Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Left Atrial Function in Patients with Coronavirus Disease 2019 and Its Association with Incident Atrial Fibrillation/Flutter

Myocardial injury in Coronavirus disease 2019 (COVID-19) has been associated with adverse outcomes; however, associations between myocardial injury and arrhythmias, such as atrial fibrillation/flutter (AF), are not well established in this population.[1,2] Recent advances in two-dimensional echocardiography (2DE), including speckle-based strain, enable the quantification of left atrial (LA) strain (LAS), a measure of atrial deformation that has previously been shown to be predictive of AF and cardiovascular events in stable outpatients.[3,4] We aimed to compare echocardiographic measures of LA function between hospitalized COVID-19 patients and COVID-19-negative controls to test the hypothesis that COVID-19 patients have reduced LA function as reflected by abnormal LAS and LA emptying fraction (LAEF). We then tested the hypothesis that among COVID-19 patients, LA dysfunction and cardiac biomarker elevation are associated with incident AF.

This study was approved by the Johns Hopkins Institutional Review Board. From March 25, 2020, to June 20, 2020, we retrospectively studied hospitalized adults who underwent clinically indicated 2DE with adequate image quality in accordance with the American Society of Echocardiography guidelines.[5,6] Our cohort included 80 patients with COVID-19 and 34 controls without COVID-19, selected by frequency matching from patients admitted to intensive or intermediate care units with one or more respiratory problems. All patients had 2DE during admission and were followed to discharge or death. Patients were excluded for any history of atrial arrhythmia. The 2DEs were blindly analyzed offline for LAEF and reservoir (peak longitudinal) LAS using a vendor-independent strain application (TomTec Imaging Systems, Munich, Germany). Demographic, clinical, and biomarker data, obtained within 72 hours of 2DE, were taken from the electronic medical record. Atrial fibrillation/flutter was diagnosed by inpatient telemetry.[7] Comparisons were made between COVID-19 patients and controls and between COVID-19 patients with and without AF. The Wilcoxon rank-sum test was used for continuous variables, and the χ^2 test was used for categorical variables. Logistic regression was performed to investigate associations between AF and clinical variables.

Patient demographics are listed in Tables 1 and 2. COVID-19 patients had lower LAS (28.2% [22.9%-34.1%] vs 32.6% [27.7%-38.8%], $P = .026$) and LAEF (55.7% [50.8%-62.6%] vs 64.1% [58.6%-71.9%], $P < .001$) compared with controls. Traditional cardiovascular risk factors, inflammatory and cardiac biomarkers, and mortality were similar between groups; however, there was a higher incidence of intensive care unit (ICU) admission and lower incidence of acute respiratory distress syndrome (ARDS) in the control group (Table 1).

COVID-19 patients who developed AF ($n = 24$; 30%) had higher troponin I, N-terminal pro-brain natriuretic peptide (NT-proBNP), ICU admission, ARDS, and shock; they were overall older and more often Caucasian compared with COVID-19 patients without AF (Table 2). Despite similar LA volume index (LAVI) and LAEF, LAS was significantly lower in the AF versus non-AF group of COVID-19 patients (22.3% [20.6%-27.8%] vs 30.4% [26.1%-35.8%], $P < .001$; Figure 1). On univariable logistic regression, LAS, ICU admission, and ARDS were associated with AF, while troponin and NT-proBNP levels were not. These findings persisted on multivariable regression adjusted for age, sex, and body mass index (BMI; Supplemental Table 1).

These findings show that hospitalized COVID-19 patients have reduced LA function compared with COVID-19-negative controls with similar degrees of critical illness, and this dysfunction is more pronounced in COVID-19 patients who develop AF. Importantly, we report an independent association between LAS and AF among COVID-19 patients, even after adjustment for confounders.

