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Hidden systolic dysfunction of the right ventricle in patients with increased pulmonary vascular resistance 3 months after COVID-19 pneumonia

Aim	To study the relationship of echocardiographic right ventricular (RV) structural and functional parameters and indexes of pulmonary vascular resistance (PVR) in patients 3 months after COVID-19 pneumonia.
Material and methods	This cross-sectional, observational study included 96 patients aged 46.7±15.2 years. The inclusion criteria were documented diagnosis of COVID-19-associated pneumonia and patient's willing to participate in the observation. Patients were examined upon hospitalization and during the control visit (at 3 months after discharge from the hospital). Images and video loops were processed, including the assessment of myocardial longitudinal strain (LS) by speckle tracking, according to the effective guidelines. The equation [tricuspid regurgitation velocity/time-velocity integral of the RV outflow tract × 10 + 0.16] was used to determine PRV. Patients were divided into group 1 (n=31) with increased PRV ≥1.5 Wood units and group 2 (n=65) with PRV <1.5 Wood units.
Results	At baseline, groups did not differ in main clinical functional characteristics, including severity of lung damage by computed tomography (32.7±22.1 and 36.5±20.4%, respectively. p=0.418). Echocardiographic linear, planimetric and volumetric parameters did not significantly differ between the groups. In group 1 at the control visit, endocardial LS of the RV free wall (FW) (– 19.3 [– 17.9; – 25.8] %) was significantly lower (p=0.048) than in group 2 (– 23.4 [– 19.8; – 27.8] %), and systolic pulmonary artery pressure (sPAP) according to C. Otto (32.0 [26.0; 35.0] mm Hg and 23.0 [20.0; 28.0] mm Hg) was significantly higher than in group 2 (p<0.001). According to the logistic regression, only endocardial RV FW LS (odds ratio, OR, 0.859; 95% confidence interval, CI, 0.746–0.989; p=0.034) and sPAP (OR, 1.248; 95% CI, 1.108–1405; p<0.001) were independently related with the increase in PVR. Spearman correlation analysis detected a moderate relationship between PVR and mean PAP according to G. Mahan (r=0.516; p=0.003) and between PVR and the index of right heart chamber functional coupling with the PA system (r= – 0.509; p=0.007) in group 1 at the control visit.
Conclusion	In patients 3 months after COVID-19 pneumonia, hidden RV systolic dysfunction defined as depressed endocardial RV FW LS to –19.3% is associated with increased PVR ≥1.5 Wood units.

Keywords	COVID-19; pneumonia; pulmonary vascular resistance; right ventricle; echocardiography; global longitudinal strain
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Introduction

The Euler-Liljestrand reflex, also known as hypoxic pulmonary vasoconstriction (HPV), is a homeostatic response to alveolar hypoxia as a spasm of the intrapulmonary arteries. The ventilation/perfusion ratio (VA/Q ratio) is improved by diverting blood to oxygen-rich segments of the lungs [1]. According to Gattinoni et al. [2], HPV is a criterion for COVID-19-associated severe pneumonia (type H phenotype). The type L phenotype is characterized by a low VA/Q ratio, which is described as a regulation inhibition because of the loss of HPV.

Pulmonary hypertension (PH) in COVID-19 patients is associated with higher mortality [3]. Ulett et al. [4] described the LH reclassification in 578 patients with a history of LH: 58% of patients had systolic pulmonary artery pressure (sPAP) >35 mm Hg, however, after the sex and age adjustment, LH was diagnosed in only 36% of cases. Increased pulmonary vascular resistance (PVR) ≥2 Wood units was detected in 31% of patients. Moreover, PVR assessment showed that 6% of patients with sPAP≤35 mm Hg had LH [4].

Given the rough correlation between PVR assessed by the echocardiography and catheterization of the right heart,

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it appears appropriate to use this indicator in COVID-19 patients to assess HPV [5, 6].

