Diagnosis and Treatment of Right Ventricular Dysfunction in Patients with COVID- 19 on Veno-Venous Extra-corporeal Membrane Oxygenation

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Abstract

Background: Veno-venous (VV) extracorporeal membrane oxygenation (ECMO) is an effective, but highly resource intensive salvage treatment option in COVID patients with acute respiratory distress syndrome (ARDS). Right ventricular (RV) dysfunction is a known sequelae of COVID-19 induced ARDS, yet there is a paucity of data on the incidence and determinants of RV dysfunction on VV ECMO. We retrospectively examined the determining factors leading to RV failure and means of early identification of this phenomenon in patients on VV ECMO.

Methods: The data was extracted from March 2020 to March 2021 from the regional University of Washington Extracorporeal Life Support database. The inclusion criteria included patients >18 years of age with diagnosis of COVID-19. All had already been intubated and mechanically ventilated prior to VV ECMO deployment. Univariate analysis was performed to identify risk factors and surrogate markers for RV dysfunction. In addition, we compared outcomes between those with and without RV dysfunction.

Results: Of the 33 patients that met inclusion criteria, 14 (42%) had echocardiographic evidence of RV dysfunction, 3 of whom were placed on right ventricular assist device (RVAD) support. Chronic lung disease was an independent risk factor for RV dysfunction (p=0.0002). RV dysfunction was associated with a six-fold increase in troponin I (0.07 ng/ml vs 0.44 ng/ml, p=0.039) and four-fold increase in brain natriuretic peptide (BNP) (158 pg/ml vs 662 pg/ml, p=0.037). Deep vein thrombosis (DVT, 21% vs 43%, p=0.005) and pulmonary embolism (PE, 11% vs 21%, p=0.045) were found to be nearly twice as common in the RV dysfunction group. Total survival rate to hospital discharge was 39%. Data trended towards shorter duration of hospital stay (47 vs. 65.6 days, p=0.15), shorter duration of ECMO support (21 days vs 36 days, p=0.06) and improved survival rate to hospital discharge (42.1% vs. 35.7%, p=0.47) for those with intact RV function compared to the RV dysfunction group.

Conclusions: RV dysfunction in critically ill patients with COVID-19 pneumonia in common. Trends of troponin I and BNP may be important surrogates for monitoring RV function in patients on VV ECMO. We recommend echocardiographic assessment of the RV on such patients.

Background

The outbreak of COVID-19 shocked many health care systems across the world, taking millions of lives[1–5]. During H1N1 and MERS-CoV outbreaks, Mechanical circulatory support (MCS) had been utilized in severe cases refractory to optimal ventilator therapy and prone positioning with some success[6]. Although MCS has proved to be an effective salvage strategy in the immediate term in severe COVID-19 induced ARDS, the mortality rate has remained very high[6]. COVID-19 proved to have caused not only ARDS and respiratory failure but also right ventricular dilatation and dysfunction[7]. Right ventricular (RV) dilatation has been associated with significantly worse outcome in COVID-19 patients[7]. This phenomenon, likely reflects the increased afterload on the RV from secondary pulmonary hypertension as well as primary cardiomyopathic insult from the viral infection, often rendering VV ECMO strategy *per se*

ineffective due to the resultant low cardiac output and end organ dysfunction. Utilization of right ventricular assist devices (RVAD) with oxygenators can mitigate both respiratory and right heart failure with some reported success[8]. Earlier case series have reported RV dilation to be present in as much as 41% of patients with COVID-19 induced ARDS and 27% of patients had impaired RV function[9] and identified C-reactive protein (CRP) and D-dimer as associated biomarkers of RV dysfunction[9, 10].

