European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 09, Issue 03, 2022

ORIGINAL RESEARCH

To evaluate the cardiovascular changes associated with covid-19

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ABSTRACT

Aim: To evaluate the cardiovascular changes associated with covid-19

Methods: One hundred consecutive patients diagnosed with COVID-19 infection underwent complete echocardiographic evaluation within 24 hours of admission and were compared with reference values. Echocardiographic studies included left ventricular (LV) systolic and diastolic function and valve hemodynamics and right ventricular (RV) assessment, as well as lung ultrasound. A second examination was performed in case of clinical deterioration.

Results: Clinical data were collected in 120 consecutive patients hospitalized with COVID-19 infection. A total of 20 patients were excluded because they did not undergo echocardiographic assessment. The reasons for not performing the echocardiogram were as follows: hospital discharge within 24 hours of admission (8 patients), patient refusal (2 patient), and death shortly after hospitalisation (8 patients, all >80 years of age and with a "do not resuscitate" status).

Conclusions: patients presenting with clinical deterioration at follow-up, acute RV dysfunction, with or without deep vein thrombosis, is more common, but acute LV systolic dysfunction was noted in ≈20%.

Keywords: Cardiovascular changes, Covid-19

Introduction

Coronavirus disease 2019 (COVID-19) was first reported in Wuhan, China, in late December 2019.[1-3] Since then, COVID-19 has spread rapidly worldwide and has become a global pandemic affecting >200 countries and territories, with an unprecedented effect not

only on public health, but also social and economic activities. The exponential increase in the number of patients with COVID-19 in the past 6 months has overwhelmed health-care systems in numerous countries across the world. At present, preventive vaccines and prophylactic therapies for COVID-19 are not available.

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is a member of the genus Betacoronavirus like the two other coronaviruses that have caused pandemic diseases (severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV)).[1–4] As with SARS-CoV and MERS-CoV, SARS-CoV-2 causes a respiratory infection, which leads to viral pneumonia and acute respiratory distress syndrome (ARDS) in some patients.[1]However, in addition to respiratory symptoms, uncontrolled SARS-CoV-2 infection can trigger a cytokine storm, whereby pro-inflammatory cytokines and chemokines such as tumour necrosis factor-α, IL-1β and IL-6 are overproduced by the immune system, resulting in multiorgan damage.[5] Furthermore, COVID-19 causes coagulation abnormalities in a substantial proportion of patients, which can lead to thromboembolic events.[6,7] The genomic sequence[1–3,8] and viral protein structure[9–11] of SARS-CoV-2 have been studied intensively since its emergence. To date, research shows that SARS-CoV-2 shares many biological features with SARS-CoV owing to 79.6% genomic sequence identity.[1,2] In particular, both SARS-CoV and SARS-CoV-2 use the same system of cell entry, which is triggered by binding of the viral spike (S) protein to angiotensin-converting enzyme 2 (ACE2) on the surface of the host cell.

Understanding the biological features of the virus will contribute to the development of diagnostic tests, vaccines and pharmacological therapies and can further our knowledge of tissue tropism. Early clinical data indicate that both the susceptibility to and the outcomes of COVID-19 are strongly associated with cardiovascular disease (CVD).[12–16]

Material and methods

This prospective observational study was carried out in the Department of General Medicine and Department of Paediatrics, after taking the approval of the protocol review committee and institutional ethics committee of GMC,Amritsar.

100 consecutive adult patients COVID- 19 infection were included in this study. All patients had a diagnosis of COVID-19 infection confirmed by a positive reverse-transcriptase polymerase chain reaction assay for severe acute respiratory syndrome coronavirus 2 in a respiratory tract sample. Demographic data, co-morbid conditions, medications, physical examination, lung ultrasound, and laboratory findings (including troponin-I levels) were systematically recorded. Patients were risk-stratified according to their COVID-19 Modified Early Warning Score (MEWS) and Sequential Organ Failure Assessment score.[17,18] A summary of MEWS calculation is presented in Table I in the Data Supplement. All patients underwent comprehensive transthoracic echocardiography within 24 hours of admission as part of a predefined step-by-step protocol. Clinical and imaging data were collected prospectively. Patients who then experienced clinical deterioration underwent repeat echocardiographic assessment. Clinical deterioration was defined as either death or respiratory, hemodynamic, or cardiac deterioration. Respiratory deterioration was defined as acute new-onset hypoxemia requiring mechanical ventilation, veno-venous extracorporeal membrane oxygenation, or both. Hemodynamic deterioration was defined as persistent hypotension requiring vasopressors to maintain a mean arterial

pressure ≥65 mm Hg and having a serum lactate level >2 mmol/L despite adequate volume resuscitation. Cardiac deterioration was defined as either an increase in serum levels of cardiac troponin-I above the 99th percentile upper reference limit or malignant arrhythmia (defined as rapid ventricular tachycardia lasting >30 seconds, inducing hemodynamic instability or ventricular fibrillation). The ethics committee of GMC,Amritsar approved the study (Institutional Review Board No 6547832and voided the requirement of informed consent for the echocardiographic assessment. To evaluate the presence of subtle echocardiographic abnormalities, we compared the echocardiographic characteristics in patients with COVID-19 infection with the reference values previously published.[19,2021]

Echocardiography

Echocardiography was performed in a standard manner with the same equipment (CX 50, Philips Medical Systems, Bothell, WA) by cardiologists with expertise in echocardiographic recording and interpretation. In accordance to current guidelines,[22] the following measures were undertaken to minimize the risk of infection: (1) All echocardiographic studies were bedside studies performed at the designated COVID-19 intensive care or internal ward units. (2) All echo- cardiographic examinations were performed with small dedicated scanners because their disinfection is easier than that of larger machines with high-end ultrasound systems.

