# Early Reversal of Right Ventricular Dysfunction after Venovenous Extracorporeal Membrane Oxygenation in Patients with COVID-19 Pneumonia

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*To the Editor*:

Right ventricular (RV) dysfunction is a frequent complication of acute respiratory distress syndrome (ARDS). It occurs in 20–25% of cases (1) and in 28–42% of individuals with refractory ARDS requiring venovenous extracorporeal membrane oxygenation (VV-ECMO) (2). RV size and function are highly afterload dependent, and VV-ECMO might alleviate RV dysfunction by decreasing pulmonary artery vasoconstriction (3–5). We aimed to describe the effect of VV-ECMO on hemodynamics and RV function in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–related refractory ARDS. This observational retrospective single-center study included patients with coronavirus disease (COVID-19)–related ARDS having met EOLIA (Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome) criteria (6) and given VV-ECMO, who underwent comprehensive echocardiographic examinations (CX50; Philips) within 6 hours before (echo H−6), 24 hours after (echo H+24), and 3 days after (echo H+72) VV-ECMO initiation (Figure 1). The following parameters were collected: left ventricular ejection fraction, cardiac index, estimated systolic pulmonary arterial pressure (sPAP), tricuspid annular plane systolic excursion (TAPSE), tricuspid annular systolic velocity (S′ wave), RV fractional area change (FAC), and RV free wall longitudinal strain (RVFWLS). RV FAC/sPAP ratio was chosen as a noninvasive surrogate of RV–pulmonary artery coupling (7). Vasoactive inotropic score (VIS) was defined as dobutamine dose (μg/kg/min) + 100 × epinephrine dose (μg/kg/min) + 100 × norepinephrine dose (μg/kg/min). Acute cor pulmonale (ACP) was defined as the presence of paradoxical septal motion and a ratio of RV end-diastolic area to left ventricular end-diastolic area >0.6 (1).

Continuous variables are expressed as median (interquartile range) and were compared using the Wilcoxon test. Categorial variables are expressed as *n* (%) and were compared using the Fisher exact test. In agreement with French law, written informed consent was not needed for this observational study, but patients and/or their relatives were informed of the use of their data. The study was approved by the ethics committee of Société de Réanimation de Langue Française (CE-SRLF-21-39).

Between April 2020 and April 2021, 151 patients with ARDS and COVID-19 who received VV-ECMO were treated at our center, of whom 15 who underwent implantation in our unit and had both pre- and post-ECMO echocardiographic examinations were included (40% women; median age, 54 [46–62] years) (Table 1). None had a cardiopulmonary medical history, body mass index was 33 (26–38) kg/m$^2$, and pre-ECMO Simplified Acute Physiology Score II was 46 (30–55). The time from mechanical ventilation to VV-ECMO initiation was 6 (4–11) days, and the pre-ECMO $Pa_{O_2}/FI_{O_2}$ ratio was 60 (56–72) mm Hg. All patients had received neuromuscular blockade and prone positioning before VV-ECMO, and eight (53%) had received inhaled nitric oxide. Norepinephrine was given to eight (53%) patients, and the median VIS was 6 (0–30) μg/kg/min at baseline. Echo H−6 revealed ACP in seven patients (47%), with elevated sPAP, slightly reduced RV FAC and RVFWLS, and normal TAPSE and S′ wave (Table 1).

After VV-ECMO initiation, $Pa_{O_2}/FI_{O_2}$ ratio increased to 250 (150–326) mm Hg, $P_{CO_2}$ decreased to 44 (39–47) mm Hg, and ACP risk score decreased from 3 (3–4) to 1 (1–1). sPAP decreased between echo H−6 and echo H+24 ($P = 0.03$), while RV FAC ($P = 0.001$), RVFWLS ($P = 0.007$), and RV FAC/sPAP ratio ($P = 0.03$) improved (Table 1). All instances of ACP reversed between echo H−6 and echo H+24 ($P = 0.03$), with a significant decrease in VIS ($P = 0.03$). RV dimensions decreased between echo H−6 and echo H+24 ($P = 0.001$). Median VV-ECMO duration was 20 (16–39) days, and six (40%) patients were alive at 90 days.

We herein report a thorough description of RV dysfunction evolution after VV-ECMO initiation in patients with refractory ARDS.

