ORIGINAL ARTICLE

Impaired left ventricular deformation and ventricular-arterial coupling in post-COVID-19: association with autonomic dysregulation

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Abstract

Coronavirus disease-19 (COVID-19) has extended implications namely the long COVID-19 syndrome. We assessed over-time changes in left ventricular (LV) function, aortic stiffness, autonomic function, and ventricular-arterial coupling (VAC) in post-COVID-19 patients. We followed 34 post-COVID-19 subjects, up to 6 months post-hospital discharge. Subjects without COVID-19 served as control. We evaluated LV global longitudinal strain (LV-GLS), arterial stiffness [carotid-femoral pulse wave velocity (cf-PWV)], and heart rate variability -standard deviation of normal RR intervals (SDNN). VAC was estimated as the ratio of cf-PWV to LV-GLS. Post-COVID-19 individuals (1-month post-hospital discharge) presented with impaired LV-GLS [−18.4%(3.1) vs. −22.0%(2.7), $P < 0.001$], cf-PWV [12.1 m/s (3.2) vs. 9.6 m/s (1.9), $P < 0.001$], SDNN [111.3 ms (22.6) vs. 147.2 ms (14.0), $P < 0.001$], and VAC [−0.68 (0.22) vs. −0.44 (0.10), $P < 0.001$] compared to control. LV-GLS, SDNN, and VAC improved at the 6-month follow-up however they did not reach control levels. In post-COVID-19 subjects, SDNN and VAC were correlated at the 1-month ($R = 0.499$, $P = 0.003$) and 6-month ($R = 0.372$, $P = 0.04$) follow-up. Long COVID-19 syndrome was associated with impaired LV-GLS, SDNN, and VAC. Post-COVID-19 subjects presented with autonomic dysregulation associated with aortic stiffness, ventricular-arterial impairment, and LV dysfunction, even 6-months post-hospital discharge. These abnormalities may be related to the presence of long COVID-19 syndrome.

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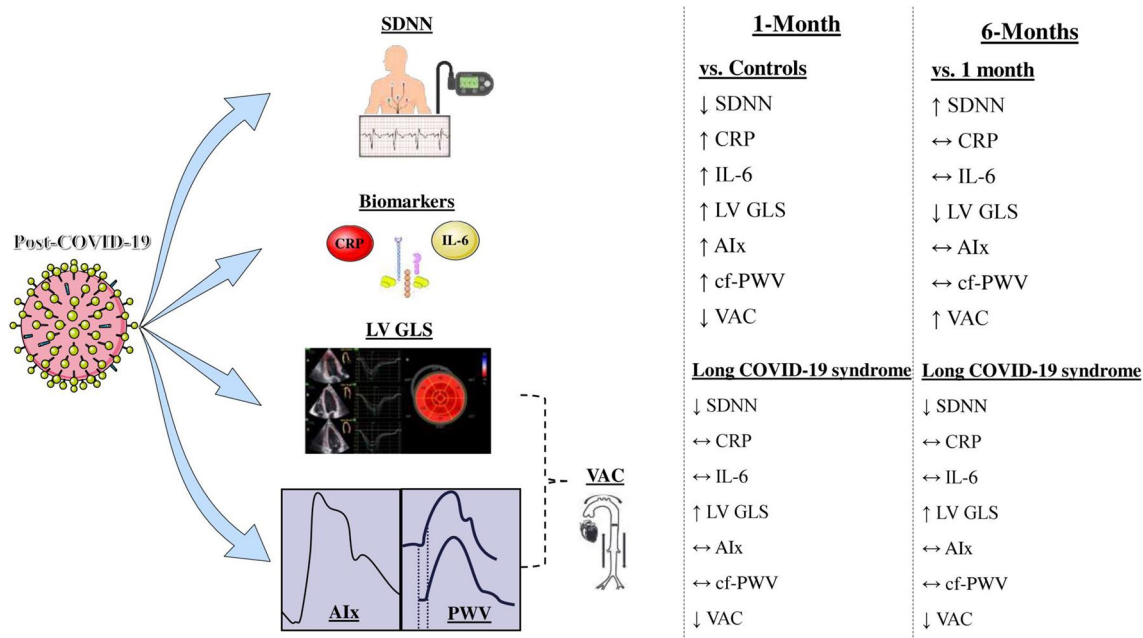
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Graphical abstract

	1-Month	6-Months
	vs. Controls	**vs. 1 month**
	↓ SDNN	↑ SDNN
	↑ CRP	↔ CRP
	↑ IL-6	↔ IL-6
	↑ LV GLS	↓ LV GLS
	↑ AIx	↔ AIx
	↑ cf-PWV	↔ cf-PWV
	↓ VAC	↑ VAC
	Long COVID-19 syndrome	**Long COVID-19 syndrome**
	↓ SDNN	↓ SDNN
	↔ CRP	↔ CRP
	↔ IL-6	↔ IL-6
	↑ LV GLS	↑ LV GLS
	↔ AIx	↔ AIx
	↔ cf-PWV	↔ cf-PWV
	↓ VAC	↓ VAC

Introduction

Since 31 December 2019 when Coronavirus disease (COVID-19) was first reported by the World Health Organization (WHO), over 540 million cases of infection have been recorded worldwide. Beyond acute effects of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection the long-lasting (post-acute infection) persistent symptoms of COVID-19, such as fatigue, joint and muscle pain, muscle weakness, dyspnea on exertion, and breathlessness that is described as "long COVID-19" or "post-COVID-19" syndrome raised concerns [1, 2]. Up to 20%–30% of patients hospitalized with COVID-19 have evidence of myocardial involvement not only in the acute but also in the post-acute phase of the disease [3]. The cardiac and vascular expression of angiotensin-converting enzyme 2 (ACE2) receptors, which are used by the SARS-CoV-2 to bind with its "spike" protein, is implicated in the pathophysiology of the associated cardiovascular complications [4, 5]. Accordingly, microvascular endothelial damage and micro thrombosis of coronary and capillary vessels lead to multiple pathways of myocardial injury and related myocarditis, vasculitis, and severe endotheliitis that is induced by a systemic inflammatory response following the "storm" of circulating pro-inflammatory cytokines [6, 7]. Regarding post-acute COVID-19 and especially the long COVID-19 syndrome inappropriate sinus tachycardia or rhythm disturbances have been reported, which may be linked to impaired sympathetic drive activation [8]. Furthermore, the implications of SARS-CoV-2 infection on the left ventricular function in the absence of clinically evident myocarditis or myocardial injury are undetermined. To address the gap, in this study we evaluated in post-COVID-19 subjects over time changes in left ventricular function properties and how sympathetic drive activity may be implicated in central arterial stiffness and ventricular-arterial coupling (VAC) performance.