These echocardiographic scanners were set aside in each COVID-19–designated ward to minimize the risk of infection spread. (4) Personal protection at the time of echocardiographic recordings included airborne precautions, made up of N-95 respirator masks, fluid-resistant gowns, 2 sets of gloves, head covers, eye shields, and shoe covers. (5) Electrocardiographic monitoring during imaging was omitted, and all measurements were performed offline to reduce exposure and contamination.

Left ventricular (LV) diameters, volumes, ejection fraction (LVEF), and mass were measured as recommended.[19]Measurements of mitral inflow included the peak early filling (E wave) and late diastolic filling (A wave) velocities, E/A ratio, and deceleration time of early filling velocity. Early diastolic mitral septal and lateral annular velocities were measured in the apical 4-chamber view.[20] Left atrial volume was calculated with the biplane area-length method at end systole. Forward stroke volume was calculated from the LV outflow tract with subsequent calculation of cardiac output and index.

Right Ventricular Assessment

From 4-chamber views encompassing the entire right ventricle (RV), end-systolic and end-diastolic RV areas and tricuspid annulus were measured. Apart from qualitative grading, RV function was evaluated by tricuspid annular plane systolic excursion, systolic tricuspid lateral annular velocity (RV S') measured in the apical 4-chamber view, fractional area change, and index of myocardial performance (Tei index).[19,23] Hemodynamic right-sided assessment included the measurement of the pulmonic flow acceleration time (AT) velocity to assess pulmonary vascular resistance.[21]

Lung Ultrasound

We performed lung ultrasonography on all patients with COVID-19 infection using a 6-zone method for each lung, including a scan of the anterior, lateral, and posterior aspects of the thorax. A point scoring system was used for each region and ultrasound pattern: A lines (normal reverberation artifacts of the pleural line that, when accompanied by lung sliding, correspond to normal aeration of the lung) were equal to 0 points; B lines (shining lines vertical to the pleural line, arising from it and reaching the edge of the screen erasing A

lines, which represent reverberation artifact through edematous interlobular septa or alveoli) were divided into B1 (separated B lines that correspond to moderate lung aeration loss), equal to 1 point, and B2 (coalescent B lines that correspond to severe lung aeration loss), equal to 2 points. Lung consolidation received 3 points. Thus, a lung ultrasound score of 0 was normal and 36 was the worst.[24]

Results

the study group included 100 patients who underwent echocardiographic evaluation (66.1±17.3 years of age, 63% male). At the time of baseline echocardiographic evaluation, all patients had dyspnea at rest, stratified to mild disease (oxygen saturation ≥94% at room air) in 61, moderate disease (need for noninvasive oxygen) in 29, and severe disease (need for mechanical ventilation) in 10. Table 1 shows the baseline characteristics and echocardiographic assessments of all patients and stratified by echocardiography results. Comorbidities were present in 18 of patients, with hypertension being the most common, followed by diabetes mellitus, obesity, and coronary artery disease. The most common symptoms on admission were respiratory, followed by only fever, chest pain, and fatigue. Troponin-I, CRP, BNP, and D- dimer were elevated in 22%, 88%, 30%, and 60%, respectively. Bilateral infiltration was the most common chest x-ray manifestation. Pleural effusion and lobar infiltration were rare. Baseline echocardiographic characteristics of patients with COVID-19 infection compared with reference values[19,20,21]are shown in Table II in the Data Supplement. Compared with reference values, patients had smaller LVs and lower LVEF, resulting in

Table 1. Baseline Characteristics\

Parameter	All (n=100)	Normal Echocardiogram (n=30)	Abnormal Echocardiogram (n=70)	P Value
Age, mean±SD, y	66.1±17.3	65.9±20	69.8±16	0.57
Male, n (%)	65(65)	19 (63.33)	47(78.33)	0.24
Cause of admission, %				0.45
Respiratory	65	53	63	
Fever	8	14	8	
Chest pain	9	7	11	
Fatigue	5	9	4	
Neurological	4	0	4	
Gastrointestinal	8	5	4	
Comorbidity	18	12	6	