It should be noted that right ventricular (RV) dysfunction in COVID-19 patients is associated with all-cause mortality [7]. According to Bieber et al. [8], strain indicators of both ventricles improve two months after the disease.

Objective

To Examine the relationship of structural and functional echocardiographic parameters of RV with PVR in patients 3 months after COVID-19 associated pneumonia.

Materials and Methods

The cross-sectional observational study included 96 patients with echocardiographic images of high quality who had a history of COVID-19 pneumonia, three months after two negative polymerase chain reaction test results (45.8% were male, mean age 46.7±15.2 years). The severity of lung damage was estimated based on chest computed tomography (CT) findings.

Inclusion criteria: documented diagnosis of COVID-19 associated pneumonia, patient's willingness to take part in the follow-up.

Exclusion criteria: active chronic diseases, less than 5-year history of cancer, tuberculosis and other diseases associated with pneumofibrosis, HIV, heart defects, chronic hepatitis.

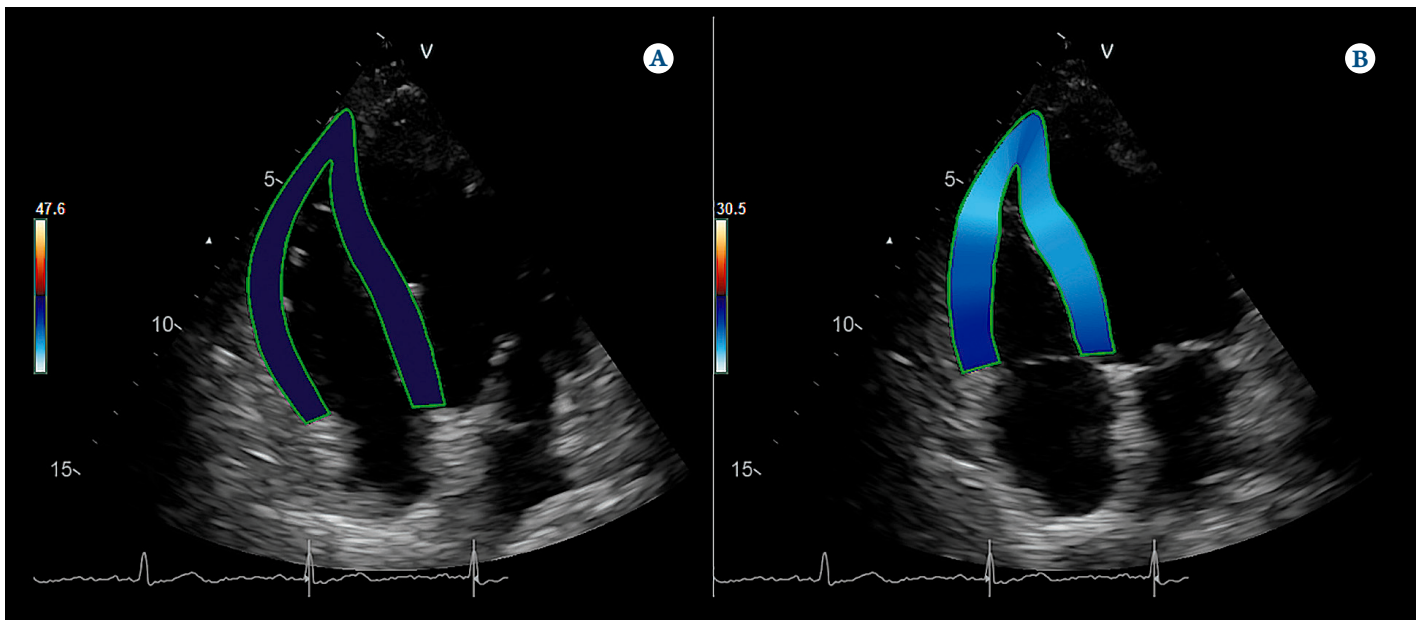
Echocardiography was conducted using an expert grade Vivid S70 ultrasound scanner and an M5Sc-D array transducer (1.5–4.6 MHz); data were stored in the DICOM format. Image and cineloop processing, including the assessment of longitudinal strain (LS) of the myocardium using speckle tracking and the analysis of all myocardial layers, was carried out on an IntelliSpace Cardiovascular workstation and TomTec software tools following the current guideline [9] (Figure 1).