The main finding of our study was a rapid improvement of RV function within 24 hours of VV-ECMO initiation, reversal of all episodes of ACP, and a concomitant decrease in VIS, suggesting that ACP-induced circulatory failure may be alleviated by VV-ECMO. This comprehensive description of RV function evolution brings complementary information to previous studies highlighting the effects of VV-ECMO on pulmonary artery vasoconstriction (3) and the prognostic value of RV failure in patients with ARDS meeting the EOLIA criteria (8) or on VV-ECMO (5).

RV dysfunction resolution may be explained by VV-ECMO–related correction of hypoxic and hypercapnic vasoconstriction associated with a reduction of positive intrathoracic pressure by ultraprotective mechanical ventilation. Altogether, these may reduce RV afterload and improve the coupling of RV contractility to pulmonary arterial pressure, which determines RV size and function.

In practice, this potential for rapid reversal of RV dysfunction should be taken into account when discussing extracorporeal membrane oxygenation (ECMO) indication and configuration and venovenous versus venoarterial ECMO in a patient with severe ARDS-induced circulatory failure and may contribute to explaining the low rate of venovenous to venoarterial or venovenoarterial conversion in this setting (9).



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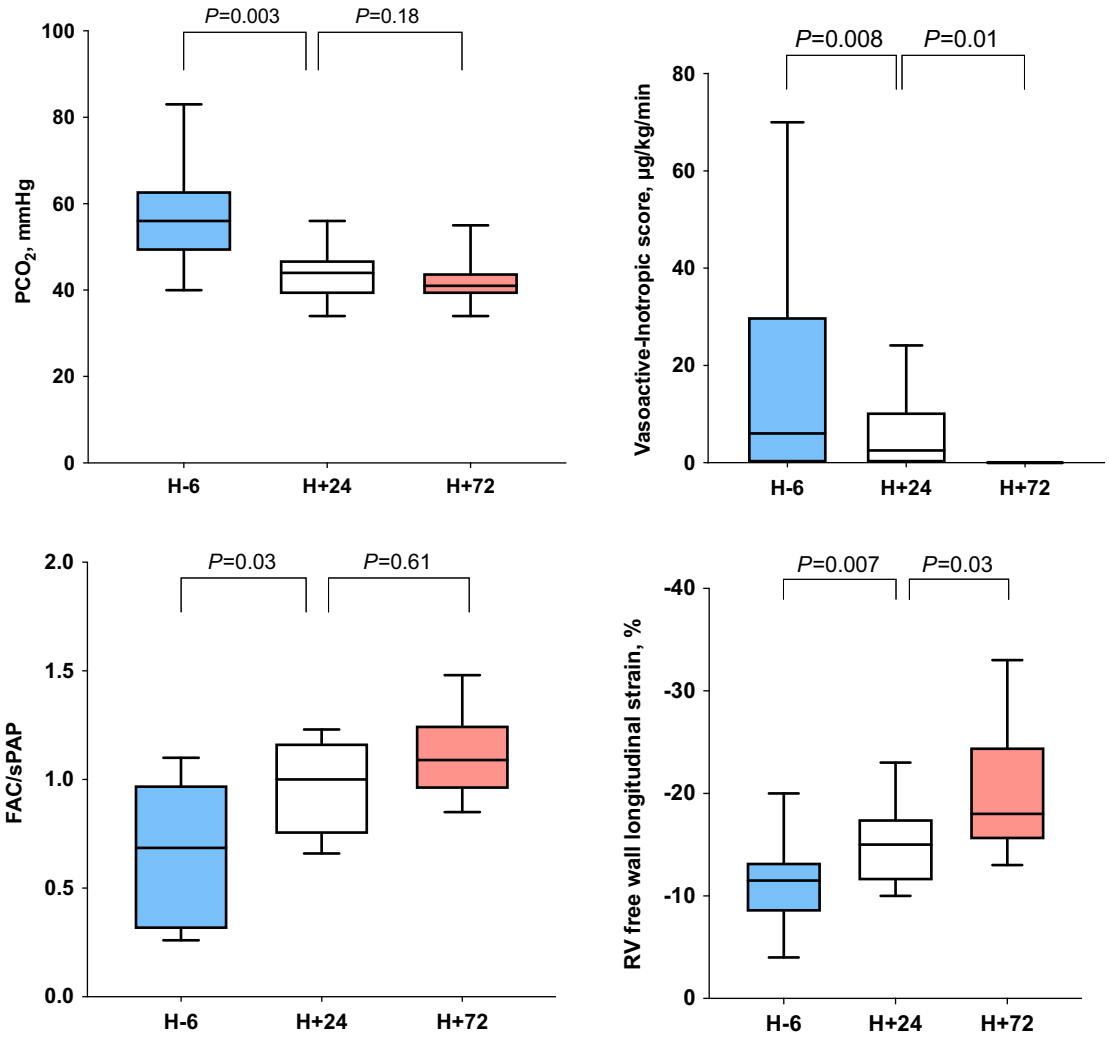