Body surface area, mean±SD, m2	1.90±0.2	1.84±0.3	1.10±0.3	0.17
Ischemic heart disease, n (%)	18 (18)	5 (16.6)	13 (18.57)	0.47
Congestive heart failure, n (%)	10 (10)	5 (16.6)	5 (7.1)	0.81
S/P coronary artery bypass graft, n (%)	6 (6)	2 (6.6)	4 (5.7)	0.52
Atrial fibrillation/flutter, n (%)	17 (15)	5 (16.6)	11 (15.7)	0.59
Transient ischemic attack/stroke, n (%)	13 (11)	5 (16.6)	8 (10)	0.75
Peripheral artery disease, n (%)	4 (3)	0 (0)	4 (5.7)	0.11
Chronic obstructive pulmonary disease, n (%)	5 (4)	3 (10)	2 (2.8)	0.06
Asthma, n (%)	9 (7)	3 (10)	6 (8.5)	0.81
Chronic kidney disease, n (%)	12 (10)	3 (10)	9 (12.8)	0.35
Diabetes mellitus, n (%)	31 (29)	8 (26.6)	23 (32.8)	0.27
Smoking, n (%)	10 (8)	3 (10)	7 (10)	0.63
Hypertension, n (%)	60 (57)	16 (53.3)	44 (62.8)	0.13
Obesity, n (%)	31 (29)	10 (33.3)	21 (30)	0.98
Malignancy, n (%)	7 (5)	2 (6.6)	5 (7.1)	0.52
Aspirin, n (%)	26 (24)	9 (30)	17 (24.2)	0.75
P2Y12 inhibitor, n (%)	7 (5)	3 (10)	4 (5.7)	0.70
Direct oral anticoagulant, n (%)	15 (13)	4 (13.3)	11 (15.7)	0.42
Angiotensin-converting enzyme, n (%)	19 (17)	9 (30)	10 (14.2)	0.15
Angiotensin receptor blocker, n (%)	19 (17)	5 (16.6)	14 (20)	0.37
Diuretics, n (%)	20 (18)	5 (16.6)	15 (21.4)	0.47
β-Blocker, n (%)	27 (25)	7(23.3)	20 (28.5)	0.22

Systemic corticosteroids, n (%)	4 (2)	2 (6.6)	2 (2.8)	0.60
Other anti-inflammatories, n (%)	5 (3)	2 (6.6)	3 (4.2)	0.98
Hemoglobin, mean±SD, g/dL	14.1±1.10	14.5±1.10	13.9±1.10	0.18
White blood cells, mean±SD, 103/μL	8.9±4.3	8.5±2.10	9.1±4.7	0.76
Neutrophils, mean±SD, 103/μL	6.9±3.10	6.7±3.1	7.1±4.3	0.68
Lymphocytes, mean±SD, 103/μL	2.2±1	2.1±0.8	2.3±1.2	0.57
Platelets, mean±SD, 103/μL	211±87	216±86	207±86	0.71
Sodium, mean±SD, mmol/L	137.5±4.6	138.6±4.6	137.0±4.6	0.11
Potassium, mean±SD, mmol/L	5.1±0.4	5.1±0.4	5.1±0.5	0.88
Creatinine, median (IQR), mg/dL	0.10 (0.7–1.2)	0.86 (0.6–1.0)	0.96 (0.7–1.3)	0.03
Blood urea nitrogen, mean±SD, mg/dL	24.2±17.1	23.8±19	24.4±14	0.43
Lactate dehydrogenase, median (IQR), U/L	475 (364–677)	391 (278–605)	494 (373–683)	0.70
Bilirubin, mean±SD, mg/dL	0.58±0.41	0.50±0.21	0.62±0.48	0.76
Aspartate aminotransferase, median (IQR), U/L	36 (26–61)	36 (25–65)	35 (27–61)	0.76
Alanine transaminase, median (IQR), U/L	28 (19–55)	29 (20–61)	32 (18–51)	0.87
Albumin, mean±SD, g/L	39.5±5.1	40.1±5.3	39.3±5.0	0.66
C-reactive protein, mean±SD, mg/L	80.1±66	63.8±72	81.4±62	0.44
C-reactive protein >5 mg/L, n (%)	86 (88)	23 (76.6)	63 (90)	0.05
Troponin-I, median (IQR), ng/L	12 (5–39)	12 (3–33)	12 (6–46)	0.39
Troponin-I >28 ng/L, n (%)	22 (22)	6 (20)	16 (22.8)	0.44
BNP, median (IQR), pg/mL	44 (18–144)	32 (18–23)	44 (18–160)	0.44

BNP >80 pg/mL, n (%)	32 (30)	6 (20)	26 (37.1)	0.01
D-dimer, mean±SD, mg/L	0.9 (0.4–1.7)	0.9 (0.2–0.9)	0.7 (0.3–1.4)	0.67
D-dimer >0.5 mg/L, n (%)	60 (60)	19 (63.3)	41 (58.5)	0.82
Fibrinogen, mean±SD, mg/dL	551.3±150	513.1±182	566.0±133	0.24
Ferritin, median (IQR), ng/mL	404 (171–835)	311 (162–626)	526 (193–945)	0.26
Lung crackles, n (%)	28 (28)	9 (30)	19 (27.1)	0.87
Leg edema, n (%)	6 (6)	0 (0)	6 (8.5)	0.05
Heart rate, mean±SD, bpm	84±15	81.1±15	84.4±14	0.41
Systolic blood pressure, mean±SD, mm Hg	134±23	123±19	140±20	0.004
Diastolic blood pressure, mean±SD, mm Hg	76±14	77±14	71±13	0.32
O2 saturation, median (IQR)	96 (89–98)	93.5 (91.2–98)	94 (92–98)	0.74
Temperature, median (IQR), °C	38.1 (36.7–37.7)	38.2 (36.8–37.5)	38.1 (36.6–37.6)	0.38
Lobar infiltration, n (%)	14 (14)	3 (10)	11 (15.7)	0.27
Bilateral infiltration, n (%)	47 (47)	14 (46.6)	33 (47.1)	0.55
Pleural effusion, n (%)	18 (18)	6 (20)	12 (17.1)	0.94
Hilar congestion, n (%)	10 (10)	3 (10)	7 (10)	0.66
Normal sinus rhythm, n (%)	79 (79)	24 (88)	55 (78.5)	0.41
Atrial fibrillation/flutter, n (%)	8 (8)	4 (13.3)	4 (5.7)	0.34
Right bundle-branch block, n (%)	7 (7)	3 (10)	4 (5.7)	0.69
Left bundle-branch block, n (%)	4 (4)	0 (0)	4 (5.7)	0.21
ST-segment elevation, n (%)	4 (4)	0 (0)	4 (5.7)	0.21
ST-segment depression, n (%)	6 (6)	0 (0)	4 (5.7)	0.07
T-wave inversion, n (%)	12 (10)	4 (13.3)	8 (11.4)	0.88
Long QT, n (%)	8 (6)	2 (6.6)	6 (8.5)	0.38