Materials and methods

Study design

This is a prospective, observational, case–control study conducted in the "Sotiria" General Hospital for Chest Diseases, Athens, Greece from March 2021 to December 2021. The recruitment period was up to June 2021. We consecutively included 34 patients, who had been admitted at the "Sotiria" General Hospital for Chest Diseases with COVID-19 confirmed by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay of nasopharyngeal or bronchial swabs, in at least one biological sample. The dominant (> 90%) SARS-CoV-2 variant during the recruitment period according to the National Public Health Organization (NPHO) was alpha (B.1.1.7). All patients' study parameters

were examined at 1 and 6 -months post-hospital discharge (Fig. 1).

From the study, we excluded subjects aged < 18 years old and subjects with (a) end-stage renal failure; (b) active malignancy; (c) previous or current autoimmune diseases, and (d) abnormal thyroid function tests. We also excluded subjects who had been vaccinated against SARS-CoV-2. From the follow-up, we excluded subjects who had been vaccinated following COVID-19. Subjects with evidence suggestive of acute myocardial infarction, myocardial injury, pulmonary embolism, or myocarditis following COVID-19 diagnosis were excluded. Control group was selected from non-COVID-19 subjects after applying appropriate age-, sex- and cardiovascular risk factors propensity score matching from the historical records of our research group.

This study was carried out in accordance with the Helsinki Declaration in collaboration with Athens Medical School of the National and Kapodistrian University of Athens, Greece, and adhered to the STROBE statement for case–control studies [9]. The study protocol was approved by the hospital's Ethics Committee (protocol number: 29542/6-11-20).

Clinical and laboratory measurements

Demographics and medical history data of post-COVID-19 subjects were recorded. Regarding treatment, all subjects have been treated with remdesivir and the majority of them (80%) with Dexamethasone. Subjects abstained from food, caffeine, and alcohol prior to the examinations. Symptoms suggestive of long COVID-19 syndrome were recorded at 1 and 6 months post-hospital discharge examination.

In this analysis, patients were characterized as having long COVID-19 syndrome based on the definition by the Centers for Disease Control and Prevention (CDC) [10]. Accordingly, in all subjects, symptoms involving many organs, such as fatigue, shortness of breath, anxiety, chest pain, altered mental status, cough, depression, tachycardia/palpitation, joint and muscle pain, muscle weakness, and mobility problems were evaluated. Long COVID-19 syndrome was established if symptoms lasted at least four weeks after infection with SARS-CoV-2. To finally conclude on long COVID-19 syndrome diagnosis, other causes of symptoms (especially heart failure with preserved ejection fraction) were excluded based on clinical evaluation and diagnostic tests as per physician suggestion and type of symptoms (i.e., echocardiography, blood count test, C-reactive protein, markers of myocardial injury, B-type natriuretic peptide, etc.).

Standard laboratory parameters evaluated on both post-COVID-19 and control subjects [C-reactive protein (CRP), fibrin degradation products (D-dimers), high-sensitivity troponin I (hsTnI), Lactate dehydrogenase (LDH), Creatinine, Urea, Total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), platelets (PLT), white blood cells (WBC), Hematocrit, Hemoglobin] were evaluated at the same time points of left ventricular function, heart rate variability and arterial stiffness assessment. Blood samples were also collected at the prespecified time points, were centrifuged at
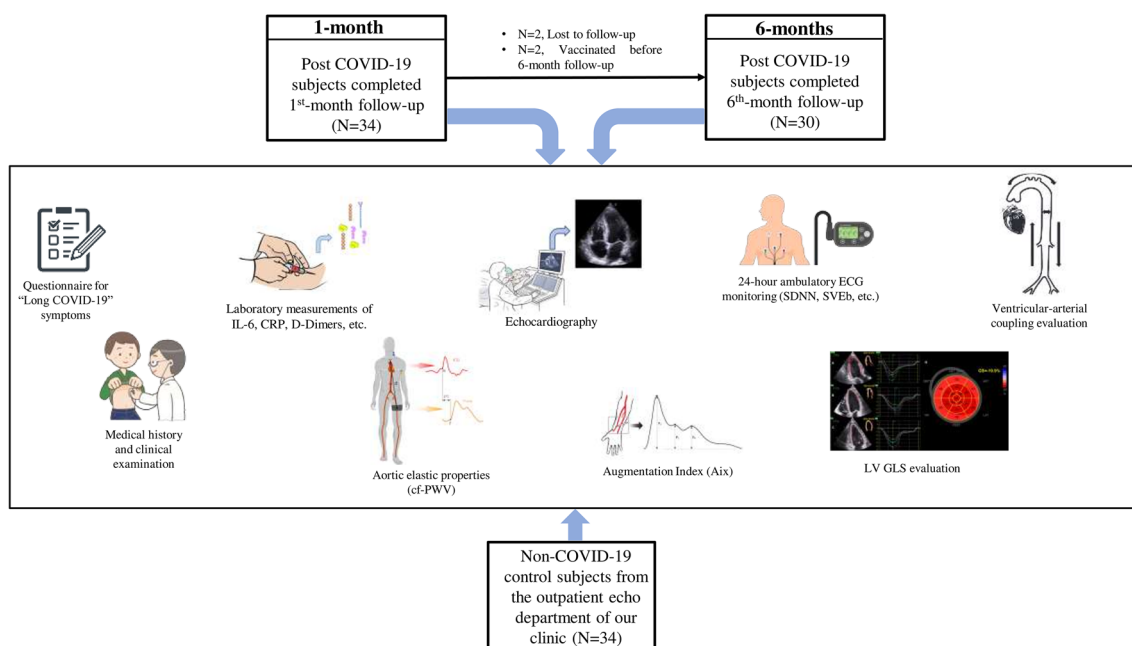

Fig. 1 Study design and parameters examined in post-COVID-19 subjects at 1 and 6 -months post-hospital discharge and in the control group

3000 rpm and serum was collected and stored at $-80\ °C$ until assayed. Serum levels of interleukin-6 (IL-6)—a well-established inflammatory cytokine were measured by commercially available ELISA kits.