**Figure 1.** Clinical and echocardiographic parameters before and after VV-ECMO initiation. FAC = right ventricular fractional area change; H−6 = clinical and echocardiographic data within 6 hours before VV-ECMO initiation; H+24 = clinical and echocardiographic data at 24 hours after VV-ECMO initiation; H+72 = clinical and echocardiographic data 3 days after VV-ECMO initiation; RV = right ventricular; sPAP = systolic pulmonary arterial pressure; VV-ECMO = venovenous extracorporeal membrane oxygenation.

However, it should be noted that rapid correction of hypercapnia is associated with intracranial bleeding and should be avoided after ECMO initiation (10).

Our study has some limitations. First, the study's external validity is limited by its single-center and observational nature. The sample size also limited our ability to evaluate the prognostic value of the evolution of these RV systolic function parameters. Second, we included only patients with COVID-19–related ARDS. Even though the prevalence of ACP in COVID-19–related ARDS was reported to be similar to that with other etiologies of ARDS (1), SARS-CoV-2 infection may cause specific microvascular involvement, and we cannot extend our results to patients without COVID-19.

Third, we did not perform invasive measurement of hemodynamic parameters, because it is not part of our usual management of patients with ARDS, and pulmonary arterial catheter insertion is complex with the ECMO right jugular cannula. Fourth, because of the complex three-dimensional RV shape and limited echocardiographic window due to its position, RV echocardiographic measurements, including RV strain parameters, are sensitive to small variations of echocardiographic windows and subject to inter- and intraobserver variability.

Fifth, we observed improvements in RV FAC and RVFWLS, whereas S′ wave and TAPSE remained unchanged. These discordances could be explained by high heterogeneity in local RVFWLS with preserved basal and severely depressed apical contraction. In addition, RV longitudinal strain is not dependent on angulation and may be more sensitive to subtle changes in myocardial function than conventional parameters to assess RV function.

Last, other factors, such as the frequent use of inhaled nitric oxide before VV-ECMO, fluid resuscitation, and need for vasopressors, could also interfere with the evolution of hemodynamic and RV function parameters.

In conclusion, in COVID-19–related refractory ARDS, VV-ECMO initiation was associated with a rapid decrease in pulmonary arterial pressure, alleviation of RV dysfunction, and resolution of ACP-induced circulatory failure. ■

**Table 1.** Respiratory, Right Ventricular, and Hemodynamic Parameters before and after Venovenous Extracorporeal Membrane Oxygenation Initiation