QTc, mean±SD, ms	417.3±53	422.7±26	414.8±62	0.84
Sequential Organ Failure Assessment score, median (IQR)	4 (0–3)	2 (0–4)	2 (0–3)	0.72
MEWS, median [IQR]	6 (2–7)	5.5 (2–8)	5 (3–7)	0.63
MEWS 3 grades, n (%)				0.78
Low	55 (55)	17 (56.6)	38 (54.2)	
Medium	22 (22)	7 (23.3)	14 (20)	
High	30 (30)	11 (36.6)	19 (27.1)	
Lung ultrasound score, median (IQR)	16 (7–21)	17 (6–22)	16 (7–20)	0.92

lower stroke volume. Nevertheless, 90% of patients had normal LVEF. Low LVEF caused by ischemic heart disease was known in 2 of the 10 patients with low LVEF. Evaluation of indexes of LV filling pressure showed enlarged left atrial volume and increased average E/e ratio compared with reference values. Nevertheless, most patients (80%) did not have clearly elevated LV filling pressure (E/e'≥14). On the other hand, RV was enlarged in ≈40% of patients. In terms of indexes of RV function, pulmonary AT was shorter and RV S' and RV fractional area change were lower than reference values, but tricuspid annular plane systolic excursion and Tei index were in the normal range in the majority of patients.
The most common echocardiographic pattern among patients with COVID-19 infection was RV dilatation with or without dysfunction (39%), followed by LV diastolic dysfunction (16%), LV systolic dysfunction (10%), and valvular heart disease (3 patients: 1 with severe organic mitral regurgitation and 2 with moderate aortic regurgitation). The remaining 32 patients (32%) had a normal echocardiogram. Baseline characteristics and echocardiographic assessments in patients with normal baseline echocardiogram versus abnormal echocardiogram are shown in Table 1. Most clinical characteristics were similar between these groups except for higher creatinine, increased prevalence of elevated BNP and CRP, higher systolic blood pressure, and more peripheral edema in patients with an abnormal echocardiogram.

Clinical Severity Grade and Echocardiography

We assessed all LV and RV parameters in patients with COVID-19 infection stratified by clinical presentation at baseline echocardiogram. Patients with worse clinical grade had shorter pulmonary AT, suggesting increased RV afterload (Table 2). Of note, there were no significant differences in LV systolic or diastolic function between the patients with worsening clinical grades.

Pulmonary AT

The most common echocardiographic pattern among patients with COVID-19 infection was RV dilatation related to elevated pulmonary vascular resistance. We assessed all

clinical characteristics, including comorbidities, stratified by AT tertiles and present them in Table III in the Data Supplement. Patients with shorter AT (suggesting increased pulmonary vascular resistance) were older, had more comorbidities, and had worse lung disease (based on chest x-ray, lung ultrasound, and lower oxygen saturation). They also had higher levels of biomarkers of adverse prognosis (D-dimer, BNP, troponin-I, and CRP).

Biomarker Levels

Similar to previous reports,[25] 20% of patients with COV- ID-19 infection had troponin levels above the 99th percentile at presentation. Patients with elevated troponin levels were older and had higher BNP levels and MEWS and Sequential Organ Failure Assessment scores but were otherwise similar to patients with nonincreased troponin levels. All LV linear dimensions and parame- ters of radial LV systolic function were similar between patients with and without troponin elevation (Table IV in the Data Supplement). However, patients with high troponin levels had a significantly elevated average E/e′ ratio, suggesting that patients with elevated troponin have worse LV diastolic function and higher left atrial pressure. Indexes of RV hemodynamics and function were poorer in patients with elevated troponin. Pulmonary AT was shorter, RV fractional area change was worse, and RV S' and tricuspid annular plane systolic excursion were lower, suggesting inefficient RV function secondary to increased afterload. Troponin was negatively associated with stroke volume, AT, tricuspid annular plane systolic excursion, and RV fractional area change and positively associated with E-wave velocity, left atrial volume, E/e' ratio, and Tei index in unadjusted analyses. Spearman correlation analyses with the cor- relations coefficients and P values between all biomarkers and LV and RV parameters are shown in Table V in the Data Supplement. The addition of age, MEWS, D- dimer, CRP, and BNP improved the predictive value of all the models (P<0.0001 for all models), but BNP removed troponin from all the models with the exception of RV fractional area change.

