Original Article

Pericardial Effusion in Postcoronavirus Disease Patients with Preserved Ejection Fraction of the Left Ventricle and Normal Values of N-Terminal-Pro B-Type Natriuretic Peptide-Link with C-Reactive Protein and D-Dimer

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Abstract

Aim: The aim of this study was to link the values of D-dimer and C-reactive protein (CRP), with the occurrence of pericardial effusion in patients who had coronavirus disease 2019 (COVID-19) and have preserved systolic function of the left ventricle (LV). **Methods:** This was a prospective study and included 146 patients who underwent echocardiographic examination 30 days after the acute phase of COVID-19. Patients who were placed on mechanical ventilation, patients who had pulmonary thromboembolism or acute coronary syndrome during the acute period of the disease, patients who had an ejection fraction of the LV <50%, patients who were diagnosed with pericarditis during acute illness or clinical signs of heart failure (or had elevated N-terminal-pro hormone B-type natriuretic peptide value), with verified renal or hepatic dysfunction were excluded from the study, including patients with diabetes mellitus Type 1, patients with cancer, connective tissue disease, or pregnant women. The existence of cardiovascular risk factors (hypertension, diabetes mellitus Type 2, and hyperlipidemia), the presence of previous ischemic heart disease, maximum values of D-dimer, and CRP (during the first 15 days of the disease) was taken into the analysis. **Results:** Effusion was verified around the right atrium (RA) in 104 patients (3.85 ± 1.75 mm), in 135 patients next to the free wall of the right ventricle (RV) (5.24 ± 2.29 mm), in front of the apex of the LV in 27 patients (2.44 ± 0.97 mm), next to the lateral wall of LV in 35 patients (4.43 ± 3.21 mm), and behind the posterior wall of LV in 30 patients (2.83 ± 1.62 mm). Mean CRP values during the acute phase of the disease were 43.0 mg/L (8.6–76.2 mg/L), whereas D-dimer mean value was 880.00 μg/L (467.00 –2000.00 μg/L). CRP values correlated with effusion next to the free wall of RV (rho = 0.202; P = 0.018). The D dimer correlated with effusion around RA (rho = 0.308; P = 0.0001). **Conclusion:** The clinical picture of the post-COVID patients could be explained by the appearance of pericardial effusion. D-dimer value correlates with the occurrence of effusion around RA, whereas CRP value correlates with effusion next to the free wall of RV.

Keywords: *Coronavirus disease 2019, echocardiography, heart*

Introduction

Pericardial diseases are divided into three segments: acute fibrinous pericarditis, pericardial effusion without signs of compression, and compression syndrome (cardiac tamponade and constrictive pericarditis).[1,2] Exudate in the pericardium occurs as acute idiopathic, due to viral, bacterial, fungal or parasitic disease, due to malignant process, after myocardial infarction, after chest trauma, surgery, radiotherapy, connective tissue disease, hypothyroidism, during hemodialysis, or as iatrogenic.[2,3] By distribution, it is divided into diffuse and localized. Localized is important to recognize, because as such, it can cause disturbances in the diastolic function of the ventricles.[4,5] The exact amount of exudate is difficult to determine, but it is considered that 1 cm in front of the free wall of the right ventricle (RV) is 800 mL of exudate.[6] It is also important to note that if exudate accumulation occurs slowly, an effusion of 1000 mL may not cause interference with ventricular filling, and if it is rapidly formed, even 100 mL may cause a significant increase in intracardiac pressure.[7] Acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the pathogen responsible for the coronavirus disease 2019 (COVID-19),

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which is characterized by hypercoagulability (endothelial dysfunction, pathway, and hypercoagulable state) and systemic inflammatory response. Post-COVID syndrome (long COVID) represents persistent physical, medical, and cognitive sequelae after COVID-19, as well as clinical symptoms that interfere with the patient's daily functioning.[7,8]

Transthoracic echocardiographic examination has established as the part of the diagnostic modality in post-COVID syndrome, which attempts to explain the problems in the form of fatigue, tachycardia, intolerance to exertion, or oppression in the chest. The appearance of pericardial exudate and the interpretation of its appearance are a real problem in the daily work of clinicians. The literature reports the occurrence of acute complications of COVID-19 in the form of myocarditis, pericarditis, myopericarditis, pericardial effusion, tamponade, and even their occurrence in the post-COVID period.[9-12] The question is whether if it is localized, if it is minimal (<0.5 cm) or if it is small (up to 1 cm), without hemodynamic significance, when it is an indication for the treatment or when it is understood as a pericardial effusion.

Aim

The aim of this study was to correlate the values of D-dimer and C-reactive protein (CRP), with the occurrence of pericardial exudation in patients who had COVID-19 and have preserved systolic function of the left ventricle (LV).