sPAP, right atrial (RA) pressure was measured according to Otto et al. (2016.), mean pulmonary artery pressure (mPAP) was estimated using the formula by Mahan et al. [10]. Right ventricle-pulmonary artery coupling (RV/PA coupling) was defined as the RV fractional area change (FAC)/sPAP ratio [11]. Wood units were calculated using the formula suggested by Abbas et al. [12]. Patients with PVR≥1.5 Wood units and PVR<1.5 Wood units were included in Group 1 (n=31) and Group 2 (n=65), respectively.

The study was conducted following the Good Clinical Practice and the Declaration of Helsinki. The study protocol was approved by the local ethics committee (Protocol №159 dated 23/07/2020). All included patients signed the informed consent.

The data obtained were analyzed using SPSS Statistics 21.0. The type of variable distribution was determined using the Kolmogorov-Smirnov test. Pearson's chi-square test and Fisher's exact test were used to compare categorical variables. The normally distributed quantitative variables were analyzed using the Student's t-test; the results are expressed as the means and standard deviations (M±SD). The non-normally distributed quantitative variables were analyzed using the Mann-Whitney test; the results are

Figure 1. Assessment of RVFW and LS using the speckle tracking method



A – end of RV diastole; B – end of RV systole; RV endocardial FWLS – 20.3%
RVFW, right ventricular free wall; LS, longitudinal strain. RV, right ventricle.

presented as the medians and interquartile ranges (Me [25 th percentile; 75 th percentile]). Spearman's correlation analysis was conducted to determine the intensity of correlations. Logistic regression forced entry method was used to identify an independent correlation of PVR with functional characteristics of RV. The analysis results are presented as the odds ratios (OR) and the corresponding 95% confidence intervals (CI). The two-sided value $p<0.05$ was used the level of statistical significance of the differences between variables.

Results

The groups were comparable in basic clinical and functional characteristics at the follow-up visit (Table 1). Chest CT complete lung recovery in most patients in both groups; three patients in each group had residual lung damage; no statistically significant intergroup differences were observed (6.0±4.0% and 4.3±1.5%, respectively; p=0.537). The rest have isolated localized foci of fibrosis and calcifications up to 5 mm in size. There were no significant baseline differences in the severity of lung damage (32.7±22.1% and 36.5±20.4%, respectively; p=0.418). No statistically significant differences in the RV morphology were detected between the groups at the follow-up visit (Table 2).

Endocardial LS of the right ventricular free wall (RV FW), endocardial LS of the RV FW middle segment, tricuspid annular plane systolic excursion (TAPSE), tricuspid annular peak systolic velocity, and tricuspid annular peak early diastolic velocity were statistically significantly lower in Group 1 at the follow-up visit. Systolic pulmonary pressure, according to Otto et al., was statistically significantly higher in Group 1 (Table 3). There were no statistically significant differences between the groups in RV myocardial LS (–19.2±5.4% and –19.8±4.1%, respectively; p=0.891) and RV endocardial LS (– 19.9±5.4% and –21.3±4.0%, respectively; p=0.407).

Spearman's correlation analysis showed the correlations of the average intensity between PVR and mPAP (by G. Mahan) (r=0.516; p=0.003), and PVR and RV/PA coupling (r= – 0.509; p=0.007) in Group 1.

According to the logistic regression analysis, only RVFW LS (OR 0.859; 95% CI 0.746–0.989; p=0.034) and sPAP (OR 1.248; 95% CI 1.108–1405; p<0.001) were independently correlated with PVR≥1.5 Wood units in the baseline set of variables characterizing the RV performance and the relation of the right heart with the PA system (RVFW endocardial LS, TAPSE, tricuspid annular peak systolic and early diastolic velocities, FAC, mPAP, sPAP, RV/PA coupling).