We performed analyses on the echocardiographic and clinical predictors of clinical deterioration or death alone. The only baseline clinical parameters associated with clinical deterioration during hospitalisation were obesity (2.7 [hazard ratio (HR), 1.05–6.8]; P=0.03), lower platelet count (0.98 [HR, 0.97–0.98]; P=0.004), lower O2

Table 2. Patients Stratified by Clinical Presentation at Baseline Echocardiogram

Variables	Clinical Grade*			P Value
	Grade 1(n=60)	Grade 2(n=30)	Grade 3(n=10)	
Age, mean±SD, y	64.2±16	72.3±12	70.4±20	0.06
Male, n (%)	34 (56.6)	20 (66.6)	7 (70)	0.25
MEWS, mean±SD	4.0±1	8.9±2	12.0±3	<0.0001
Acuity score (COVID-19 MEWS), (%)				<0.0001
Low	40	3	0	
Medium	17	10	2	

High	13	17	8	
Troponin-I, mean±SD, ng/L	21.8±49	35.3±52	942±2139	0.0005
Positive end-expiratory pressure, mean±SD, cm H2O	0±0	0±0	12.1±3.1	<0.0001
Fraction of inspired O2, mean±SD, %	23±3	50±30	71±25	<0.0001
O2 saturation, mean±SD, %	96.9±2	94.0±3	94.6±3	0.02
Systolic blood pressure, mean±SD, mm Hg	136±21	135±20	130±20	0.78
Diastolic blood pressure, mean±SD, mm Hg	76±13	74±17	73±23	0.73
Vasopressor requirement, n (%)	0 (0)	0 (0)	3 (30)	0.0006
LV assessment				
EF, %	59.2±3	59.2±4	57.0±4	0.32
LV S', cm/s	8.8±2	8.0±1	7.5±1	0.74
LVEDD, mm	43.3±5	46.1±6	42.7±3	0.20
LVESD, mm	27.8±4	30.2±5	28.8±4	0.21
Heart rate, bpm	76.8±13	82.2±18	94.7±24	0.01
Stroke volume, mL	60.9±15	62.3±21	47.8±16	0.09
Cardiac output, L/min	5.6±1.3	5.8±2.0	5.0±1.3	0.44
LA volume, mL	56.7±23	60.6±25	61.6±29	0.64
E wave, m/s	0.67±0.25	0.65±0.17	0.56±0.17	0.41
A wave, m/s	0.65±0.25	0.63±0.13	0.68±0.17	0.74
E/A	1.13±0.3	1.09±0.6	0.76±0.1	0.14
e' Septal, cm/s	6.8±1	5.8±1	5.8±1	0.14
e' Lateral, cm/s	8.8±2	7.9±2	7.6±1	0.39
E/e' average	10.6±7	10.5±3	9.0±3	0.80
RV assessment				
RA pressure, mm Hg	7.3±3.1	8.7±4.4	9.5±5.4	0.22
Volume overload, n (%)	25 (41.6)	11 (36.6)	6 (60)	0.82

PAT, ms	103±29	82±23	87±30	0.01
PAT <100 ms, n (%)	28 (46.6)	26 (86.6)	9 (90)	0.0002
RVEDA, cm2	22.8±4	21.7±4	22.0±5	0.84
RVESA, cm2	13.5±2	13.0±3	15.1±5	0.44
RVFAC, %	45.4±9	41.7±9	33.8±10	0.09
TAPSE, mm	2.4±0.4	2.4±0.3	2.2±0.6	0.62
RV S', cm/s	12.3±2	12.3±3	11.1±2	0.54
Tei index	0.45±0.25	0.39±0.17	0.43±0.25	0.72

COVID-19 indicates coronavirus disease 2019; EF, ejection fraction; LA, left atrial; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; MEWS, Modified Early Warning Score; PAT, pulmonic acceleration time; RA, right atrium; RV, right ventricular; RVEDA, right ventricular end-diastolic area; RVESA, right ventricular end-systolic area; RVFAC, right ventricular fractional area change; and TAPSE, tricuspid annular plane systolic excursion.
*At the time of baseline echocardiographic evaluation, all patients had dyspnea at rest, stratified to mild disease (oxygen saturation ≥94% at room air; grade 1) in 60, moderate disease (need for noninvasive oxygen; grade 2) in 30, and severe disease (need for mechanical ventilation; grade 3) in 10.
Saturation on ambient air (0.93 [HR, 0.85–1.01]; P=0.03), higher Sequential Organ Failure Assessment score (1.16 [HR, 1.03–1.34]; P=0.02), and higher MEWS (1.17 [HR, 1.06–1.32]; P=0.006). The only baseline echocardiographic parameters significantly associated with clinical deterioration were low LVEF (2.8 [HR, 1.2–8.0]; P=0.02 for 10% difference) and shorter AT (2.8 [HR, 1.03–8.6]; P=0.03 for AT<100 milliseconds; Figure 2A). The only baseline echocardiographic parameters significantly associated with mortality were low LVEF (3.1 [HR, 1.02–8.2]; P=0.03 for 10% difference), elevated E/e' ratio (1.09 [HR, 1.02–1.3]; P=0.02), increased RV end diastolic area (1.15 [HR, 1.02–1.33]; P=0.04 for 1 cm2), and higher Tei index (1.30 [HR, 1.03–1.8]; P=0.02)

