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Cardiac Involvement in COVID-19–Related Acute Respiratory Distress Syndrome



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The cardiac involvement in Coronavirus disease (COVID-19) is still under evaluation, especially in severe COVID-19-related Acute Respiratory Distress Syndrome (ARDS). The cardiac involvement was assessed by serial troponin levels and echocardiograms in 28 consecutive patients with COVID-19 ARDS consecutively admitted to our Intensive Care Unit from March 1 to March 31. Twenty-eight COVID-19 patients (aged 61.7 ± 10 years, males 79%). The majority was mechanically ventilated (86%) and 4 patients (14%) required veno-venous extracorporeal membrane oxygenation. As of March 31, the Intensive Care Unit mortality rate was 7%, whereas 7 patients were discharged (25%) with a length of stay of 8.2 ± 5 days. At echocardiographic assessment on admission, acute core pulmonale was detected in 2 patients who required extracorporeal membrane oxygenation support. Increased systolic arterial pressure was detected in all patients. Increased Troponin T levels were detectable in 11 patients (39%) on admission. At linear regression analysis, troponin T showed a direct relationship with C-reactive Protein (R square: 0.082, F: 5.95, $p = 0.017$). In conclusions, in COVID-19-related ARDS, increased in Tn levels was common but not associated with alterations in wall motion kinesis, thus suggesting that troponin T elevation is likely to be multifactorial, mainly linked to disease severity (as inferred by the relation between Tn and C-reactive Protein). The increase in systolic pulmonary arterial pressures observed in all patients may be related to hypoxic vasoconstriction. Further studies are needed to confirm our findings in larger cohorts. © 2020 Elsevier Inc. All rights reserved. (Am J Cardiol 2020;132:147–149)

Coronavirus -19 disease (COVID-19) is an emerging worldwide pandemic, whose clinical course, in up to 15% of infected patients, can evolve in a severe form of acute respiratory syndrome (ARDS) requiring mechanical ventilation and admission to Intensive Care Unit (ICU). A meta-analysis,¹ including 341 patients 36% with severe disease^{2–5} reported that troponin (Tn) I were increased in patients with severe SARS-CoV-2 infection compared with those with milder disease. The clinical and/or prognostic role of increased Tn is still under evaluation, especially in severe COVID-19-related ARDS. We describe our initial experience as of March 31 with 28 consecutive patients with COVID-19-related ARDS admitted to our ICU. We specifically investigated the cardiac involvement by COVID-19 infection, by assessing serial troponin T levels and serial echocardiograms during ICU.

Methods

In this case series study we enrolled all patients with COVID-19 ARDS consecutively admitted to our ICU (which is an ECMO referral center) from March 1 to March 31. The study protocol was approved by our Ethical Committee (n.17024, approved on March 31, 2020). ARDS was defined according to the Berlin definition.⁶

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On ICU admission we measured: Troponin T (pg/ml), N-terminal-pro Brain Natriuretic Peptide (NT-BNP, pg/ml), C-reactive Protein (CRP, mg/dl) creatinine (mg/dl), Lactose dehydrogenase (LDH, UI/L), alanine transaminase (ALT, UI/L), D-dimer (ng/ml), procalcitonin (PCT, ng/ml), and interleukin 6 (IL-6, pg/ml). Troponin T and cardiopulmonary resuscitation were measured every day and peak levels were recorded.

According to our standard protocol, an echocardiogram was performed on ICU admission and, afterwards on clinical judgment, as previously described.⁷ The right ventricle size was assessed by the RV end-diastolic area (EDA) and the ratio between EDAs of the right and left ventricles was calculated. Systolic pulmonary artery pressure was obtained using the simplified Bernoulli's equation: $4 \cdot (V_{\max} \text{ tricuspid regurgitation})^2 + \text{central venous pressure}$. Each measure was performed 3 times, and the mean value was recorded. Tricuspid Annular Plane Excursion was also measured, as the difference of displacement during diastole and systole.

Echocardiogram was repeated at least once a week, in case of increased Tn levels, on clinical judgment (i.e., Onset of atrial fibrillation, need of increased dose of vasoactive drugs) and at discharge. The echocardiographic examination was blinded to the troponin T results. Myocarditis was defined according to American Heart Association.⁸

Electrocardiogram (ECG) testings' were performed simultaneously to the echocardiograms on ICU admission ECG was repeated whenever increased Tn I values were detected.