Evaluation of aortic elastic properties

Arterial stiffness was evaluated in all subjects with carotid-femoral pulse wave velocity (cf-PWV) measurements. Measurement of PWV was performed using the SphygmoCor device (AtCor Medical). Two different pulse waves were obtained at 2 sites (at the base of the neck for the common carotid and over the right femoral artery) by use of a hand-held tonometer with a high-fidelity pressure (piezoelectric) sensor located at the tip of the tonometer. Aortic stiffness was calculated from measurements of pulse transit time and the distance traveled between 2 recording sites. Distance was defined as the distance from the suprasternal notch to the femoral artery minus the distance from the carotid artery to the suprasternal notch. For the synchronization of the continuous pressure waves recorded at the carotid and the brachial arteries, simultaneous acquisition of ECG was performed. All measurements were performed with the subject at the supine position after 10 min rest [11], by the same expert operator. According to the Bland–Altman method, the repeatability coefficient for cf-PWV was 4.2%.

Measurement of wave reflection indexes

Following calibration of the radial pressure waveforms based on sphygmomanometric systolic and diastolic blood pressures measured in the brachial artery, the augmentation index (AIx) of the central (aortic) pressure waveform was estimated as an index of wave reflection. Arterial stiffness affects the timing of the wave reflection. Therefore, AIx is the composite of the magnitude of wave reflection and arterial stiffness. AIx is influenced by changes in heart rate, and it is corrected accordingly (corrected for a steady heart rate of 75 beats per minute—AI75). AI75 was estimated with a validated, commercially available system (Sphygmo-Cor, AtCor Medical) that uses the principle of applanation tonometry and appropriate acquisition and analysis software for noninvasive recording and analysis of the arterial pulse, as previously described [12, 13].

Echocardiography

Transthoracic echocardiography exams were performed with Philips EPIQ CVx (Philips, Andover, MA, USA) at both post-COVID-19 and control group subjects by the same expert operator. Image analysis was performed with the Philips Q station ultrasound software. Echo protocol included all standard views according to the American

Society of Echocardiography. Automated Cardiac Motion Quantification[A.I] applied to the apical 4, 3, and 2 chambers views and after manual adjustment was used for assessment of deformation using 2D speckle tracking technology. Accordingly, the left ventricular Global Longitudinal Strain (GLS) was estimated. Automated 2D Cardiac Quantification[A.I] was used for two-dimension left ventricular ejection fraction calculation while manual corrections and adjustments were applied when necessary [14, 15]. Intraobserver reliability was excellent for EF (repeatability coefficient 3.2%), LVEDD (repeatability coefficient 4%), LVESD (repeatability coefficient 4.1%), and LV GLS (repeatability coefficient 5.2%).

Ventricular-arterial coupling

We also calculated the ratio of carotid-femoral pulse wave velocity (cf-PWV) to left ventricle global longitudinal strain (LV GLS), which is a novel and more sensitive marker of myocardial and arterial function and a robust marker of global cardiovascular performance. The PWV/GLS ratio has been shown to correlate with subclinical target organ damage and it is described as VAC. New data has emerged which is in favor of PWV/GLS as a superior marker of VAC compared to the echocardiographic derived Ea/Ees, as it can be used as a risk stratification tool for therapeutic success in a number of cardiovascular disease risk conditions such as Diabetes mellitus, hypertension, and coronary artery disease [16]. The intraobserver variability was low (repeatability coefficient 4.3%).

Assessment of heart rate variability

Heart rate variability (HRV) was evaluated using 24-h ambulatory ECG recordings through a multichannel electronic data recording system. Philips DigiTrak XT, a 3 channel 0.05 Hz to 60 Hz at -3 dB with 12-lead ST-segment analysis with 3-D graphics was used on both post-COVID-19 and control subjects. The recordings' data were transferred from the Holter ECG recorder to the arrhythmology laboratory of the Cardiology department and underwent digital filtering accompanied by manual filtering to eliminate artifacts. Series greater than 95% of sinus heart rate were included in the study. HRV was evaluated with the measure of the standard deviation of normal RR intervals in 24 h (SDNN). SDNN values equal to or lower than 100 ms were considered as abnormal/impaired or otherwise indicative of compromised health [17, 18]. Moreover, supraventricular ectopic beats (SVEb) and ventricular ectopic beats (VEb) were characterized and recorded, being expressed as a percentage of the total beats.

Statistical analysis

Continuous variables were tested for normality of distribution with the Kolmogorov–Smirnov test and visual inspection of P–P plots. Since the variables followed a normal distribution, they were presented as mean with standard deviation (SD). Categorical variables are displayed as frequencies and percentages. A Student's t test was used to compare differences between two groups of normally distributed continuous data. Adjustment for multiple comparisons was performed as appropriate. Differences between categorical variables were tested by forming contingency tables and performing χ^2-tests. Analysis of variance (ANOVA) for repeated measures was used to assess the over-time changes in normally distributed variables. The correlation coefficient between SDNN and PWV/GLS ratio was assessed using the Pearson correlation coefficient. Patients after hospitalization for COVID-19 were matched with a control group using propensity scores (variables adjusted for: age, sex, BMI, current smoking, arterial hypertension, diabetes mellitus, dyslipidemia, and coronary artery disease). Propensity scores were based on logistic regression analysis. Balance of the propensity scores was tested visually by comparing distribution in the different study groups. Optimal matching was applied, and balance was checked with comparison tests as appropriate.