Sequential Echocardiogram during Clinical Deterioration
In 20 patients, sequential echocardiograms were performed because of clinical deterioration (hemodynamic instability, n=2; cardiac deterioration, n=2; respiratory deterioration, n=16). The time to deterioration was 2 to 13 days (median, 3.5 days). The only parameters that changed significantly were RV-related parameters that worsened significantly in patients once they clinically deteriorated. This included shortening of AT (96±21 milliseconds versus 73±16 milliseconds; P=0.0001), increase in RV end- diastolic area (21.7±9 cm2 versus 24.9±5 cm2; P=0.003), and increase in RV end-systolic area (12.9±6 cm2 versus 15.9±9 cm2; P=0.01, baseline versus follow-up for all). LV- related parameters did not change significantly, with only a trend for decrease in LVEF (58.5±4% versus 56.3±9%) and no consistent change in E/e'. In patients with clinical deterioration, we found several different

echocardiographic patterns. Only 5 patients (patients 8, 13, 16, 18, and 19) showed deterioration in LVEF below normal that was associated with an elevation in troponin levels, suggestive of acute LV dysfunction. An example is shown in Movie I in the Data Supplement. The most common echo- cardiographic pattern (12 of 20, 60%) among deteriorating patients was RV dilatation and dysfunction (combined with LV systolic dysfunction in patients 13 and 18) associated with shortened AT, suggesting elevated pulmonary vascular resistance (in patients 1– 4, 9, 11, 13, 14, 16–18,and 20). In 5 of the latter group (patients 1, 9, 11, 16, and 17), a deep vein thrombus was observed in the femoral or popliteal vein after 5 to 16 days (median, 8 days). An example is shown in Movie II in the Data Supplement. In 7 of them, troponin levels increased from baseline (patients 4, 9, 13, 14, 16, 17, and 20). Of note, there were no significant differences in the levels of D-dimer, CRP, any other laboratory measure, or lung ultrasound score between patients with and those without RV dysfunction (P>0.3 for all parameters).The only difference between the patients with RV dysfunction and other deteriorating patients was a higher Sequential Organ Failure Assessment score (3.1 [2–6] versus 1 [1–4]; P=0.03). The last 4 patients did not change their LV or RV echocardiographic parameters during clinical deterioration.

DISCUSSION

Although several case reports have raised concern about acute cardiac injury related to the infection or cytokine storm resulting in LV systolic dysfunction in patients with COVID-19 infection,[26,27] we found that the LVEF was only slightly lower in our patients, with 10% of patients showing a reduction of LVEF <50% at the baseline evaluation (including 2 who had documented low LVEF in a previous examination). These results suggest that although LV systolic dysfunction occurs in patients with acute COVID-19 infection, it is not very common. Compared with reference values, patients with COVID-19 infection had an increased average E/e′ ratio. However, the majority of patients (80%) did not have clearly elevated LV filling pressure (E/e'≥14).

In contrast to LV parameters, all indexes of RV hemodynamics and function were poorer in patients with COV- ID-19 infection, especially with elevated troponin, worsening disease grade, or clinical deterioration. The most common abnormal echocardiographic pattern among deteriorating patients (10 of 20, 50%) was RV dilatation and dysfunction associated with shortened AT and normal LV systolic and diastolic function. Many conditions can increase pulmonary vascular resistance or pulmonary pressure in hospitalized patients and precipitate acute RV failure. These conditions include pulmonary embolism (PE) but also hypoxic pulmonary vasoconstriction, decrease in lung volume, excessive positive end-expiratory pressure, pneumonia, hypercarbia, the use of α-agonists, elevated left atrial pressure, or a combination of all these factors. Patients with shorter AT (suggestive of higher pulmonary resistance) were older, had more co morbidities, but, most important, had worse lung disease (based on both chest x-ray and lung ultrasound), lower oxygen saturation, higher LV filling pressure, and higher bio- markers (D-dimer, BNP, troponin-I, and CRP), suggesting that elevated pulmonary vascular resistance in COVID-19 infection is multifactorial and related to parenchymal lung disease, pulmonary vascular disease, and elevated left atrial pressure, all leading to cardiac injury. In 5 of 12 of our patients (42%) with RV dilatation and dysfunction associated with shortened AT, a DVT was observed in the femoral or popliteal vein. We believe that PE is almost certain in these patients.