Myocardial injury via serum and echocardiographic findings is associated with AF in the present COVID-19 population studied. Associations between AF and inflammatory markers such as C-reactive protein in COVID-19 have been reported.[2] We found an insignificant trend toward higher inflammatory markers in COVID-19 patients compared with controls that was not associated with AF. The observation of more incident AF in patients with higher troponin and NT-proBNP levels, which are associated with worse outcomes in COVID-19, supports hypotheses involving COVID-19-related myocardial injury beyond that of generalized critical illness.[1]

The LAVI was lower in COVID-19 patients compared with controls and similar in COVID-19 patients with and without AF, suggesting that LA dysfunction developed acutely rather than in the setting of chronic remodeling. Both LAVI and LAS have been shown to predict AF and cardiovascular outcomes in the outpatient setting.[4] The association of reduced LAS with AF in COVID-19 suggests that LAS may have greater utility than LAVI in identifying atrial injury in this population. Furthermore, reduced LAS may represent a higher-risk COVID-19 phenotype that warrants closer monitoring for cardiac complications, including AF.

Limitations to our study include the modest sample size, cross-sectional design, and dependence on 2DE image quality, which allowed for LAS measurement in the two-chamber or four-chamber apical view. Since it is not routinely measured, baseline LAS remains unknown, and causality cannot be inferred based on cross-sectional design. ARDS was less frequent in the control group; however, when this was adjusted for, LAS remained significantly associated with AF ($P < .001$). Despite excluding patients with a history of AF, prior undiagnosed paroxysmal AF remains a potential confounder. Lastly, the findings here may only apply to COVID-19 inpatients.

Systemic inflammation in COVID-19 may contribute to an atrial myopathy that leads to increased risk of atrial arrhythmias. Evaluation of LA mechanics by 2DE provides useful data for risk stratification. Further studies are needed to confirm these findings in larger populations and define underlying mechanisms.

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Table 1 Characteristics of COVID-19 patients versus COVID-19-negative controls

Characteristics	Total cohort (*N* = 114)	COVID-19+ (*n* = 80)	Controls (*n* = 34)	*P* value
Age, years, median	61 [51-71]	61 [51-70]	61 [53-72]	.77
Gender, female	47 (41)	32 (40)	15 (44)	.68
Race				
White	23 (20)	13 (16)	10 (29)	.11
African American	59 (52)	39 (49)	20 (59)	.33
Hispanic	15 (13)	14 (18)	1 (3)	.035
Other	18 (16)	14 (16)	4 (12)	.44
BMI, kg/m^2	29.2 [25.6-34.5]	29.4 [26.4-34.9]	25.9 [24.1-34.1]	.09
Comorbidities				
Hypertension	80 (70)	56 (70)	24 (71)	.95
Diabetes mellitus	41 (36)	33 (41)	8 (24)	.07
Hyperlipidemia	49 (43)	39 (49)	10 (29)	.06
Congestive heart failure	14 (12)	11 (14)	3 (9)	.46
Coronary artery disease	13 (11)	10 (13)	3 (9)	.57
Clinical variables*				
Troponin I, ng/mL	0.03 [0.03-0.10]	0.03 [0.03-0.10] *n* = 74	0.03 [0.03-0.09] *n* = 26	.72
NT-proBNP, pg/mL	393 [120-1844]	337 [111-1,495] *n* = 66	1,134 [220-2,116] *n* = 17	.12
C-reactive protein, mg/dL	12 [3.8-18.0]	12 [3.9-18.4] *n* = 61	5.7 [2.9-11.6] *n* = 10	.29
Ferritin, ng/mL	786 [410-1,689]	915 [509-1,689] *n* = 57	347 [197-2,234] *n* = 12	.12
D-dimer, mg/L FEU	2.3 [0.9-7.8]	2.1 [0.8-8.1] *n* = 79	3.8 [2.2-7.6] *n* = 9	.14
Clinical events				
ICU admission	89 (78)	58 (73)	31 (91)	.03
Shock	57 (50)	44 (55)	13 (38)	.10
VTE	30 (26)	23 (29)	7 (21)	.37
ARDS	51 (45)	49 (61)	2 (6)	<.001
Death	16 (14)	11 (14)	5 (15)	.89
Time from admission to 2DE, days	3 [1-8]	4 [2-9]	3 [1-7]	.50
Echo parameters				
LVEF, %	62.5 [55.0-67.5]	62.5 [53.8-63.8]	62.5 [62.5-67.5]	.011
LAVI, mL/m^2	21.6 [17.6-29.5]	20.6 [16.3-28.7]	27.8 [20.1-33.0]	.003
LAEF, %	58.8 [50.8-64.8]	55.7 [50.8-62.6]	64.1 [58.6-71.9]	<.001
LA reservoir strain, %	29.4 [23.6-35.7]	28.2 [22.9-34.1]	32.6 [27.7-38.8]	.026

