasting blood glucose is normalized - 5,4.

In this case it is interesting that the HRV changes predict blood glucose level regularization.

**Clinical case 3**

The third patient that we present is a 35-year man, chain-smoker with 30 pack-years. His covid pneumonia was diagnosed with a complaint of a new sudden shortness of breath and stabbing chest. In addition to a lung infection, the patient develops pericardium inflammation with pericardial effusion. During the hospital treatment he received the maximum dose of colchicine, ivermectin and quinine, antibiotic coverage and symptomatic agents.

Basically, the general status is of an athletic physique, reduced subcutaneous adipose tissue, single dry wheezing in the lungs, pericardial friction rub in heart auscultation.

Notable in the biochemical tests are high blood glucose level 7,3 mmol/l, high AST 80 mmol/l and ALT 72 mmol/l. The ECG and the echocardiography are typical for a small pericardial effusion.

The study of the heart rate variability shows SDNN 34 ms, RMSSD 32 ms and pNN50 3,5%. The patient was followed for the next 2 months. During each subsequent HRV study (on a weekly basis), the trend was towards improvement, more clearly at the end of the first month, when the pericardial effusion was completely absorbed. The last tests we have are from the 75th day after discharge. Fasting blood glucose remains at an upper limit of 6.7 mmol / l, therefore, the patient is referred to an endocrinologist. The HRV indicators are almost normalised: SDNN 58 ms, RMSSD 37 ms and pNN50 16%.

**DISCUSSION**

The mechanisms maintaining cardiovascular complications in post-acute COVID-19 could be an increased cardiac stress due to raised cardiometabolic demand (especially in patients with reduced cardiac reserve), direct viral invasion, downregulation of ACE2, microvascular thrombosis, pulmonary thromboembolism, inflammation and immunologic response affecting the structural integrity of the heart muscle and conduction system, that leads to cardiomyocyte death and myocardial fibrosis (stimulating by aldosterone) and also pericardial affections occurring through a direct cytotoxic effect and/or an immune-mediated mechanism. (25, 26)

In our 3 clinical cases we collate the information for case history, general status, clinical course, changes in biochemical tests, ECG, echocardiography and heart rate variability. We observe reduced SDNN, RMSSD and pNN50 - indicative of hyper sympatheticotonia. And this is another possible mechanism that can explain both

the cardiovascular damage and the observed elevated blood sugar levels (sympathetic stimulation increases the excretion of insulin by pancreatic beta cells, but also increases insulin resistance), and also neuro-vegetative and neuro-psychological changes observed in some patients with post-COVID syndrome.

In the third patient, the persistence of sympathicotonia is remarkable. But it can be related not only to the infection experienced, but also to smoking and his stressful lifestyle.

The observations of the three clinical cases could not provide statistically significant information, but other teams that did larger studies came up with similar results. Therefore, we support the thesis that the monitoring of the HRV changes is important for both patients with coronavirus infection and convalescent patients and it makes sense to include it in the standard protocols for their treatment and rehabilitation.

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