However, because computed tomography angiography increases the risk of disease transmission during transportation from designated COVID-19 areas and inevitably increases the risk of direct contamination of the computed tomography area, we performed computed tomography angiography in only 2 of the remaining 7 patients in whom the expected information seemed to be critical for clinical management. Computed tomography angiography showed clear evidence of PE in one of these patients as well, providing further support to the notion that PE contributes to worsening of RV function in COVID-19. During acute RV pressure overload, regardless of its cause, RV systolic pressure increases until function begins to decline, resulting in decreased cardiac output and systemic blood pressure, which may result in decrease in coronary perfusion to the RV, troponin leak, and additional reduction in RV contractility? Furthermore, the decrease in the transseptal pressure gradient between the RV and LV may result in septal bowing at the expense of LV volumes, resulting in abnormal orientation of helical myofibrils and a further reduction in cardiac function. This spiral of events may explain, at least in part, the association between echocardiographic parameters of RV dilatation and dysfunction, biomarkers, and early mortality in our cohort.

Troponin Levels and Echocardiography

A recent report suggested that mortality increases with elevation of troponin levels to above the 99th percentile.[25] In that report, the prevalence of heart failure in patients with COVID-19 infection was ≈25%, but this result was based on clinical and laboratory evaluation without cardiac imaging. The 20% prevalence of elevated troponin levels in our cohort was similar to that in previous re- ports.3 However, only 3 patients (3 of 20, 15%) had an abnormal LVEF. On the other hand, 6 patients (30%) had E/e'>14 with normal LVEF. From our data, it appears that, in patients with COVID-19 infection, impaired LV diastolic function is more common than LV systolic dysfunction, similar to the results reported for patients with severe acute respiratory syndrome infection [28] or other severe infections.[29] Nevertheless, <50% of patients had either LV systolic or diastolic dysfunction in the elevated troponin COVID-19 cohort. In contrast, RV hemodynamics and function were poorer in patients with COVID-19 infection with elevated troponin, and the most common echocardiographic pattern (10 of 20, 50%) was RV dysfunction associated with shortened AT and normal LV function, suggesting that the most common mechanism for troponin elevation in COVID-19 patients is acute RV dysfunction caused by parenchymal or vascular lung disease.

Lung Ultrasound

Differentiating cardiogenic pulmonary edema from non- cardiogenic pulmonary edema resulting from acute respiratory distress syndrome or diffuse viral pneumonia can be challenging. Identification of diffuse B lines, hilar congestion, and bilateral pleural effusions, especially if they are large, can be suggestive of cardiogenic pulmonary edema from left-sided heart failure. On the other side, the presence of subpleural consolidations, pleural line abnormalities such as irregularly thickened or fragment- ed pleural line, and nonhomogeneous distribution of B lines are more suggestive of noncardiogenic edema. The current definition of acute respiratory distress syndrome requires respiratory failure not explained by cardiac failure or fluid overload and needs objective assessment by echocardiography to exclude hydrostatic edema. In our study, patients underwent lung

ultrasound by the same cardiologist performing the echocardiographic recording. E/e' ratio <15 was found in 80% of patients, and hilar congestion (9%) and pleural effusion (17%) were rare, suggesting that the most common reason for the bilateral B-line pattern in patients with COVID-19 infection was related to noncardiogenic pulmonary edema caused by the viral infection, not to elevated LV filling pressures.

Echocardiographic Findings after Clinical Deterioration

In the 20 patients who had repeat, clinically indicated echocardiography, the only parameters that changed significantly were those associated with RV dysfunction. Twenty-five percent showed deterioration in LV systolic function, but the most common echocardiographic pat- tern was RV dysfunction with or without imaging evidence for peripheral venous thrombosis. Of note, all 5 patients with evidence for DVT developed the identified thrombus despite preventive doses of low-molecular-weight heparin. This finding is in agreement with recent reports suggesting that COVID-19 is associated with high venous thromboembolism rates, elevated D-dimer and fibrinogen levels, and pathological evidence for microvascular lung thrombosis and occlusion.[30] Furthermore, in several small reports, anticoagulant treatment or tissue plasminogen activator treatment was associated with improved outcome in patients with severe COVID-19 infection.[30,31]The high rate of RV dysfunction with or without DVT in our cohort suggests that venous thromboembolism rates or local microvascular lung thrombosis and occlusion may be very common in hospitalized patients with COVID-19 infection, despite routine use of preventive doses of low- molecular-weight heparin. Whether echocardiography- directed use of higher doses of anticoagulation in these patients will reduce the rates of RV dysfunction and improve prognosis needs larger prospective studies.

Conclusions

The most frequent abnormality was RV dilation with or without dysfunction, possibly related to pulmonary parenchymal or vascular disease. During hospitalization, 20% of patients experienced clinical deterioration, and in these patients, a second echocardiogram showed further deterioration of RV parameters, probably related to increased pulmonary pressures, with or without DVT.

References

1. Zhou, P. et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 579, 270–273 (2020).
2. Wu, F. et al. A new coronavirus associated with human respiratory disease in China. Nature 579, 265–269 (2020).
3. Lu, R. et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 395, 565–574 (2020).
4. Hoffmann, M. et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 181, 271–280 (2020).
5. Tay, M. Z., Poh, C. M., Renia, L., MacAry, P. A.& Ng, L. F. P. The trinity of COVID-19: immunity, inflammation and intervention. Nat. Rev. Immunol. 20, 363–374 (2020).
6. Bikdeli, B. et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. J. Am. Coll. Cardiol. 75, 2950–2973 (2020).

