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.

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Original Research

Persistent Right Ventricle Dilatation in SARS-CoV-2–Related Acute Respiratory Distress Syndrome on Extracorporeal Membrane Oxygenation Support

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Objectives: Venovenous extracorporeal membrane oxygenation (ECMO) support may be considered in experienced centers for patients with acute respiratory distress syndrome (ARDS) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection refractory to conventional treatment. In ECMO patients, echocardiography has emerged as a clinical tool for implantation and clinical management; but to date, little data are available on COVID-related ARDS patients requiring ECMO. The authors assessed the incidence of right ventricular dilatation and dysfunction (RvDys) in patients with COVID-related ARDS requiring ECMO.

Design: Single-center investigation.

Setting: Intensive care unit (ICU).

Participants: A total of 35 patients with COVID-related ARDS requiring ECMO, consecutively admitted to the ICU (March 1, 2020, to February 28, 2021).

Interventions: Serial echocardiographic examinations. RvDys was defined as RV end-diastolic area/LV end-diastolic area >0.6 and tricuspid annular plane excursion <15 mm.

Measurements and Main Results: The incidence of RvDys was 15/35 (42%). RvDys patients underwent ECMO support after a longer period of mechanical ventilation ($p = 0.006$) and exhibited a higher mortality rate ($p = 0.024$) than those without RvDys. In nonsurvivors, RvDys was observed in all patients (n = nine) who died with unfavorable progression of COVID-related ARDS. In survivors, weaned from ECMO, a significant reduction in systolic pulmonary arterial pressures was detectable.

Conclusions: According to the authors' data, in COVID-related ARDS requiring ECMO support, RvDys is common, associated with increased ICU mortality. Overall, the data underscored the clinical role of echocardiography in COVID-related ARDS supported by venovenous ECMO, because serial echocardiographic assessments (especially focused on RV changes) are able to reflect pulmonary COVID disease severity.

Key Words: right ventricle; echocardiography; extracorporeal membrane oxygenation; SARS-CoV-2 infection; acute respiratory distress syndrome; prognosis

THE CLINICAL COURSE of coronavirus disease 2019 (COVID-19) is known to evolve, in as many as 15% of infected patients, into a severe form of acute respiratory syndrome (ARDS) requiring mechanical ventilation and admission to an intensive care unit (ICU). Treatment for these patients comprises conventional therapies established for ARDS, including lung-protective ventilatory strategies, neuromuscular blockade, and prone positioning.[1,2] For those patients who exhibit progression of respiratory failure despite conventional treatment, venovenous extracorporeal membrane oxygenation (ECMO) support may be considered in experienced centers.[3-10]

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In COVID patients with respiratory failure, right ventricular (RV) dysfunction is a common finding and associated with worse outcome,[11-16] underscoring the clinical role of echocardiography, especially in critically ill COVID patients.

Also, in patients on ECMO support, echocardiography has emerged as a clinical tool for implantation and clinical management. To date, little data are available on echocardiographic findings in COVID-related ARDS patients requiring ECMO.

The authors performed serial echocardiographic examinations in 35 patients with COVID-related ARDS requiring ECMO, consecutively admitted to the ICU (which is an ECMO referral center). The objective was to determine the incidences of RV dilatation and dysfunction (RvDys) before ECMO implantation, after its removal, and at discharge (in survivors) and on the day of death (in nonsurvivors).

Methods

In the authors' case series study, they enrolled all patients with COVID-related ARDS refractory to conventional treatment submitted to VV ECMO and consecutively admitted to the ICU (which is an ECMO referral center, Azienda Ospedaliero-Universitaria Careggi) from March 1, 2020, to February 28, 2021. The study protocol was approved by the ethical committee (n. 17024, approved on March 31, 2020) ("Florence COVID ICU Registry").

The written inform consent for each patient was waived for emerging infectious disease. Patients' relatives were informed every day by phone on the clinical conditions of their kin. The need for ECMO support was communicated by phone to the patients' relatives before implantation.

Upon ICU admission the authors measured troponin (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), D-dimer (ng/mL), and interleukin 6 (IL-6, pg/mL).

According to the authors' protocol,[13,14,17] an echocardiographic examination was performed before and during ECMO implantation, the first 24 hours in the ICU when clinically indicated, and at discharge. Overall, 321 examinations were performed in the series (per each patient; median eight, range five-15). Among these 321 examinations, 56 (53%) were both transesophageal and transthoracic examinations because of ECMO implantation (n = 35), suspicion for endocarditis (n = 7), and after ECMO removal (n = 14). In those patients submitted to pronation, echocardiograms were performed within two hours since returning from the prone to the supine position. The authors analyzed 87 examinations, which were performed before and during ECMO implantation, the first 24 hours (to assess RvDys incidence and whether it is potentially reversible) after ECMO removal, at discharge (in survivors), and on the day of death in nonsurvivors. The authors hypothesized that echocardiographic assessments in these two subgroups (survivors and nonsurvivors) could reflect the complex spectrum of pulmonary disease severity in COVID infection.