The Bland–Altman method was used to test for intraobserver variability. Accordingly, the repeatability coefficient was calculated based on the following formula [19]: repeatability coefficient $= 2 \times \sqrt{(\Sigma di^2/N}$, where N is the sample size and di is the difference between the 2 measurements in a pair).

All reported P values were based on two-sided hypotheses, with a P value <0.05 being considered statistically significant. All statistical calculations were performed using IBM SPSS software (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp).

Results

Characteristics of the study population

Baseline characteristics of the study population are displayed in Table 1. No differences in age, sex, BMI, and cardiovascular risk factors (smoking, history of arterial hypertension, DM, dyslipidemia, or CAD) were noted between convalescent COVID-19 patients and the matched control group. Regarding laboratory tests, levels of inflammatory markers were persistently elevated in convalescent COVID-19 patients through the follow-up period and were significantly higher compared to the control group, while

Table 1 Characteristics of study population

	Control ($N=34$)	Convalescent COVID-19 patients ($N=34$)	P
Age (years)	57.4 ± 12.8	57.2 ± 12.9	0.95
Male sex	23 (67.6)	26 (76.5)	0.42
BMI kg/m^2	28.5 ± 3.1	28.1 ± 3.6	0.63
Smoking	21 (61.8)	19 (55.9)	0.62
Hypertension	12 (35.3)	13 (38.2)	0.81
DM	6 (17.6)	5 (14.7)	0.74
Dyslipidemia	16 (47.1)	16 (47.1)	1.0
CAD	11 (32.4)	8 (23.5)	0.42

Categorical variables are presented as number (percentage %)

Continuous variables are presented as mean with standard deviation (SD)

COVID-19, coronavirus disease-19; BMI, Body mass index; DM, diabetes mellitus; CAD, Coronary Artery Disease

no differences were observed in renal function, blood counts, lipid panel, and other parameters (Table 2).

Left ventricular function in post-COVID-19 patients

Echocardiographic findings of the study population are presented in Table 3. One month after the infection, convalescent COVID-19 patients presented with impaired LV GLS compared to controls [COVID-19: −18.4% (3.1) vs. Control: −22.0% (2.7), $P < 0.001$). EF, LVEDD, and LVESD did not differ significantly between the two groups. At the 6-month follow-up, significant improvements were noted in LV GLS [1 month: −18.0% (3.1) vs. 6 months: −19.3% (2.9), $P < 0.001$] and LVEF [1 month: 55.6% (3.5) vs. 6 months: 58.2% (3.5), $P = 0.003$] (Fig. 2). LV GLS remained significantly impaired at 6 months in convalescent COVID-19 patients compared to controls [COVID-19 (6 months): −19.3% (2.9) vs. Control: −22.0% (2.7), $P < 0.001$].

Arterial stiffness in post-COVID-19 patients

We next examined parameters of arterial stiffness in our study population (Fig. 3A, B). Convalescent COVID-19 patients compared to the control group had significantly higher cf-PWV [COVID-19: 12.1 m/s (3.2) vs. Control: 9.6 m/s (1.9), $P < 0.001$] and AIx [COVID-19: 33.0% (9.7) vs. Control: 23.3% (3.0), $P < 0.001$] at the 1-month follow-up. Although an improvement of those measures was noted at the 6-month follow-up, both cf-PWV [COVID-19: 11.7 m/s (2.7) vs. Control: 9.6 m/s (1.9), $P < 0.001$] and AIx [COVID-19: 30.0% (9.3) vs. Control: 23.3% (3.0), $P < 0.001$] remained impaired compared to controls.

Table 2 Differences in laboratory values between controls and convalescent COVID-19 patients at 1- and 6-month follow-up

Lab tests	Control (N = 34)	Convalescent COVID-19 patients		P^*	$P^\dagger$	$P^\ddagger$
		1-month (N = 34)	6-month (N = 30)			
IL-6, pg/ml	1.07 (0.77)	1.91 (1.02)	2.17 (1.09)	**< 0.001**	**< 0.001**	0.20
CRP, mg/dl	0.30 (0.09)	0.68 (0.59)	0.54 (0.58)	**< 0.001**	**0.015**	0.06
LDH, IU/l	229 (29)	231 (47)	211 (29)	0.80	0.022	0.017
D-Dimers, µg/ml	0.43 (0.22)	0.73 (0.55)	0.54 (0.14)	**0.004**	0.03	0.07
hs-Tn, pg/ml	4.4 (3.1)	6.7 (6.0)	4.8 (5.6)	0.05	0.76	0.38
Total Chol, mg/dl	190 (52)	201 (44)	188 (37)	0.34	0.85	0.04
HDL-C, mg/dl	46 (10)	42 (8)	43 (6)	0.09	0.19	0.34
LDL-C, mg/dl	128 (39)	145 (34)	139 (36)	0.051	0.25	0.14
TG, mg/dl	117 (34)	140 (48)	147 (58)	0.03	0.017	0.41
Creatinine, mg/dl	0.93 (0.17)	1.21 (1.21)	1.01 (0.13)	0.18	0.056	0.70
Urea, mg/dl	41.9 (10.4)	41.6 (6.9)	39.6 (5.8)	0.90	0.27	0.86
Hematocrit, %	43.7 (4.8)	43.8 (6.6)	43.4 (4.8)	0.90	0.81	0.12
Hemoglobin, g/dl	13.8 (1.8)	13.7 (2.2)	13.7 (1.4)	0.86	0.75	0.45
PLT, 10^9/l	210 (70)	216 (68)	191 (28)	0.74	0.20	0.26
WBC, 10^9/l	5.82 (1.33)	6.59 (1.84)	6.08 (1.49)	0.05	0.48	0.57

Continuous variables are presented as mean with standard deviation (SD).