| Variable | Echo H−6 | Echo H+24 | Echo H+72 | *P* Value* | *P* Value† |
|---|---|---|---|---|---|
| Acute cor pulmonale | 7 (47) | 0 | 0 | 0.03 | 1 |
| Acute cor pulmonale risk score‡ | 3 [3 to 4] | 1 [1 to 1] | 1 [1 to 1] | 0.001 | 1 |
| $V_T$, ml/kg PBW | 6 [5.9 to 6.4] | 2.8 [1.4 to 3.9] | 2.7 [1.9 to 3.6] | 0.001 | 0.8 |
| Respiratory rate, breaths/min | 30 [28 to 32] | 20 [20 to 20] | 20 [20 to 20] | 0.001 | 1 |
| PEEP, cm $H_2O$ | 12 [10 to 14] | 14 [12 to 16] | 14 [12 to 17] | 0.03 | 0.5 |
| Plateau pressure, cm $H_2O$ | 30 [26 to 33] | 28 [24 to 29] | 27 [26 to 29] | 0.007 | 1 |
| Driving pressure, cm $H_2O$ | 18 [14 to 22] | 14 [12 to 14] | 14 [12 to 14] | 0.003 | 0.2 |
| Static compliance, ml/cm $H_2O$ | 19 [16 to 29] | 13 [6 to 20] | 14 [10 to 17] | 0.001 | 0.8 |
| pH | 7.32 [7.28 to 7.36] | 7.41 [7.34 to 7.48] | 7.44 [7.38 to 7.48] | 0.003 | 0.5 |
| $Pa_{O_2}/F_{I_{O_2}}$ ratio, mm Hg | 60 [56 to 72] | 250 [150 to 326] | 240 [135 to 333] | 0.001 | 0.9 |
| $P_{CO_2}$, mm Hg | 56 [49 to 63] | 44 [39 to 47] | 41 [39 to 44] | 0.003 | 0.2 |
| sPAP, mm Hg | 47 [40 to 55] | 40 [36 to 40] | 37 [34 to 45] | 0.03 | 0.9 |
| TRV, m/s | 3.1 [2.7 to 3.3] | 2.7 [2.5 to 2.8] | 2.9 [2.6 to 2.9] | 0.03 | 0.8 |
| PVR, WU | 2.2 [1.9 to 2.5] | 1.7 [1.6 to 2.0] | 1.9 [1.8 to 1.9] | 0.07 | 0.28 |
| RV FAC, % | 34 [20 to 42] | 42 [35 to 45] | 42 [40 to 46] | 0.001 | 0.1 |
| RVFWLS, three-segment average, % | −11 [−13 to −8] | −15 [−16 to −11] | −18 [−24 to −15] | 0.007 | 0.03 |
| RVFWLS, apical segment, % | −8 [−10 to −5] | −12 [−13 to −8] | −16 [−22 to −12] | 0.006 | 0.02 |
| RVFWLS, medial segment, % | −10 [−12 to −6] | −13 [−14 to −8] | −16 [−21 to −13] | 0.007 | 0.03 |
| RVFWLS, basal segment, % | −18 [−22 to −15] | −22 [−25 to −19] | −25 [−27 to −23] | 0.005 | 0.02 |
| Tricuspid annular diameter, mm | 36 [33 to 37] | 32 [28 to 36] | 33 [30 to 36] | 0.001 | 0.92 |
| S′ wave, cm/s | 17 [13 to 20] | 15 [12 to 20] | 14 [11 to 26] | 0.8 | 0.2 |
| TAPSE, mm | 21 [19 to 27] | 21 [17 to 26.5] | 23 [19 to 25] | 0.2 | 0.5 |
| RV FAC/sPAP ratio§ | 0.68 [0.31 to 0.97] | 1 [0.74 to 1.2] | 1.1 [0.96 to 1.3] | 0.03 | 0.6 |
| LVEF, % | 60 [57 to 67] | 59 [54 to 61] | 60 [55 to 61] | 0.18 | 0.61 |
| Cardiac index, L/min/$m^2$ | 3.3 [3.0 to 4.2] | 3.1 [2.9 to 3.9] | 3.2 [2.6 to 4.2] | 0.3 | 0.4 |
| Lactate, mmol/L | 2 [1.6 to 2] | 1.7 [1.5 to 2.3] | 1.6 [1 to 1.7] | 0.3 | 0.03 |
| Vasoactive inotropic score, μg/kg/min | 6 [0 to 30] | 2.5 [0 to 10.4] | 0 | 0.008 | 0.012 |
| Renal replacement therapy | 1 (7) | 2 (13) | 3 (20) | 0.33 | 0.33 |
| Creatinine concentration, μmol/L | 76 [64 to 169] | 72 [61 to 173] | 75 [63 to 192] | 0.46 | 0.48 |
| Total bilirubin concentration, mmol/L | 8 [6 to 12] | 7 [6 to 11] | 7 [5 to 13] | 0.72 | 0.73 |

*Definition of abbreviations*: FAC = fractional area change; H−6 = clinical and echocardiographic data within 6 hours before VV-ECMO initiation; H+24 = clinical and echocardiographic data at 24 hours after VV-ECMO initiation; H+72 = clinical and echocardiographic data 3 days after VV-ECMO initiation; LVEF = left ventricular ejection fraction; PBW = predicted body weight; PEEP = positive end-expiratory pressure; PVR = echocardiography-estimated pulmonary vascular resistance (11); RV = right ventricular; RVFWLS = right ventricular free wall longitudinal strain; sPAP = systolic pulmonary arterial pressure; S′ wave = tricuspid annular systolic velocity; TAPSE = tricuspid annular plane systolic excursion; TRV = tricuspid regurgitation velocity; VV-ECMO = venovenous extracorporeal membrane oxygenation; WU = Wood units.
Results for continuous variables are presented as median (interquartile range) and were compared using the Wilcoxon rank test. Results for categorical variables are presented as *n* (%) and were compared using the Fisher exact test.
*$P$ value for comparison between echo H−6 and echo H+24.
†$P$ value for comparison between echo H+24 and echo H+72.
‡Acute cor pulmonale risk score is a clinical risk score based on four variables: pneumonia as the cause of acute respiratory distress syndrome, driving pressure, $Pa_{O_2}/F_{I_{O_2}}$ ratio, and $Pa_{CO_2}$.
§Normal values of FAC/sPAP ratio are >0.94 (7).