All ultrasound cardiac procedures were performed using the necessary protective equipment for professionals. Dedicated machines were used in the COVID ICU and transducers were wrapped in single-use plastic covers.[13,14]

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 (RVEDA/LVEDA). Systolic pulmonary artery pressure (sPAP) was obtained using the simplified Bernouilli's equation: $4 \times (\text{Vmax tricuspid regurgitation})^2$ + central venous pressure (CVP). Each measurement was performed three times, and the mean value was recorded. Tricuspid annular plane excursion (TAPSE) also was measured, as the difference of displacement during diastole and systole, to assess RV function. The E/e1 ratio also was calculated as the ratio between E wave velocity and e′ wave, early diastolic mitral annular velocity. RV dilatation and dysfunction (RvDys) were defined as RVEDA/LVEDA >0.6 and TAPSE <15 mm.

The authors considered VV ECMO in COVID when respiratory failure persisted despite optimum management including controlled ventilation with tidal volume 6 mL/kg, plateau pressure <30 cm H_2O, use of neuromuscular blockers, high positive end-expiratory pressure (PEEP), and repeated prone positioning sessions.[2,6-9] All patients were encouraged to mobilize early.[17] Primary outcome was death in the ICU.

Statistical Analysis

Data have been stored in a dedicated database and analyzed with SPSS for Windows 20.0 (SPSS Inc, Chicago, IL). A p value <0.05 was considered statistically significant. Categorical variables are reported as frequencies and percentages; continuous variables are reported as mean ± standard deviation (SD) or median (range), as needed. Comparisons between the groups were performed using chi-square for categorical data, and Student *t* test and Kruskal-Wallis test for continuous data.

Results

The study population comprised 35 consecutive patients with severe respiratory failure due to COVID infection, refractory to conventional treatment and requiring VV ECMO support. The series included mostly males (80%) and obese patients (body mass index [BMI] >30, 71%). The majority of the patients came from peripheral hospitals (69%). The most common risk factors were hypertension and diabetes mellitus (34% and 31%, respectively). Inhaled nitric oxide was used in eight patients (8/35, 23%) with no improvement in oxygenation.

Table 1 shows the comparison between patients with RvDys before ECMO implantation and those without. In the series, the incidence of RvDys was 15/35 (42%). No differences between these two subgroups were detectable with regard to age, BMI, risk factors, and ventilatory parameters. In this series, continuous renal replacement therapy was needed in 23% of the population (8/35), with no difference between the

Table 1
Study Population

	All n = 35	No RV Dilatation = 20 (58%)	RV Dilatation = 15 (42%)	
Age, mean ± SD	54 ± 11	52 ± 13	57 ± 8	0.199*
Sex, n (%)	28 M (80%)	13 M (65%)	15 M (100%)	
BMI, mean ± SD	34 ± 6	33 ± 5	34 ± 7	0.625*
BMI >30, n (%)	25 (71%)	16 (80%)	9 (69%)	0.359†
Transferred from peripheral hospitals, n (%)	24 (69%)	15 (75%)	9 (69%)	0.563†
Risk factors, n (%)				
Hypertension	12 (34%)	7 (35%)	5 (33%)	
Diabetes	11 (31%)	6 (30%)	5 (33%)	
Previous heart disease	1 (3%)	0	1 (6%)	
Chronic renal failure	1 (3%)	1 (5%)	0	
Vasoactive drugs, n (%)	32 (91%)	20 (100%)	12 (80%)	0.397†
CRRT, n (%)	8 (23%)	2 (10%)	6 (40%)	0.092†
LOS, d, median (range)	24 (4-185)	25.5 (12-185)	20 (4-55)	0.432‡
ICU death, n (%)	18 (51%)	7 (35%)	11 (73%)	0.024†
Ventilatory Parameters				
Time MV to ECMO, d, median (range)	10 (3-19)	8.5 (2-16)	12 (7-19)	0.006‡
Time MV to ECMO >10 d, n (%)	15	5 (25%)	10 (66%)	0.034†
PEEP, median (range)	12 (8-16)	12 (7-15)	11 (8-16)	0.532‡
TV, mL, median (range)	350 (140-420)	348 (140-480)	315 (150-480)	0.777‡
pH, median (range)	7.25 (7.1-7.47)	7.27 (7.15-7.34)	7.25 (7.1-7.39)	0.383‡
P_{CO_2}, mmHg, median (range)	73 (54-103)	72 (51-97)	73 (55-103)	0.611‡
P_{O_2}, mmHg, median (range)	73 (37-117)	69 (35-113)	73 (37-136)	0.473‡
P/F, median (range)	87 (37-155)	69 (50-141)	74 (37-155)	0.478‡
Echocardiographic Data				
LVEF, % (mean ± SD)	60 ± 6	61 ± 5	62 ± 7	0.625*
E/e′, mean ± SD	10 ± 2	9.9 ± 2	13 ± 3	0.001*
sPAP, mmHg, mean ± SD	59 ± 6	58 ± 8	61 ± 6	0.215*