Discussion

BUnder the European Society of Cardiology and the European Respiratory Society guidelines [13], PVR>3

Table 1. Clinical and functional characteristics of patients at the follow-up visit

Parameter	Group 1 (n=31)	Group 2 (n=65)	p
Male, %	58.1	39.7	0.124
Age, years	50.3±18.1	46.2±13.7	0.248
BMI, kg/m2	27.4±5.1	28.7±5.8	0.279
CAD, %	3.2	4.6	1.000
AH, %	54.8	46.2	0.514
HRD, %	16.1	9.2	0.326
NYHA CHF FC, %			
I	19.4	15.4	
II	6.5	4.6	0.232
III	12.9	3.1	
DM, %	9.7	7.7	0.710
LVEF, %	65.7±6.5	68.0±5.4	0.071
GLS, %	–20.5±3.2	–20.2±2.0	0.605
Complete lung recovery shown by chest CT, %	58.6	58.3	1.000

BMI, body mass index; CAD, coronary artery disease; HA, arterial hypertension; HRD, heart rhythm disorders; FC, functional class; CHF, congestive heart failure; NYHA, New York Heart Association; DM, diabetes mellitus; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; CT, computed tomography.

Table 2. Morphological characteristics of the right ventricle at the follow-up visit

Parameter	Group 1 (n=31)	Group 2 (n=65)	p
Anteroposterior RV dimension, mm	24.9±3.0	25.2±3.4	0.666
RV free wall thickness, mm	4.1±0.9	3.9±0.8	0.186
Proximal RV dimension, mm	27.8±2.6	28.0±2.9	0.696
Basal RV dimension, mm	20.7±2.7	21.1±2.7	0.572
PA diameter, mm	18.8±2.5	18.3±2.0	0.244
RV diastolic area, cm^2	14.3±4.4	15.9±4.1	0.088
RV systolic area, cm^2	7.0±2.1	7.5±2.9	0.355
RV length, mm	65.6±13.4	65.6±17.4	0.996
Middle transverse RV dimension, mm	25.7±5.0	25.1±6.9	0.648
Basal transverse RV dimension, mm	29.7±5.6	30.1±6.6	0.805
Longitudinal RA dimension, mm	49.0±6.1	47.9±6.1	0.401
Transverse RA dimension, mm	35.6±5.0	33.8±4.8	0.095
RA volume, mL	34.1±11.4	30.0±9.6	0.064
IVC at rest, mm	17.2±4.2	17.6±3.8	0.629
IVC during inhale, mm	8.8±3.1	8.2±3.0	0.348
Epicardial fat, mm	7.3±1.4	7.3±1.8	0.933

RV, right ventricle; PA, pulmonary artery; RA, right atrium; IVC, inferior vena cava.

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Table 3. Functional characteristics of the right ventricle at the follow-up visit