Methods

Research has been prospective and included 146 patients who underwent to an echocardiographic examination within 30 days of undergoing COVID-19 from January 2021 to July 2021. Patients who were placed on mechanical ventilation, patients who had pulmonary thromboembolism or acute coronary syndrome during the acute period of the disease, patients who had an ejection fraction of the LV <50%, patients who were diagnosed with pericarditis during acute illness or clinical signs of heart failure (or had elevated N-terminal-pro hormone B-type natriuretic peptide [NT-proBNP] value), with verified renal or hepatic dysfunction were excluded from the study, including patients with diabetes mellitus type 1, patients with cancer, connective tissue disease, or pregnant women. The existence of cardiovascular risk factors (hypertension, diabetes mellitus Type 2, and hyperlipidemia), the presence of previous ischemic heart disease, and maximum values of D-dimer and CRP (during the first 15 days of the disease) were taken into the analysis. Moreover, patients underwent transthoracic echocardiographic examination. The pericardium was analyzed, and the presence of pericardial effusion in diastole was monitored in relation to the localization (right atrium [RA], RV, posterior wall of the LV, left ventricular apex, and lateral wall of the LV). The results are presented by the number of cases, percentages, arithmetic mean, standard deviation, and median with an interquartile range. Since there was no normal sample distribution, the Spearman correlation coefficient was used. All analyses results with $P < 0.05$ or at a 95% confidence level were considered statistically significant.

Results

The mean age of the patients was 50.42 ± 16.45 years (63.5% were male). The mean age of males was 52.87 ± 1.7 years, whereas the mean age of females was 45.8 ± 19.2 years (P = 0.015). Out of the total number, 89 (65%) had a diagnosis of arterial hypertension in the anamnestic data, 58 (42.3%) had a diagnosis of diabetes mellitus, 69 (50.4%) had hyperlipidemia, while 20 (14.6%) patients had previously verified coronary artery disease. Effusion was verified around the RA in 104 patients (3.85 ± 1.75 mm), in 135 patients next to the free wall of the RV (5.24 ± 2.29 mm), in front of the apex of the LV in 27 patients (2.44 ± 0.97 mm), next to the lateral wall of LV in 35 patients (4.43 ± 3.21 mm), behind the posterior wall of LV in 30 patients (2.83 ± 1.62 mm) [Table 1]. Mean CRP values during the acute phase of the disease were 43.0 mg/L (8.6–76.2 mg/L), whereas D-dimer mean value was 880.00 μg/L (467.00–2000.00 μg/L) [Tables 2 and 3]. CRP values correlated with effusion next to the free wall of RV (rho = 0.202; $P = 0.018$). Patients with the higher values of CRP and D-dimer had bigger effusion, and they were older. The D-dimer correlated with effusion around RA (rho = 0.308; $P = 0.0001$). The presence of effusion behind RA correlates positively with the presence and effusion around other walls of the heart ($P < 0.05$) [Table 4].

Discussion

The pathophysiology of pericardial effusion in COVID-19 as well as in post-COVID patients is unknown, but it is suspected that occurs due to a systemic inflammatory response and the cytotoxic effect of SARS-CoV-2.[13] There is currently no clear explanation regarding the cause of the effusion, and the treatment is also not clearly defined.[14] There is no clear incidence of pericarditis, and it is mostly presented in individual case reports, both in acute COVID-19 itself and up to 6 months after infection.

The term acute cardiac injury, or elevation of cardiac troponin I over 99th percentile upper reference limit, occurs with an incidence of 8%–22% (up to 59% in those who died with COVID-19), leads to probably excessive referral of patients for echocardiography after acute infection. Doctors often have found pericardial effusions up to 5 mm, behind one or more segments of the heart muscle, and there is question of whether these patients should be treated.[15,16]

In acute COVID-19, it is questionable to treat pericardial effusion a standard algorithm which includes nonsteroidal

Table 1: Analysis of the presence of pericardial effusion in relation to the segment of the heart

Pericardial effusion (mm)	*n* (%)	Mean±SD	Minimum	Maximum	25th	50th	75th
Around the RA	104 (75.9)	3.85±1.756	2	10	3.00	3.00	4.75
Next to the free wall of the RV	135 (98.5)	5.24±2.296	2	16	4.00	5.00	7.00
In front of the apex of the LV	27 (19.7)	2.44±0.974	1	5	2.00	2.00	3.00
Next to the lateral wall of the LV	35 (25.5)	4.43±3.211	2	16	2.00	3.00	5.00
Behind the posterior wall of LV	30 (21.9)	2.83±1.621	2	8	2.00	2.00	3.00