Abbreviations: BMI, body mass index; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; E/e′, E wave/e′ wave, early diastolic mitral annular velocity; ICU, intensive care unit; LOS, length of stay; LVEF, left ventricular ejection fraction; M, male; MV, mechanical ventilation; P/F ratio, P_{aO_2}/F_{IO_2} ratio; PEEP, positive end-expiratory pressure; sPAP, systolic pulmonary arterial pressure; SD, standard deviation; TV, tidal volume.

* Student *t* test.

† Chi-square test.

‡ Kruskal-Wallis test.

two subgroups. Among these eight patients, CRRT already was ongoing at the time of ECMO implantation in the majority of patients (six of eight). Only two patients developed acute renal failure during ECMO support, both in the presence of RvDys. Patients with RvDys underwent ECMO support after a longer period of mechanical ventilation (p = 0.006) and exhibited a higher mortality rate (p = 0.024). With use of echocardiographic assessment, no differences were observed in LVEF and sPAP between the two subgroups (patients with RvDys *v* those without), and patients with RvDys showed higher values of E/e1. In the series, only one patient exhibited LVEF <50%, due to previous chronic heart disease.

The type of cannulation was dual-lumen cannula (right internal jugular vein) in 32 patients (91.4%) and femorofemoral in three patients (8.6%) (who showed thrombosis in the right jugular vein). No complications were observed during ECMO implantation. Twelve patients (34%) were submitted to prone positioning during ECMO support.

As shown in Table 2, patients with RvDys showed significantly higher values of transaminases. No other differences between the two subgroups were detectable in regard to biohumoral factors.

In the 24 hours following ECMO implantation, six patients (6/20, 30%) showed normalization of RV alterations, and all patients survived.

Table 3 shows echocardiographic findings in nonsurvivors on the day of death. All patients still were on ECMO support. In nonsurvivors, RvDys was observed in nine patients (50%) who died with progressive unfavorable evolution of COVID pulmonary disease characterized by bilateral lung consolidations. Higher values of E/e1 were observed in nonsurvivors with RvDys. In the subgroup of nonsurvivors without RvDys, higher values of LVEF were observed. The cause of death in these patients was septic shock.

Table 4 depicts echocardiographic findings in survivors on the day of removal (within four hours after removal) and at discharge. A progressive reduction in systolic pulmonary arterial pressure was observed, associated with a reduction in E/e1.

Discussion

The main findings of the single-center investigations, performed in consecutive patients with COVID-related ARDS

Table 2
Biochemical Data

Median (range)	All n = 35	No RV Dilatation = 20 (58%)	RV Dilatation = 15 (42%)	
CRP, mg/dL	115 (8-416)	143.4 (44-416)	83 (8-337)	0.208*
IL-6, pg/mL	35 (4-315)	42 (7.7-315)	33 (4-271)	0.632*
D-dimer, ng/mL	4,195 (617-55,678)	3,799 (685-55,679)	5,874 (617-49,452)	0.120*
LDH, IU/L	480 (165-665)	271 (175-621)	496 (276-695)	0.403*
Creatinine, mg/dL	0.93 (0.4-3.71)	0.8 (0.4-3.71)	1.91 (0.66-3.5)	0.447*
NT-pro BNP, pg/mL	763 (98-11,4 48)	592 (98-3,225)	1073.5 (315-11,448)	0.112*
Troponin, pg/mL	32 (2-205)	35 (5-189)	26 (13-205)	0.855*
ALT, IU/L	45 (24-76)	28 (19-49.5)	76 (54 -138)	0.048*

Abbreviations: ALT, alanine transferase; CRP, C-reactive protein; IL-6, interleukin-6; LDH, lactose dehydrogenase; NT-pro BNP, N terminal pro brain natriuretic peptide; RV, right ventricle.
* Kruskal-Wallis test

refractory to conventional treatment treated with ECMO support,[2,6-9,18] were as follows: (1) RV dilatation and dysfunction were common findings, being detectable in 42% of the entire population and potentially reversible (about one-third showed normalization of the RV chamber within 24 hours after ECMO start); (2) RvDys was associated with longer mechanical ventilation before ECMO implantation and with a higher ICU mortality rate; (3) in nonsurvivors RvDys was detectable in those who died with progressive refractory COVID-related respiratory failure; and (4) in survivors, weaned from ECMO support, a progressive reduction in sPAP was detectable.