Parameter	Group 1 (n=31)	Group 2 (n=65)	p
RVOT flow acceleration, m/s	112.8±23.4	115.5±20.9	0.579
RVOT TVI, mm	14.4 [12.6; 15.6]	20.4 [18.4; 21.7]	<0.001
PVR, Wood units	1.8 [1.6; 2.0]	1.2 [1.0; 1.3]	<0.001
TR velocity, m/s	2.3 [2.2; 2.5]	2.0 [1.8;2.2]	<0.001
TR gradient, mm Hg	22.0 [18.0; 25.0]	15.0 [12.0; 20.0]	<0.001
FAC, %	50.0 [44.4; 54.8]	53.7 [47.0; 59.4]	0.102
TAPSE, mm	21.7±3.8	23.3±3.4	0.040
RV S', cm/s	12.3±2.4	13.4±2.0	0.024
RV E', cm/s	8.0 [7.0; 11.0]	11.0 [9.0; 14.0]	0.002
IVC inspiratory collapse, %	64.3	80.0	0.123
RV pressure (by C. Otto), mm Hg	8.8±3.3	7.9±3.2	0.247
sPAP (by C. Otto), mm Hg	32.0 [26.0; 35.0]	23.0 [20.0; 28.0]	<0.001
mPAP (by G. Mahan), mm Hg	28.2±10.5	27.0±9.4	0.579
RV/PA coupling	1.6 [1.4; 1.8]	2.2 [1.9; 2.9]	<0.001
RV free wall endocardial longitudinal strain			
Basal segment, %	–27.3±6.4	–28.3±6.2	0.476
Middle segment, %	–21.9±7.1	–25.5±6.8	0.028
Apical segment, %	–20.8±9.0	–23.5±7.1	0.142
RVFW, %	–19.3 [–17.9; –25.8]	–23.4 [–19.8; –27.8]	0.048

RVOT, right ventricular outflow tract; TVI, time velocity integral; PVR, pulmonary vascular resistance; TR, tricuspid regurgitation; FAC, fractional area change; TAPSE, tricuspid annular plane systolic excursion; RV S', right ventricular velocity, tissue Doppler imaging, peak s', RV E', right ventricular velocity, tissue Doppler imaging, peak e'; IVS, inferior vena cava; RA, right atrium; sPAP, systolic pulmonary artery pressure; mPAP, mean pulmonary artery pressure; RV/PA, right ventricle-pulmonary artery coupling; RVFW, right ventricular free wall.

Wood units is a part of the hemodynamic definition of the term LH. Some authors consider PVR≥2 Wood units appropriate to establish LH [4]. Farzaneh-Far et al. [14] estimated PVR<1.5 Wood units to be normal.

Medvedofsky et al. [15] used RVFW endocardial LS<– 22% as a marker of RV systolic dysfunction. Inhibition of RV endocardial LS≤ –23% is associated with higher mortality in patients with a history of COVID-19 [16]. It was established earlier that many indicators of the RV performance (TAPSE, RV S', RVFWS LS) in patients with COVID-19 and acute respiratory distress syndrome remain normal. Moreover, it was shown that RVFW LS is a less sensitive marker of RV dysfunction than RV FAC [11].

According to our findings, most indicators of the RV performance were statistically significantly lower in patients with PVR≥1.5 Wood units. RVFW endocardial LS was the only parameter in Group 1 that was below the expected normal range. It should be noted that sPAP remained within the reference values too. The assessment of regional contractility showed that only the middle RVFW endocardial LS was inhibited in Group 1. It should be noted that the groups were comparable in the severity of lung damage (chest CT), both at baseline and at the follow-up visit.

Bleakley et al. [11] showed a correlation between PVR and RV/PA coupling in patients with COVID-19 and acute respiratory distress syndrome. We also detected moderate correlations between PVR and RV/PA coupling, mPAP (by G. Mahan) in the group with PVR ≥1.5 Wood units. There is likely a correlation between RV function depression, signs of LH, and RV/PA decoupling in patients with PVR≥1.5 Wood units three months after COVID-19 pneumonia.

According to the Redox theory of HPV, inhibition of O2 sensitive Kv channels depolarizes PA smooth muscle cells, activating voltage-dependent calcium channels and causing vasoconstriction [17]. Archer et al. [18] suggested that calcium channel blockers (CCBs) worsened hypoxemia in COVID-19 pneumonia. At the same time, it was shown that using amlodipine was associated with lower mortality in patients with COVID-19 and arterial hypertension as the only comorbidity and in elderly patients [19, 20]. Thus, it seems relevant to study the use of CCBs in patients with increased PVR.

Conclusion

Hidden RV systolic dysfunction defined as decreased endocardial RV FW LS to –19,3 is associated with increased PVR≥1.5 WU in patients 3 months after COVID-19 pneumonia.

No conflict of interest is reported.

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