Data are presented as median [interquartile range] or *n* (%). *GLS*, global longitudinal strain; *LVEF* , left ventricular ejection fraction; *VTE*, venous thromboembolism.

*Johns Hopkins Hospital laboratory reference ranges: troponin I <0.04 ng/mL; NT-ProBNP 0-125 pg/mL; C-reactive protein <0.05 mg/dL; ferritin 13-150 ng/mL; D-dimer <0.49 mg/L fibrinogen-equivalent units.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.echo.2021.05.015.

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Table 2 Characteristics of COVID-19 patients who did and did not develop AF

	COVID-19 + No-AF (*n* = 56)	COVID-19+ AF (*n* = 24)	*P* Value
Age, years	60 [48-68]	66 [60-75]	.017
Gender, female	21 (38)	11 (46)	.49
Race			
White	4 (7)	9 (38)	.001
African American	28 (50)	11 (46)	.73
Hispanic	11 (20)	3 (13)	.44
Other	13 (23)	1 (4)	.040
BMI, kg/m^2	29.2 [26.4-34.9]	30.1 [26.3-36.8]	.79
Comorbidities			
Hypertension	39 (70)	17 (71)	.92
Diabetes mellitus	23 (41)	10 (42)	.96
Hyperlipidemia	25 (45)	14 (58)	.26
Congestive heart failure	9 (16)	2 (8)	.36
Coronary artery disease	7 (13)	3 (13)	>.99
Clinical variables*			
Troponin I, ng/mL	0.03 [0.03-0.05]	0.07 [0.03-0.17]	.011
NT-proBNP, pg/mL	231 [97-846] *n* = 47	946 [388-3,997] *n* = 19	<.001
C-reactive protein, mg/dL	13 [2.5-18.0] *n* = 42	11.8 [4.3-20.0] *n* = 19	.66
Ferritin, ng/mL	945 [529-1,860] *n* = 40	758 [506-1,077] *n* = 24	.41
D-dimer, mg/L FEU	1.8 [0.7-7.6]	3.1 [1.1-9.7]	.41
Clinical events			
ICU admission	35 (63)	23 (96)	.002
Shock	26 (46)	18 (75)	.019
VTE	17 (30)	6 (25)	.63
ARDS	30 (54)	19 (79)	.03
Death	6 (11)	5 (21)	.23
Time from admission to 2DE, days	4 [2-7]	5 [2-16]	.29
Echo parameters:			
LVEF, %	62.5 [55.0-67.5]	57.5 [47.3-62.5]	.044
LV GLS, absolute value, %	16.9 [14.4-19.5] *n* = 50	16.7 [15.0-17.4] *n* = 13	.56
LAVI, mL/m^2	20.1 [16.0-26.6]	21.6 [17.4-28.9]	.30
LAEF, %	57.3 [47.5-62.6]	54.6 [51.2-61.7]	.70
LA reservoir strain, %	30.4 [26.1-35.8]	22.3 [20.6-27.8]	<.001

Data are presented as median [interquartile range] or *n* (%). *GLS*, global longitudinal strain; *LVEF* , left ventricular ejection fraction; *VTE*, venous thromboembolism.
*Johns Hopkins Hospital laboratory reference ranges: troponin I <0.04 ng/mL; NT-ProBNP 0-125 pg/mL; C-reactive protein <0.05 mg/dL; rerritin 13-150 ng/mL; D-dimer <0.49 mg/L fibrinogen-equivalent units.