Adjustment for multiple comparisons was applied. Statistically significant differences are presented in bold

BP, blood pressure; PLT, platelets; WBC, white blood cells; LDH, lactate dehydrogenase; CRP, C-reactive protein; hs-Tn, high sensitivity troponin; IL-6, interleukin-6; Chol, cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides

*Denotes comparison between patients 1-month post-COVID-19 and controls

†Denotes comparison between patients 6-month post-COVID-19 and controls

‡Denotes comparison between 1-month and 6-months post-COVID-19

Heart rate variability and sympathetic drive evaluation

The subjects underwent a 24-h holter electrocardiographic monitoring. As shown in Table 3, convalescent COVID-19 patients presented with decreased SDNN [COVID-19: 111.3 ms (22.6) vs. Control: 147.2 ms (14.0), $P < 0.001$] (Fig. 3 C) and a higher burden of SVEb [COVID-19: 1.09% (1.15) vs. Control: 0.15% (0.18), $P < 0.001$], and VEb [COVID-19: 0.60% (0.76) vs. Control: 0.14% (0.12), $P < 0.001$] 1-month after the acute phase compared to controls. Those differences were attenuated remarkably at a 6-months follow-up. While 29.4% of convalescent COVID-19 individuals had SDNN values below 100 ms at 1-month follow-up, the prevalence of such values dropped to 8% at 6 months ($P = 0.01$). No subjects from the control group presented such SDNN value (SDNN < 100 ms) ($P < 0.001$ compared to COVID-19 at 1 month and $P = 0.06$ compared to post-COVID-19 at 6 months).

Ventricular-arterial coupling and autonomic dysfunction in convalescent COVID-19 patients

We also calculated the PWV/GLS ratio, a marker of VAC. This marker was significantly reduced in convalescent COVID-19 patients both at 1-month [COVID-19: −0.68 m/s% (0.22) vs. Control: −0.44 m/s% (0.10), $P < 0.001$] and 6-months [COVID-19: −0.62 m/s% (0.19) vs. Control: −0.44 m/s% (0.10), $P < 0.001$] compared to controls (Fig. 3D). A significant improvement was noted across the follow-up period for the convalescent COVID-19 patients ($P < 0.001$).

Furthermore, we tried to assess the relationship between VAC and autonomic dysfunction. A significant correlation between PWV/GLS ratio and SDNN was noted in the convalescent COVID-19 group at the 1-month ($R = 0.499$, $P = 0.003$) and 6-month follow-up ($R = 0.372$, $P = 0.04$). Individuals with impaired SDNN values (SDNN < 100 ms) had significantly lower PWV/GLS ratio at 1-month [Impaired SDNN: −0.85 (0.25) vs. Normal SDNN: −0.61 (0.17), $P = 0.003$].

Long-COVID-19 syndrome

Finally, at 1-month follow-up 56% of patients were diagnosed with the long-COVID-19 syndrome, and at the 6-month follow-up 30% of subjects have been found with long COVID-19. We assessed whether the presence of long COVID-19 syndrome was associated with impaired left ventricular deformation, VAC, and autonomic dysfunction.

Table 3 Differences in measures of arterial stiffness, cardiac function, and 24-h ambulatory ECG between controls and convalescent COVID-19 patients at 1- and 6-month follow-up

	Control (N=34)	Convalescent COVID-19 patients		P^*	$P^†$	$P^‡$
		1-month (N=34)	6-month (N=30)			
Cardiac function						
LVEF, %	57.9 (4.3)	55.9 (3.5)	58.2 (3.5)	0.04	0.76	**0.003**
LV GLS, %	−22.0 (2.7)	−18.4 (3.1)	−19.3 (2.9)	**< 0.001**	**< 0.001**	**< 0.001**
LVEDD, mm	46.4 (4.5)	46.5 (5.1)	45.7 (6.8)	0.90	0.65	0.41
LVESD, mm	32.8 (1.6)	33.9 (6.7)	32.7 (3.6)	0.35	0.90	0.23
Arterial stiffness						
cf-PWV m/s	9.6 (1.9)	12.1 (3.2)	11.7 (2.7)	**< 0.001**	**< 0.001**	0.11
Peripheral AIx, %	23.3 (3.0)	33.0 (9.7)	30.0 (9.3)	**< 0.001**	**< 0.001**	0.019
Ventricular-arterial coupling						
PWV/GLS ratio, (m/s%)	−0.44 (0.10)	−0.68 (0.22)	−0.62 (0.19)	**< 0.001**	**< 0.001**	**< 0.001**
24-h ambulatory ECG						
SDNN, ms	147.2 (14.0)	111.3 (22.6)	133.0 (23.5)	**< 0.001**	**0.004**	**< 0.001**
SDNN < 100 ms (%)	0	10 (29.4)	3 (10.0)	**< 0.001**	0.06	**0.005**
SVEb, %	0.15 (0.18)	1.09 (1.15)	0.27 (0.51)	**< 0.001**	0.22	**< 0.001**
VEb, %	0.14 (0.12)	0.60 (0.76)	0.05 (0.06)	**0.001**	**0.003**	**0.003**

Continuous variables are presented as mean with standard deviation (SD)

Adjustment for multiple comparisons was applied. Statistically significant differences are presented in bold

LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; cf-PWV, Carotid–femoral PWV; Peripheral Aix, Peripheral Augmentation Index; SDNN, standard deviation of all N–N intervals; SVEb, supraventricular ectopic beat; VEb, ventricular ectopic beat

*Denotes comparison between patients 1-month post-COVID-19 and controls

†Denotes comparison between patients 6-month post-COVID-19 and controls

‡Denotes comparison between 1-month and 6-months post-COVID-19

Interestingly, we noted that convalescent COVID-19 patients with long COVID-19 syndrome had significantly impaired LV GLS and SDNN, together with lower PWG/GLS ratio both at 1 month and 6 months of follow-up compared to those without long COVID-19 syndrome (Fig. 4).