In the authors' series, ICU mortality rate was 51%, a value comparable with previous investigations in ECMO COVID, despite wide ranges due to differences in number consistency, selection criteria, and follow-up duration among previous reports.[8,10] Although the clinical characteristics (age, gender, and comorbidities) of the population were comparable to previous investigations, the series comprised mainly COVID-related ARDS from peripheral centers and it was characterized by the coexistence of other organ dysfunction (as indicated by the incidence of renal replacement therapies).

In the authors' opinion, the novelty of their investigation is represented by the fact that they performed systematic serial echocardiographic examinations in COVID-related ARDS on ECMO support. Although previous investigations[16,19,20] performed echocardiographic assessment in these patients by means of only one examination, the authors took serial echocardiograms in each patient, presenting data at three time points (before and after the start of the VV ECMO and just before death or discharge of the survivors). This may allow a more comprehensive view of RV changes before and during ECMO support.

Before ECMO support, high incidences of RV dilatation and dysfunction were observed in the authors' patients. Right ventricle alterations have been focused in several investigations mainly performed in mild-moderate COVID disease, documenting RV dilatation and dysfunction in about one-third of patients, associated with disease severity, progression, and outcome.[15,16,21]

Several factors may account for RV abnormalities in COVID disease,[13-16] mainly including COVID-related alterations in lung parenchyma, in primis atelectasiae (responsible for increased RV afterload), and the effects of mechanical ventilation (increased intrathoracic pressures). The effects of hypoxemia-induced increase in pulmonary arterial resistance are debated in COVID disease due to the loss of pulmonary hypoxic vasconstriction in these patients. The incidences of RV dilatation and dysfunction were assessed specifically by echocardiography in COVID-related refractory ARDS requiring VV ECMO in a small series of patients[21] in whom, in keeping with the results of the present investigation, RV alterations were reported in a high proportion of enrolled patients (63.3%). However, different from the authors' study, echocardiography was performed only once, in quite a limited number of patients, retrospectively analyzed at different time intervals since ECMO run, since echocardiographic examination was triggered by hemodynamic instability and/or refractory

Table 3
Echocardiographic Findings in Nonsurvivors on the Day of Death

	Nonsurvivors = 18	RvDysn = 9	No RvDysn = 9	
LVEF, %, mean ± SD	56.6 ± 10	49 ± 8	64 ± 6	0.004*
E/e′, mean ± SD	13 ± 3	14 ± 1.4	11 ± 3	0.015*
RV/LV	0.6 ± 0.15	0.76 ± 0.09	0.49 ± 0.07	0.001*
TAPSE, mm	17 ± 6	11 ± 3	22 ± 2	<0.001*
Pericardial effusion <5 mm	18	9	9	

Abbreviations: E/e′, E wave/e′ wave, early diastolic mitral annular velocity; LVEF, left ventricular ejection fraction; RV/LV, right ventricle/left ventricle ratio; RvDys, right ventricular dilatation and dysfunction; SD, standard deviation; TAPSE, tricuspid annular plane systolic excursion.
* Student *t* test.

Table 4
Echocardiographic Findings in Survivors (17 Patients)

	On the Day of ECMO Removal	At Discharge	
LVEF, %, mean ± SD	65 ± 3	65 ± 2	0.907
E/e′, mean ± SD	14 ± 0.06	11 ± 0.05	0.009
RV/LV	0.46 ± 0.1	0.44 ± 0.2	0.453
TAPSE, mm	23 ± 3	22 ± 2	0.776
sPAP	48 ± 3	43 ± 2	0.002

Abbreviations: E/e′, E wave/e′ wave, early diastolic mitral annular velocity; LVEF, left ventricular ejection fraction; RV/LV, right ventricle/left ventricle ratio; SD, standard deviation; sPAP, systolic pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion.

hypoxemia. In refractory ARDS from different etiologies from COVID on ECMO support, the reported incidence of RV dysfunction varied[22] from 18% (8/56)[23] to 32.6% (30/92)[24] and 37% (13/35),[25] so that a comparison with the authors' results is difficult to perform.