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## Accuracy of Nasal Pressure Swing to Predict Failure of High-Flow Nasal Oxygen in Patients with Acute Hypoxemic Respiratory Failure

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*To the Editor*:

The risk of deterioration during acute hypoxemic respiratory failure (AHRF) treated by noninvasive respiratory support demands monitoring of the patient's inspiratory effort (1, 2) to avoid delay to mechanical ventilation (MV) (3–5). Despite the fact that respiratory rate (RR) and composite indices such as respiratory rate-oxygenation (ROX) (6) and heart rate, acidosis, consciousness, oxygenation, and respiratory rate (HACOR) (7) might recognize patients at major failure risk, these only indirectly account for the inspiratory effort. Esophageal manometry provides an accurate quantification of effort; however, it is unpractical in real life (8, 9). The nasal pressure swing ($\Delta P_{nose}$) during tidal breathing is highly correlated with the esophageal pressure swing ($\Delta P_{es}$) in patients with AHRF (10). The aim of this *post hoc* analysis of a prospective study (www.clinicaltrials.gov, NCT 03826797) was to assess the accuracy of $\Delta P_{nose}$ in predicting early (24-h) failure of high-flow nasal oxygen (HFNO) to treat AHRF.

Consecutive patients with AHRF who were admitted into the respiratory intensive care unit (RICU) of the University Hospital of Modena in Modena, Italy, between January 1, 2021 and June 30, 2022 and started on HFNO were eligible for enrollment (Optiflow and AIRVO, Fisher and Paykel Healthcare Ltd.). Verbal or written informed consent was obtained as appropriate. An age >18 years, peripheral $Sp_{O_2}$ <90% under conventional oxygen supply by Venturi mask with an inspiratory fraction of 0.5 and consent to receive nasal manometry were criteria for inclusion. The need for immediate intubation, use of noninvasive ventilation (NIV) or MV within the same admission, concomitant hypercapnia, cardiogenic pulmonary edema, chronic obstructive pulmonary disease, chest wall neuromuscular diseases, parenchymal interstitial abnormalities, nasal tract anatomical alterations, and long-term oxygen regimen were criteria for exclusion.

Patients' characteristics were collected on admission into the RICU when all patients started HFNO (Time 1 [T1]). $\Delta P_{nose}$ was measured by attending staff who were blinded to the purpose of the study. In 69 patients (68%) out of the total, $\Delta P_{es}$ recording was simultaneously taken. At T1 and 2 hours after HFNO initiation (Time 2 [T2]), $\Delta P_{nose}$, $\Delta P_{es}$, arterial blood gases, $Pa_{O_2}/Fi_{O_2}$ ratio, RR, HACOR, and ROX were assessed.

The decision to escalate from HFNO either to helmet/facemask NIV or MV (i.e., failure) was taken by the attending physician (8), who was blinded to the results for $\Delta P_{nose}$.

The primary outcome was the accuracy of $\Delta P_{nose}$ in predicting failure of HFNO at T2. The comparison between $\Delta P_{nose}$ and the ROX index in predicting failure and the correlation between $\Delta P_{nose}$ and $\Delta P_{es}$ at different time points were also considered.

Receiver operating characteristic curves and the area under the curve (AUC) were calculated to test accuracy. The optimal cutoff of $\Delta P_{nose}$ was chosen according to Youden's J statistic to maximize the sum of sensitivity and specificity.

The comparison of accuracy between $\Delta P_{nose}$ and the ROX index tailed was assessed using Delong's test. Correlation analysis using Pearson's *r* or Spearman's ρ coefficient, as appropriate, was conducted at different time points.

*Post hoc*, we tested the accuracy and the optimal cutoff of $\Delta P_{nose}$ in predicting escalation to MV and the correlations between $\Delta P_{nose}$, and $\Delta P_{es}$, and the ROX index. A two-sided test