Discussion

In this study, we documented that convalescent COVID-19 patients present impaired left ventricular function, especially left ventricular global longitudinal strain, and VAC. Moreover, post-COVID-19 patients present sympathetic drive activation, as evaluated with heart rate variability, which is associated with central aortic stiffness. Significantly, we documented an association between post-COVID-19 sympathetic drive activation with impaired VAC and ventricular performance possibly through changes in central aortic functional properties. Moreover, we found that subjects with long COVID-19 syndrome present changes in VAC and performance of the left ventricle. Importantly, in covalense COVID-19 patients there are overtime improvements in left

ventricular performance, VAC, and sympathetic drive over a 6 months follow-up period.

Myocardial deformation in COVID-19

Cardiovascular complications of COVID-19 are detrimental to the prognosis of hospitalized patients. Therefore, echocardiographic evaluation is of importance in the early identification of acute complications. In a recently reported study, left ventricular and right ventricular dysfunction were reported in 30% and 20% of patients in the acute setting, respectively [20]. Among the studied markers, LV GLS appears to be an indicator of incident in-hospital mortality [20]. However, residual myocardial dysfunction may be present even in the recovery period. In this regard, several studies have assessed the echocardiographic course of LV GLS in convalescent COVID-19 patients. Impaired LV GLS represents a prevalent echocardiographic feature in such patients 1 month after hospitalization, being observed in as many as 90% of patients with severe disease in the acute phase, with a mean value of −15.5% [21]. In patients with moderate disease severity, as in our study population, a mean LV GLS of −18.1% was reported [21], which is in
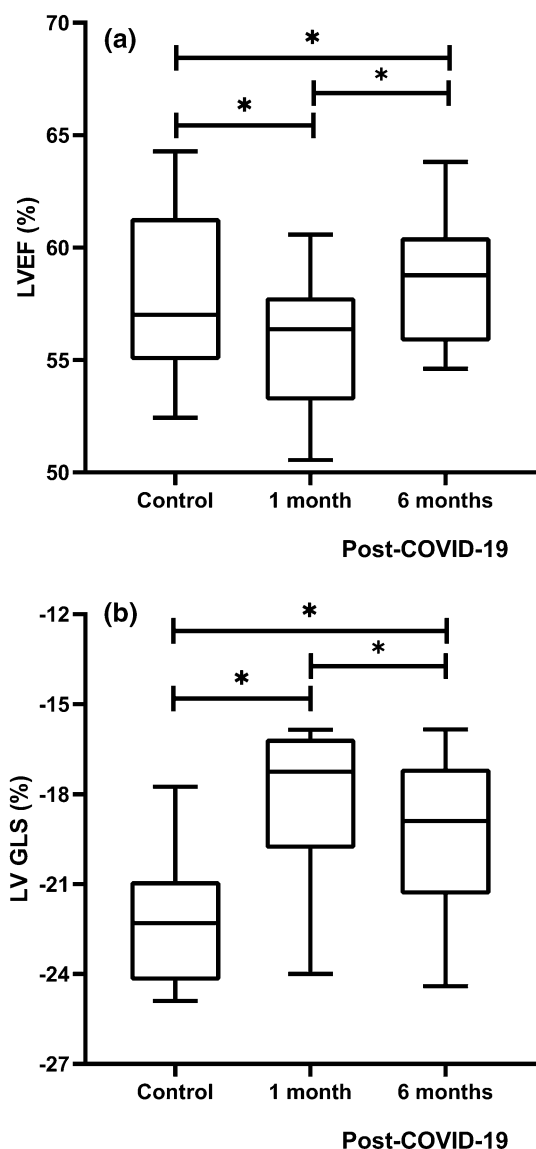
Fig. 2 Differences in **A** left ventricular ejection fraction (LVEF) and **B** global longitudinal strain (LV GLS) between the control group and post-COVID-19 patients 1 and 6 months after hospital discharge. *Indicates statistically significant difference ($P < 0.0125$)

accordance with our findings at a 1-month follow-up. Of interest is also the recovery of LV GLS over time and as we have documented left ventricular function is improved for at least 6-month post hospital discharge.

However, it should be noted that the presence of long COVID-19 syndrome may indicate the persistence of deformation abnormalities beyond 6 months, as we and others have shown [22]. Importantly, VAC may be more relevant regarding the association with symptoms, since it represents the ratio or the balance between the pump function of the heart and the load opposed by the arterial system [23]. Indeed, in cardiovascular disease, VAC has been associated with prognosis, functional performance, and symptoms [16].

However, in the setting of COVID-19, or even regarding long COVID-19 syndrome, there is no data on how arterial and left ventricular performance interacts and how they may affect the clinical course of the disease. We documented the parallel impairment in arterial stiffness and left ventricular performance which is highly relevant to long COVID-19 syndrome even 6 months post-hospital discharge. Importantly, these findings may be more relevant when long COVID-19 syndrome is predominated by symptoms such as fatigue, reduced effort capacity, or impaired functional status.

Another point of interest is the underlying mechanisms implicated in the impairment of cardiac performance in patients during the acute, sub-acute or long-term COVID-19 period. Several mechanisms have been proposed such as inflammation, immune-mediated myocarditis or abnormalities in coronary microcirculation [24–27]. Additionally, we documented the parallel over time changes in sympathetic drive, arterial stiffness, and ventricular-arterial performance which may broaden our understanding of the mechanisms implicated in myocardial function during and post-acute COVID-19.