Data have been stored in a dedicated data-base and analyzed with SPSS for Windows 20.0 (SPSS Inc., Chicago, IL). p value less than 0.05 was considered statistically

significant. Categorical variables are reported as frequencies and percentages; continuous variables are reported as mean \pm standard deviation or median (range), as needed. Pearson's linear regression analysis was used to detect correlations between both troponin T levels and CRP. Between group's comparisons are performed by means of chi-square (categorical data) or, for continuous data, with with Student's *t* test.

Results

Our population included 28 consecutive COVID-19 patients, admitted to ICU, mainly males (22/28, 79%). The main age was 61.7 ± 10 years and more than a half showed a Body mass index ≥ 28 . Hypertension was the commonest risk factor (89%), whereas diabetes was detected in 39%. Previously known ischemic heart disease was present in about one third of the entire population (28.6%). The majority of our patients were mechanically ventilated (86%) and 4 patients (14%) required veno-venous extracorporeal membrane oxygenation (ECMO).

As of March 31, the ICU mortality rate was 7%, whereas 7 patients were discharged (25%) with a length of stay of 8.2 ± 5 days. Troponin T levels upper the 99th percentile (28 ng/ml) were detectable in 11 patients (39%), on ICU admission. At

Table 1
Clinical characteristics (n.28)

Variable	
Age (mean \pm SD) (years)	61.7 \pm 10
Men	22 (79%)
BMI (mean \pm SD) (kg/m ²)	28.4 \pm 5
BMI ≥ 28	17 (60.7%)
Risk factors	
Smoker	21 (75%)
Hypertension	25 (89%)
Diabetes mellitus	11 (39%)
Ischemic heart disease	8 (28.6%)
Chronic renal failure	1 (3.5%)
COPD	2 (7%)
Mechanical ventilation	24 (86%)
Veno-venous ECMO	4 (14%)
ICU death	2 (7%)
Laboratory findings	
Creatinine (mg/dl) (mean \pm SD)	1.08 \pm 0.5
ALT (U/L) (median, range)	28 (9–205)
LDH (U/L) (median, range)	379 (200–1900)
NT pro BNP (pg/ml) (median, range)	390 (56–12800)
Procalcitonin (pg/ml) (median, range)	0.24 (0.06–9)
Interleukin-6 (pg/ml) (median, range)	66 (4–354)
Interleukin – 6 > 40 ng/ml (n.%)	20 (71%)
D-dimer (ng/ml) (median, range)	1571 (513–55758)
Troponin T (median, range)	
Admission	17 (8–180)
Peak	32 (8–253)
C-Reactive protein	
Admission	175 (5–760)
Peak	241 (5–780)

ALT = Alanine transaminase; COPD = chronic obstructive pulmonary disease; ECMO = extra corporeal membrane oxygenation; ICU = intensive care unit; , LDH = Lactose dehydrogenase; NT-BNP = N terminal Brain Natriuretic Peptide; SD = standard deviation.

Table 2
Echocardiographic findings

	On admission	March 31	p
LV dimension (mm/m ²)	27.5 \pm 1.8	27.2 \pm 2	0.557
LV ejection fraction (%)	55 \pm 13	55 \pm 14	0.893
LV segmental abnormalities	6 (21%)	6 (21%)	
RV/LV	0.39 \pm 0.1	0.34 \pm 0.1	0.568
RV wall thickness (mm, mean \pm SD)	5.3 \pm 0.5	5.9 \pm 0.7	0.001
sPAP (mm Hg, mean \pm SD)	51 \pm 6	46 \pm 10	0.038
PE > 5 mm	2 (7%)	28 (100%)	

LV = left ventricle;; PE = pericardial effusion; RV = right ventricle;; sPAP = systolic pulmonary arterial pressure.

linear regression analysis, troponin T showed a direct relationship with CRP (R square: 0.082, F: 5.95, p = 0.017). [Table 1](#)

[Table 2](#) depicts echocardiographic findings on ICU admission and at discharge in 7 patients and as of 31 in the remaining 21 patients.