In this retrospective study we assessed our outcomes of MCS for COVID-19 patients in a regional high-volume center with a large geographic catchment area encompassing the pacific northwest of the United States. The aim of this study is to assess the efficacy of VV ECMO in supporting patients with severe ARDS associated with COVID-19 with particular attention to surrogate laboratory markers predicting RV dysfunction requiring inotropic and RVAD support. To this effect we trended the end organ dysfunction, ICU length of stay, duration of mechanical circulatory support (if applicable), any complications related to right heart failure, and survival rate to hospital discharge. We also developed an algorithm (Fig. 1) to facilitate early diagnosis of RV dysfunction and the need escalation of support (including placement of RVAD) before end organ dysfunction sets in.

Materials And Methods

All adults, 18 years or older, with COVID-19 infection, confirmed via reverse transcriptase-polymerase chain reaction (RT-PCR) for SARS-CoV-2 virus (i.e. COVID-19) with acute respiratory distress syndrome (ARDS) refractory to intubation and mechanical ventilation, requiring Veno-venous Extracorporeal Membrane Oxygenation (VV ECMO) hospitalized at the University of Washington Medical Center or Harborview Medical center in Seattle, Washington were included in this study. ARDS was identified with the observation of bilateral pulmonary infiltrates on computed tomography (CT) scan. Our patient cohort included patients across the WWAMIO region (Washington, Wyoming, Alaska, Montana, Idaho, and Oregon), covering a population of approximately 11.8 million people according to the U.S Census Bureau and approximately 1/5th of the USA landmass.

Institution Review Board (IRB) approval was obtained from the University of Washington human subjects division research review board. Patients' charts were accessed and reviewed. Information regarding basic demographic background (age, race, gender) as well as body mass index (BMI), comorbidities, and smoking history were gathered. The serial pre-VV ECMO cannulation arterial blood gases (ABG) and ventilator settings were obtained to assess whether the severity of ARDS and higher ventilator settings were correlated with RV dysfunction. Key organ functions were evaluated using surrogate peak biomarkers values for creatinine, aspartate aminotransferase (AST), troponin I, and brain natriuretic peptide (BNP). Transthoracic echocardiography (TTE) data for all patients that had a TTE performed during their hospital course were reviewed. RV dysfunction was defined as tricuspid annular plane systolic excursion (TAPSE) of < 17 mm or right ventricular fractional area change (RV FAC) of < 35% in accordance with the criteria developed by the American Society of Echocardiography[11]. Accordingly, patients were categorized into two groups: no RV dysfunction and RV dysfunction. The patients with no TTE studies were presumed to have no RV dysfunction and were placed in the no RV dysfunction group

accordingly. The criteria for percutaneous right ventricular assist device (RVAD) support were RV dysfunction leading to hemodynamic instability and/or progressive end organ (liver and renal) dysfunction, and available ECMO capacity in the university hospital capable of managing patients with MCS. All RVADs were placed percutaneously in the hybrid suite and using the right internal jugular vein or left subclavian vein approach (Tandem Heart Protek Duo, dual lumen cannula). Additionally, the severity of lung injury was assessed using pre-VV ECMO ventilation settings, PaO2/FiO2 ratio, and ABGs. Hospital course and outcomes were evaluated by comparing rates of complications, survival to discharge, and duration of mechanical and circulatory support.

Statistical analysis

Univariate analysis was performed to identify the prognostic indicators. All data were compared across the two groups by calculating statistical p-values using the chi-squared test for qualitative parameters and the t-test for the quantitative measure. The value of 0.05 or less was deemed statistically significant.

Results

We identified 33 patients that met the aforementioned inclusion criteria, Baseline demographic characteristics, as well as risk factors and comorbidities, are summarized in Table 1. The mean age was 49 ± 9 years. 73% (n = 24) of patients were male. The majority of our patients were non-white (79%, n = 26). This was a significant finding as the WWAMIO region is overwhelmingly populated by white Caucasians, indicating ethnic minorities are more severely affected by COVID-19.

Table 1
Patient related factors and comorbidities and the prevalence of right ventricular dysfunction.