Arterial stiffness and COVID-19

Regarding the arterial consequences of COVID-19, the associated long-standing endothelial dysfunction and hyperinflammatory response may be associated with altered vascular integrity [3, 28]. Arterial stiffness could be the outcome of impaired endothelial function and inflammation [29], as seen in COVID-19. Studies have assessed arterial stiffness indices in the acute and recovery phase of COVID-19. In a large Spanish cohort of 12,170 patients hospitalized for COVID-19, arterial stiffness, assessed by pulse pressure with a threshold of 60 mmHg, was an independent predictor of in-hospital mortality [30]. Increased cf-PWV was also observed in hospitalized patients with COVID-19 compared to controls, with the highest values being associated with increased mortality rate and hospital length of stay [31]. Cf-PWV was impaired in the study of Labadiari et al. 4 months after SARS-CoV-2 infection [32], with values resembling the ones observed in our study. High cf-PWV and AIx were also observed in healthy young adults 1 month after SARS-CoV-2 infection [33, 34]. To our knowledge, we are the first to demonstrate no improvement in cf-PWV across our 6-month follow-up. This might be of particular importance, since it may indicate either pre-COVID-19 impairment of PWV, permanent PWV changes following COVID-19, or slow recovery of post-COVID-19 arterial function properties changes beyond a 6-month follow-up period. Therefore, infected individuals could be faced with an increased risk of incident adverse cardiovascular events which should be further documented.
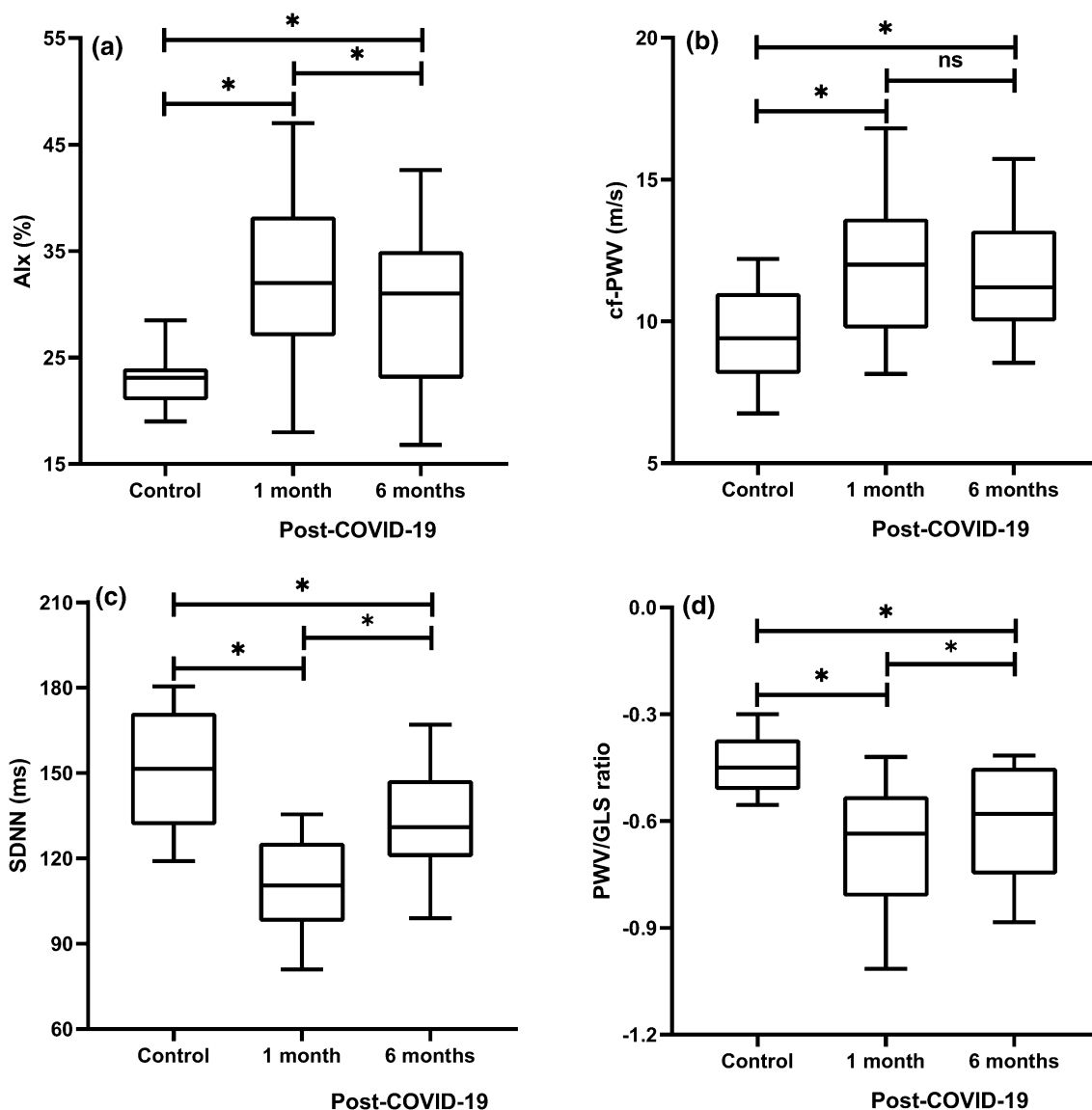
Fig. 3 Differences in **A** augmentation index (AIx), **B** carotid-femoral pulse wave velocity (cf-PWV), **C** standard deviation of all N–N intervals (SDNN), and **D** PWV/GLS ratio between the control group and post-COVID-19 patients 1 and 6 months after hospital discharge. *Indicates statistically significant difference ($P < 0.0125$)

Autonomic dysregulation in COVID-19

Autonomic nervous system dysregulation has been observed in the post-acute COVID-19 phase with relevant symptoms of cardiovascular origin (i.e. orthostatic hypotension, orthostatic tachycardia, etc.) [34]. Regarding the COVID-19-related autonomic nervous system impairment, the underlying pathophysiologic mechanisms remain largely unknown and we can only speculate direct damage to nerve and ganglia or indirect effects caused by cytokine release or immune-mediated damage [35]. Other proposed mechanisms include hypovolemia, brainstem damage, autoimmunity, and mast cell activation [36]. Studies have documented HRV impairment as a prognostic factor in COVID-19 patients [37]. We found that even 6 months post-hospital discharge, COVID-19 patients present impaired HRV with increased sympathetic drive, based on SDNN. The consequences of the increased sympathetic drive on cardiovascular components of post-COVID-19 patients are largely unknown. Through sympathetic drive activation, sympathetic activity may increase arterial stiffness and, to a further stem, malignant ventricular-arterial coupling which may precede heart failure with preserved ejection fraction [38]. In our cohort of post-COVID-19 subjects, we identified sympathetic drive activation and altered HRV which remained impaired in the mid-term