In the authors' series, patients with RV dilatation and dysfunction showed a longer period of mechanical ventilation (protective ventilatory strategies in all patients), suggesting a relation between these two factors. Although a causality cannot be affirmed due to the small number of patients, the authors' results were in keeping with the findings of a recent international multicenter registry of COVID-related ARDS patients treated with VV ECMO.[2] Survival of patients treated with ECMO after longer periods of mechanical ventilation was lower than that of patients with early ECMO implantation.[7]

However, no clear indication of the optimal duration of mechanical ventilation before ECMO implantation is so far available for COVID patients. Although ELSO guidelines reported that a period of more than ten days of mechanical ventilation represented a contraindication for ECMO support,[2] a period of seven days was reported as a cutoff by other studies.[2,4,21,26]

RvDys was associated with increased values of transaminases, probably due to hepatic stasis and suggesting systemic venous congestion. However, in RvDys patients, the authors failed to observe a higher incidence of renal replacement therapy, probably because of the high percentage of patients on renal support in the overall population, mostly before ECMO start.

Despite the limited number of patients, the results may suggest that RV alterations may be transient during ECMO support, because six patients (30%) had a normalized RV chamber within 24 hours after the ECMO run and survived. Due to the limited number of patients, further investigations are needed to confirm the results and to assess, by serial echocardiograms, whether adjunctive therapies, in selected patients on ECMO support, may reverse RV alterations.

In nonsurvivors, all still on ECMO support, two different echocardiographic patterns may be identified, despite the limited number of patients. The first one was characterized by RV dysfunction and diastolic dysfunction (as inferred by higher values of E/e1): all these patients died with unfavorable progression of COVID pulmonary disease characterized by bilateral pulmonary consolidations. The second one showed higher values of LVEF and normal RV dimensions and function, and these patients died with septic shock.

In survivors, a progressive reduction in systolic pulmonary pressures was observed after ECMO removal to ICU discharge, survivors showed a progressive reduction in systolic pulmonary pressures. This finding confirmed the ability of echocardiographic examination to follow COVID pulmonary disease progression, in keeping with previous data of the authors' group in patients with COVID-related ARDS.[13]

Among the possible etiologies of persistent RV alterations, the peculiar fibrotic and prothrombotic ARDS phenotype of COVID-19 versus ARDS from other etiologies (in primis H1N1) cannot be ruled out. In the review by Hariri et al,[27] it was reported that pulmonary microthrombi are a peculiar feature of COVID-related ARDS. Although their incidence (57%) was similar to that observed in patients with SARS (58%), this is higher than that observed in ARDS from other etiologies, in primis H1N1 (24%).

The unique phenotype of COVID-related lung injury was confirmed by Margaroli et al,[28] who, by means of a spatial transcriptomic platform on autopsy-derived lung tissue, documented a more fibro-proliferative response of SARS-CoV-2 infection versus H1N1. Overall, due to the distinct fibrotic and prothrombotic ARDS phenotype of COVID-19, pulmonary vasculature largely is affected, being responsible for the increased RV afterload, and, therefore, possibly contributing to RV alterations, especially in severe COVID-related ARDS.

The authors note some limitations. It was a single-center investigation, enrolling a limited number of patients. However, it involved a high-volume ECMO center (even for critically ill COVID patients), because the authors treated 35 COVID patients on ECMO support in an 11-month period who were managed by the same intensive care team. In a recent multicenter trial,[5] 190 COVID patients treated with ECMO were analyzed, enrolled in 35 hospitals during a five-month period (5.4 patients/hospital in the study period). A similar small-case volume at each center also was observable in an international multicenter registry.[2,4] In both multicenter investigations, differences among centers in enrollment criteria and management cannot be ruled out. Another possible limitation was the lack of data on fractional area change and velocity time integral, which were available only in a small percentage of patients, because they proved to be more sensitive for detecting RV dysfunction.[16,21]

Conclusions

In patients on ECMO support for COVID-related ARDS, RvDys is common, associated with longer mechanical ventilation and increased ICU mortality. RvDys is detectable in nonsurvivors who died with unfavorable progression of COVID pulmonary disease, and survivors weaned from ECMO support showed a progressive reduction in pulmonary arterial

pressures. Overall, the data underscored the clinical role of echocardiography in COVID-related ARDS supported by VV ECMO, because serial echocardiographic assessments (especially focused on RV changes) were able to reflect pulmonary COVID disease severity. The authors' data are to be confirmed by the systematic use of echocardiography in larger cohorts of COVID-related refractory ARDS on ECMO support.

Conflict of Interest

None.

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