On ICU admission, a reduced left ventricular ejection fraction (LVEF < 50%) was detected in 6 patients, with previously known ischemic heart disease, in whom 2 patients had posts ischemic dilatated cardiomyopathy with severe reduction of LV systolic function (< 25%) and a cardioverter defibrillator implanted. Six patients exhibited segmental cynamic abnormalities in previously known ischemic heart disease. No other alterations in wall motion kinesis were detectable. Acute cor pulmonale was detected in 2 patients who required ECMO support. Increased systolic arterial pressure was detected in all patients, with values above 45 mm Hg in all cases (range 45–60 mm Hg).

At the echocardiographic evaluation performed at discharged in 7 patients, and as of March 31 in the remaining ones, a significance reduction in systolic pulmonary arterial pressure was detectable in all patients. In discharged patients, only 2 patients had systolic pulmonary arterial pressures above 45 mm Hg (48 and 52 mm Hg, respectively) In the 4 patients on VV ECMO support, pulmonary arterial pressures cannot be measured for technical reasons. All patients developed pericardial effusion with no hemodynamical significance.

On ICU admission 2 patients showed chronic atrial fibrillation. In the remaining 26 patients, 11 patients (11/26, 42%) showed episodes of paroxysmal atrial fibrillation, all cardioverted by amiodarone infusion.

Discussion

In our investigation, performed in 28 consecutive COVID-19 patients with ARDS requiring ICU admission, cardiac involvement was assessed by means of serial troponin T assessment, echocardiographic examinations and monitoring of arrhythmic events. The main findings of our study are as follows: (1) increased Tn levels, although common, was not associated with echo wall motion abnormalities; (2) a significant direct relationship was detectable between Tn and C-reactive protein. (3) Systolic pulmonary arterial pressures were increased in all patients on ICU admission but significantly decreased during ICU stay.

In 187 COVID-19 positive patients with mild disease,⁹ elevation of Tn was observed in about one third (27.8%) but echocardiographic assessment was not performed. In 112 COVID-19 patients, retrospectively evaluated, Deng et al¹⁰ observed that most patients had normal troponin T levels on admission, which increased during hospitalization in about one third (37.5%). Typical signs of myocarditis were not detectable on serial echocardiograms and ECGs. Unlike our investigation, the study population assessed by Deng et al¹⁰ included patients with less severe COVID-19 disease since only 26 patients (23.2%) were admitted to ICU.

We confirm this finding in a subset of severe COVID-19 ARDS, mostly requiring mechanical ventilation. Differently from previous studies, in presence of an increase in Tn levels, we simultaneously assesses LV wall motion by echocardiogram and we did not observe any new onset segmental wall motion abnormalities. The hypothesis of viral myocarditis and/or myocardial infarction as possible causes for increased Tn I levels may be ruled out by our findings which are in agreement with the recent report by the American College of Cardiology on the role of biomarkers in patients with COVID-19. In patients with COVID-19 infection, troponin T elevation is likely to be multifactorial, linked to disease severity and less likely due to coronary thrombotic occlusion.^{11,12} Indeed, in our series, Tn showed a positive direct relationship with CRP values, a marker of inflammatory activation in COVID-19 disease. Furthermore, Tn increase was observed. Further studies should be performed in severe COVID-19 patients to assess whether Tn values could help to risk stratification, as previously reported in patients with mild COVID-19 disease.¹³

We did observe that systolic arterial hypertension is a common finding in severe COVID-19 ARDS. This may be related to the hypoxic vasoconstriction in compliant lungs,¹⁴ factors which seems to characterize COVID-19-related ARDS, although mechanical ventilation itself might represent also a contributing factor (by increasing RV afterload). Deng et al¹⁰ reported a lower incidence of pulmonary hypertension (13%) probably because their series was constituted mainly by patients with milder COVID-19 disease.

Furthermore, we observed a reduction in systolic pulmonary arterial pressure during ICU stay, which might be related to ventilatory strategies (protective mechanical ventilation and pronation). Further studies are needed to specifically assess the effects of strategies/therapies (pronation and/or inhaled nitric oxide) on pulmonary circulation in severe COVID-19 disease in a larger cohort of patients.

The small number of patients in a single center investigation may be a limitation, but our population is homogeneous, including severe COVID-19 ARDS requiring ICU. The strength of our study is the multimodal approach in assessing the cardiac involvement in severe COVID-19 disease.¹⁵

Author contributions

Conceptualization; CL, AP. Data curation; Formal analysis; SB, GEF. Investigation; Methodology; SB, CG. Roles/Writing - original draft; CL MB. Writing - review & editing CL, MB, AP.

Disclosures

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this report.

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