Fig. 4 Alterations in **A** left ventricular global longitudinal strain (LV GLS), **B** standard deviation of all N–N intervals (SDNN), and **C** pulse wave velocity (PWV)/GLS ratio according to the presence of symptoms. *Indicates statistically significant difference ($P < 0.05$)
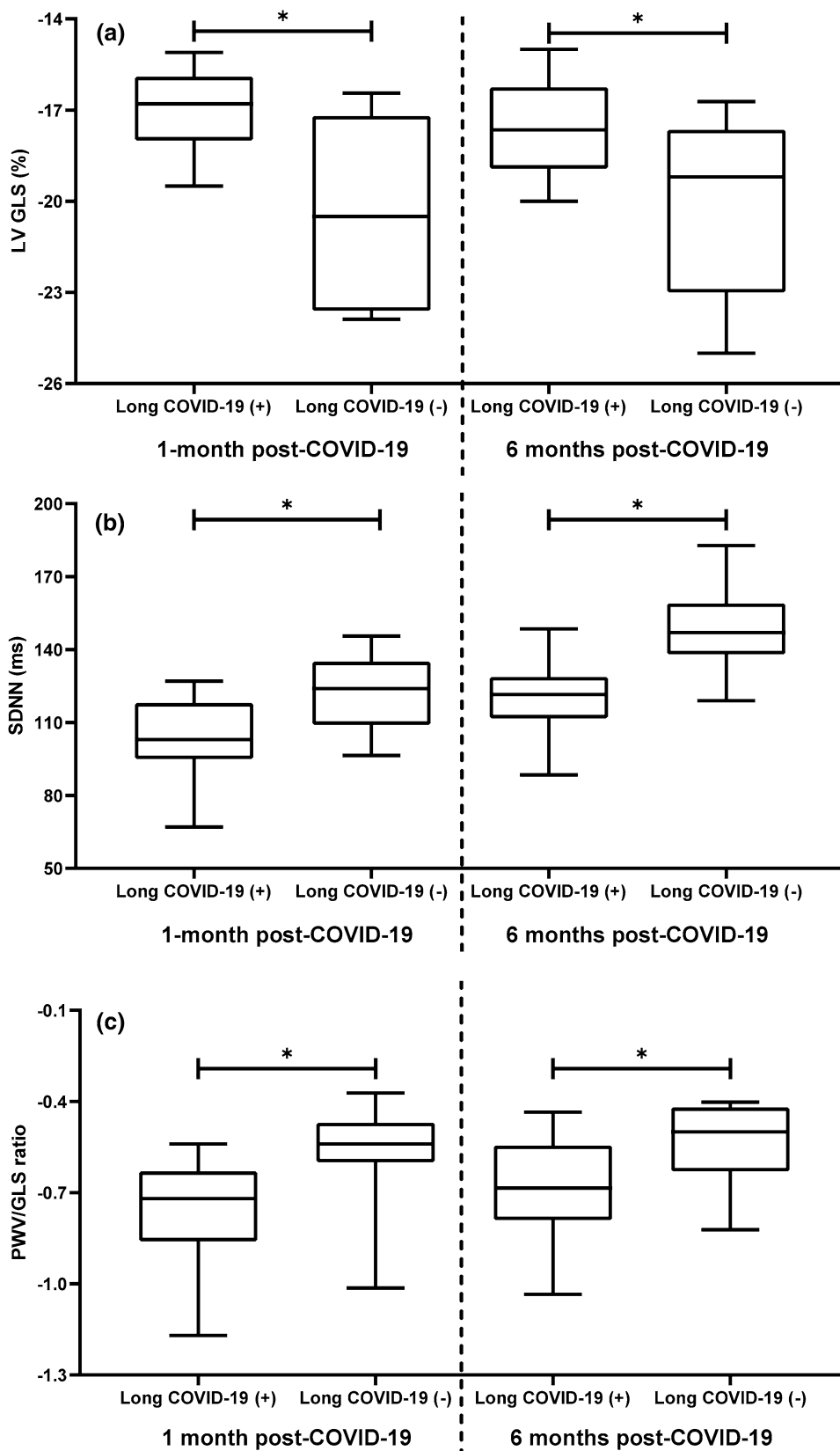
(6 months follow-up) and were associated with the long COVID-19 syndrome and left ventricular performance.

Limitations

Our study has some limitations. Being based on small sample size, it was neither designed nor powered to assess the causal association between autonomic dysregulation and VAC and cannot conclude on predictive factors for long-COVID-19 syndrome. Moreover, we cannot exclude the possibility that COVID-19 caused by different variants of SARS-CoV-2 may have interfered with the observed results. However, according to the prevalence of SARS-CoV-2 variance in Athens, Greece during the study period, this possibility is limited. Another issue of our study is the possible impact of treatment inhomogeneities in our results, which however have not been confirmed in a specific sub-analysis. There are also inherent limitations in the accurate diagnosis of long COVID-19 syndrome. Although in our study natriuretic peptides have not been measured in all subjects, heart failure as the cause of symptoms was safely excluded based on physicians' examinations, echocardiography, and measurement of natriuretic peptides in all inconclusive cases.

Conclusion

The pathophysiologic changes induced by COVID-19 in the acute and post-acute phases are complex and prolonged, affecting multiple organs and systems with various interactions. Subjects in the post-acute COVID-19 phase present autonomic dysregulation, sympathetic drive activation, and impaired heart rate variability, which are associated with central aortic stiffness, ventricular-arterial impairment, and left ventricular function impairment. These findings shed light on the cardiovascular implication of COVID-19, highlighting possible alternative mechanisms implicated in ventricular performance and functional status of post-COVID-19 patients and the relevant symptoms regarding long COVID-19 syndrome.

Declarations

Conflict of interest The authors declare that there is no conflict of interest.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Ethics approval The study was approved by the hospital's Ethics Committee and conformed to the ethical guidelines of the 2008 Declaration of Helsinki.

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