7. Connors, J. M. & Levy, J. H. Thromboinflammation and the hypercoagulability of COVID-19. J. Thromb. Haemost. 18, 1559–1561 (2020).
8. Andersen, K. G., Rambaut, A., Lipkin, W. I., Holmes, E. C. & Garry, R. F. The proximal origin of SARS-CoV-2. Nat. Med. 26, 450–452 (2020).
9. Wrapp, D. et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 367, 1260–1263 (2020).
10. Walls, A. C. et al. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell 181, 281–292 (2020).
11. Wan, Y., Shang, J., Graham, R., Baric, R. S. & Li, F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus.J. Virol. 94, e00127-20 (2020).
12. Madjid, M., Safavi-Naeini, P., Solomon, S. D. & Vardeny, O. Potential effects of coronaviruses on the cardiovascular system: a review. JAMA Cardiol. https://doi.org/10.1001/jamacardio.2020.1286(2020).
13. Clerkin, K. J. et al. COVID-19 and cardiovascular disease. Circulation 141, 1648–1655 (2020).
14. Driggin, E. et al. Cardiovascular considerations for patients, health care workers, and health systems during the COVID-19 pandemic. J. Am. Coll. Cardiol. 75, 2352–2371 (2020).
15. Zheng, Y. Y., Ma, Y. T., Zhang, J. Y. & Xie, X. COVID-19 and the cardiovascular system. Nat. Rev. Cardiol. 17, 259–260 (2020).
16. Han, Y. et al. CSC expert consensus on principles of clinical management of patients with severe emergent cardiovascular diseases during the COVID-19 epidemic. Circulation 141, e810–e816 (2020).
17. Lambden S, Laterre PF, Levy MM, Francois B. The SOFA score: develop- ment, utility and challenges of accurate assessment in clinical trials. Crit Care. 2019;23:374. doi: 10.1186/s13054-019-2663-7
18. Liao X, Wang B, Kang Y. Novel coronavirus infection during the 2019- 2020 epidemic: preparing intensive care units–the experience in Si- chuan Province, China. Intensive Care Med. 2020;46:357–360. doi: 10.1007/s00134-020-05954-2
19. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, et al. Recommen- dations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the Eu- ropean Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28:1–39.e14. doi: 10.1016/j.echo.2014.10.003
20. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocar- diography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016;29:277–314. doi: 10.1016/j.echo.2016.01.011
21. Kitabatake A, Inoue M, Asao M, Masuyama T, Tanouchi J, Morita T, Mishima M, Uematsu M, Shimazu T, Hori M, et al. Noninvasive evaluation of pulmonary hypertension by a pulsed Doppler technique. Circulation. 1983;68:302–309. doi: 10.1161/01.cir.68.2.302

22. Kirkpatrick JN, Mitchell C, Taub C, Kort S, Hung J, Swaminathan M. ASE statement on protection of patients and echocardiography service provid- ers during the 2019 novel coronavirus outbreak [published online April 6, 2020]. J Am Coll Cardiol. doi: 10.1016/j.jacc.2020.04.002

23. Topilsky Y, Khanna AD, Oh JK, Nishimura RA, Enriquez-Sarano M, Jeon YB, Sundt TM, Schaff HV, Park SJ. Preoperative factors associated with adverse outcome after tricuspid valve replacement. Circulation. 2011;123:1929– 1939. doi: 10.1161/CIRCULATIONAHA.110.991018

24. Bouhemad B, Mongodi S, Via G, Rouquette I. Ultrasound for "lung moni- toring" of ventilated patients. Anesthesiology. 2015;122:437–447. doi: 10.1097/ALN.0000000000000558

25. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, Wang H, Wan J, Wang X, Lu Z. Cardiovascular implications of fatal outcomes of patients with coro- navirus disease 2019 (COVID-19) [published online March 27, 2020]. JAMA Cardiol. doi:10.1001/jamacardio.2020.1017

26. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin [published online March 16, 2020]. Eur Heart J. doi: 10.1093/eurheartj/ehaa190

27. Zeng JH, Liu YX, Yuan J, Wang FX, Wu WB, Li JX, Wang LF, Gao H, Wang Y, Dong CF, et al. First case of COVID-19 complicated with fulmi- nant myocarditis: a case report and insights [published online April 10, 2020]. Infection. doi: 10.1007/s15010-020-01424-5

28. Li SS, Cheng CW, Fu CL, Chan YH, Lee MP, Chan JW, Yiu SF. Left ven- tricular performance in patients with severe acute respiratory syndrome: a 30-day echocardiographic follow-up study. Circulation. 2003;108:1798– 1803. doi: 10.1161/01.CIR.0000094737.21775.32

29. Landesberg G, Gilon D, Meroz Y, Georgieva M, Levin PD, Goodman S, Avidan A, Beeri R, Weissman C, Jaffe AS, et al. Diastolic dysfunction and mortality in severe sepsis and septic shock. Eur Heart J. 2012;33:895–903. doi: 10.1093/eurheartj/ehr351

30. Wang J, Hajizadeh N, Moore EE, McIntyre RC, Moore PK, Veress LA, Yaffe MB, Moore HB, Barrett CD. Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): a case series [published online April 8, 2020]. J Thromb Haemost. doi: 10.1111/jth.14828

31. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy [published online May 18, 2020]. J Thromb Haemost. doi: 10.1111/jth.14817