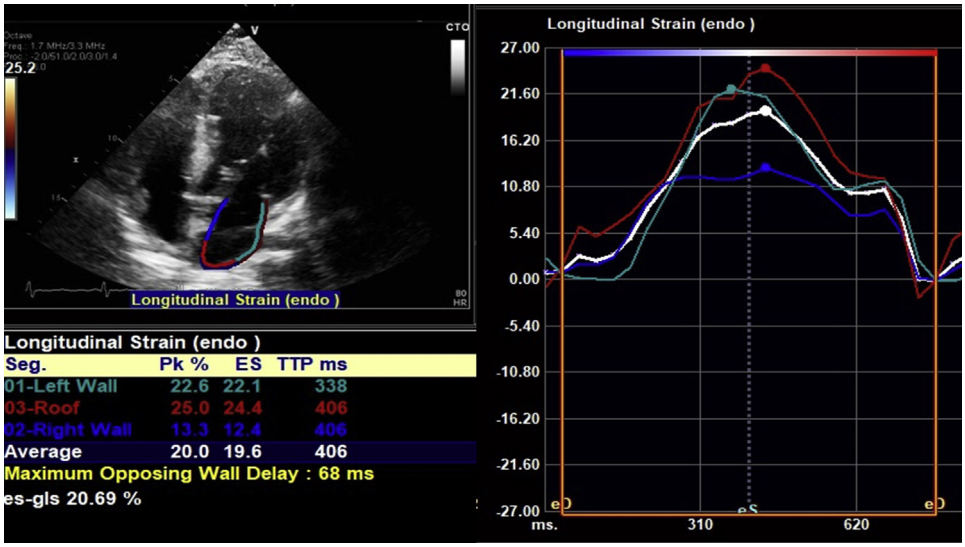

Figure 1 Example of reduced peak longitudinal/reservoir LAS in a COVID-19 patient who developed AF during admission. Average LAS here is 20% (normal, >38%).

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Ventricular Septal Defect Area by Three-Dimensional Echocardiography for Assessment of Shunt Severity in Children

Ventricular septal defect (VSD) size is a determinant of shunt severity in children. Two-dimensional (2D) echocardiography (2DE) underestimates VSD size compared with three-dimensional (3D) echocardiography (3DE) and surgical measures.[1-3] We hypothesized that VSD area obtained from 3DE could better discriminate shunt severity than VSD diameters.

Infants with isolated VSDs were included between June 2018 and May 2020. We excluded patients with multiple VSDs, patients in the neonatal period or born prematurely at ≤37 weeks, and patients with any other cardiovascular or extracardiac anomalies including idiopathic pulmonary hypertension, syndromic, and genetic anomalies. Single VSDs having several orifices opening into the right ventricle side were excluded. The study was approved by our institutional review committee, and informed consent was obtained.

From the end-diastolic frames (first frame of mitral valve closure), two orthogonal VSD diameters were measured using 2DE from the long- and short-axis views; the largest diameter was considered the maximal 2D diameter, and the smallest the minimal 2D diameter (Supplemental Figure 1). Aortic annulus diameter (AD) was measured from the parasternal long-axis (PLAX) view.[4] The pulmonary-to-systemic shunt ratio (QP/QS) was evaluated by Doppler echocardiography.[5] Left ventricular end-diastolic diameter was measured using the M mode from the PLAX view, and the *Z* score was calculated.[6] Systolic pulmonary artery pressure was calculated from a continuous Doppler pressure gradient through the VSD. A ratio of QP/QS ≥ 2 was considered significant volume overload, and a ratio of systolic pulmonary pressure/systolic arterial pressure ≥ 50% was considered pulmonary arterial hypertension (PAH). Patients were divided into three subgroups according to shunt size: small shunt (without significant volume overload or PAH), moderate shunt (volume overload without PAH), and large shunt (volume overload with PAH).

A 3D full-volume acquisition was obtained from the apical four-chamber view using the high-volume rate mode and analyzed offline using QLab 11 (EPIQ 7, Philips Medical Systems, Andover, MA). Ventricular septal defect 3D measurements were obtained from an en face view using the multiplanar reformatting mode at the end-diastolic frame, including the two orthogonal diameters of the VSD: maximal and minimal 3D diameters. Ventricular septal defect area

Conflicts of Interest: None.