25th; 50th; 75th – percentiles. *n*: Number of all patients; SD: Standard deviation; LV: Left ventricle; RV: Right ventricle; RA: Right atrium

Table 2: Correlation of C-reactive protein values and monitored parameters

	Spearman's Rho	Maximum value of CRP	Around the RA	Next to the free wall of the RV	In front of the apex of the LV	Next to the lateral wall of the LV	Behind the posterior wall of LV	Age	Gender
CRP values	Correlation coefficient	1.000	0.070	0.202*	0.102	0.126	0.147	0.451	−0.143
	P		0.417	0.018	0.237	0.143	0.087	0.0001	0.095
	n	137	137	137	137	137	137	137	137

$P < 0.05$, *P*-level of significance. *n*: Number of all patients; CRP: C-reactive protein; LV: Left ventricle; RV: Right ventricle; RA: Right atrium

Table 3: Correlation of D-dimer values and monitored parameters

	Spearman's Rho	Maximum value of D-dimer	Around the RA	Next to the free wall of the RV	In front of the apex of the LV	Next to the lateral wall of the LV	Behind the posterior wall of LV	Age	Gender
D-dimer values	Correlation coefficient	1.000	0.308	0.162	0.125	0.147	0.156	0.319	−0.072
	Significance (two-tailed)		0.0001	0.059	0.147	0.085	0.069	0.0001	0.406
	n	137	137	137	137	137	137	137	137

LV: Left ventricle; RV: Right ventricle; RA: Right atrium

Table 4: Correlation of pericardial effusion around right atrium with the presence of effusion behind other segments

	Spearman's Rho	Next to the free wall of the RV**	In front of the apex of the LV*	Next to the lateral wall of the LV**	Behind the posterior wall of LV**
Around the RA	Correlation coefficient	0.511	0.217	0.293	0.229
	Significance (two-tailed)	0.0001	0.011	0.001	0.007
	n	137	137	137	137

*Correlation is significant at the 0.05 level (two-tailed), **Correlation is significant at the 0.01 level (two-tailed). LV: Left ventricle; RV: Right ventricle; RA: Right atrium

anti-inflammatory drugs (NSAIDs), because patients are mostly in intensive care unit and are on corticosteroid therapy. Those hemodynamically significant pericardial effusions can theoretically be treated with therapy that can have some benefits (colchicine, human immunoglobulins, and anakinra).[16]

Hemodynamically significant pericardial effusion in post-COVID patients can again be treated with NSAIL, corticosteroids (with the risk of superimposed bacterial infection) or colchicine, but the question arises what to do with effusions that are not hemodynamically significant but can be considered as a reason of patient's clinical picture (shortness of breath, cough, and chest tightness). The best solution would be monitoring of patients, what probably further burdens of the already burdened health system.

This research took included patients who did not have reduced systolic function before COVID-19, who did not have elevated NT-proBNP during and after the disease, and these patients did not develop myocardial dysfunction, and have preserved left ventricular systolic function. A correlation was made between the maximum values of CRP and D-dimer during the acute phase of the disease and echocardiographic examination within a month after the acute phase of infection. Pericardial effusion was most often located behind the right cavities, which can be explained with the possible occurrence of inflammation and microthrombosis of the pulmonary circulation and correlates with the existence of effusions around other segments. CRP values correlated with effusion next to the free wall of RV, D-dimer values with around the RA, indicating a likely association and increase in D-dimer and CRP with

inflammatory process of the lungs, as well as probable endothelial dysfunction of pulmonary circulation. It should be not that the occurrence of effusion is a rare complication of the acute phase of COVID-19 and that it can be also the post-acute phase, but again hemodynamically significant pericardial effusion is very rare, and it can occur 70 days after the acute infection.[17]

Patients who had an effusion over 10 mm behind the segments of the heart muscle were considered serious and were treated with ibuprofen, methylprednisolone, and rarely colchicine. During 16 months in Sarajevo, Bosnia, and Herzegovina, there was no life-threatening cardiac tamponade related to COVID-19 (incidence in the literature is <1%).[18] Some patients were also sent for magnetic resonance imaging, which is available to us, from 1.5 Tesla, but no additional information was obtained (relation with myocarditis was not confirmed).

It is possible that in case a more sensitive device was used, these findings would be different. Similar articles with this connection could not be found in available scientific databases.

Conclusion

The fact is that the clinical picture of the post-COVID patients could be explained by the appearance of pericardial effusion. D-dimer value correlates with the occurrence of effusion around RA, whereas CRP value correlates with effusion next to the free wall of RV.

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Conflicts of interest

There are no conflicts of interest.

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