Demographics and PMH	Total, n = 33	No RV Dysfunction, n = 19	RV Dysfunction, n = 14	P value
Mean Age (yrs) +/- STDV	48.7 +/- 9.2	50.4 +/- 7.7	46.5 +/- 10.5	
Mean BMI +/- STDV	30.2 +/- 3.5	30.9 +/- 3.4	29.3 +/- 3.6	
Male	72.7%	73.7%	71.4%	
Non-White	78.8%	73.7%	85.7%	
DM %	36.36%	42.11%	28.60%	0.109
HTN %	33.33%	42.11%	21.43%	0.0104
Smoker %	35.48%	29.41%	42.86%	0.109
Lung Disease (OSA, Asthma, COPD) %	27.27%	15.79%	42.86%	0.0002

Risk Factors For Right Ventricular Dysfunction

RV dysfunction was identified in 42% (n = 14). 24% (n = 8) never had echocardiographic studies. History of lung disease including obstructive sleep apnea, asthma, and COPD were 2.7 times more prevalent in the RV dysfunction group than the no RV dysfunction group (p = 0.00021). Of the RV dysfunction cohort, 3 received percutaneous RVAD support in the form of percutaneous dual lumen cannula through the right internal jugular vein inserted under fluoroscopic guidance.

Troponin and BNP were shown to be 6 times and 4 times higher in the RV dysfunction cohort, whereas AST and creatinine levels were not observed to be statistically different between the two groups (see Table 2).

Table 2
Surrogates for end organ dysfunction.

Surrogates for End Organ Dysfunction	Total, n = 33	No RV Dysfunction, n = 19	RV Dysfunction, n = 14	P Value
Mean Peak AST	539.2	583.2	479.6	0.841
Mean Peak Creatinine	2.3	2.2	2.5	0.710
Mean Peak BNP	**433.3**	**158.5**	**662.3**	**0.037**
Mean Peak Troponin I	**0.24**	**0.07**	**0.44**	**0.039**

Complications

We observed that 69% (n = 23) of our patients developed ventilator-associated pneumonia. Hemorrhagic complications took place in 51% (n = 17), followed by thromboembolic phenomenon in 30% (n = 10) urinary tract infections in 21% (n = 7), bacteremia in 21% (n = 7), pneumothorax in 15% (n = 5) and heparin-induced thrombocytopenia (HIT) in 15% (n = 5).

A more in-depth analysis revealed that RV dysfunction was associated with a two fold increased risk of pulmonary embolism (21.42% vs. 10.53%, p = 0.04) and two fold higher risk of thrombosis/deep venous thromboses (42.85% vs. 21.05%, p = 0.0046). Table 3 summarizes complication rates as related to RV dysfunction.

Table 3
Complication rates as related to presence or absence of RV dysfunction.

Complications	Total, n = 33	No RV Dysfunction, n = 19	RV Dysfunction, n = 14	P Value (chi-square test)
Hemorrhage	51.50%	52.26%	50%	0.815
Heparin Induced Thrombocytopenia	15.15%	15.79%	14.29%	0.783
Pneumonia	69.69%	68.42%	78.57%	0.283
Thrombosis/ DVTs	**30.30%**	**21.05%**	**42.85%**	**0.005**
Urinary Tract Infection	21.21%	21.05%	21.43%	0.950
Bacteremia	21.21%	21.05%	21.43%	0.953
Pneumothorax	15.15%	15.79%	14.29%	0.783
Pulmonary Embolism	**15.15%**	**10.53%**	**21.42%**	**0.045**

Total of 9% (n = 3) patients required placement of percutaneous RVAD. All were female, aged between 31–46 years old. They all had a history of asthma, and one also had a distant history of H1N1 infection for which she had undergone intubation and ventilation. All three patients exhibited severe RV dysfunction characterized by RV FAC < 35% and elevated pulmonary artery pressures (PAPs). Two patients were able to recover from ARDS and were discharged to the inpatient rehabilitation service and later discharged to home. The other did not show any evidence of cardiopulmonary recovery despite a prolong period of support and died when support was withdrawn.

The overall survival rate in this study of our COVID-19 VV ECMO cohort was 39% (n = 13). The RV dysfunction group had a longer duration of mechanical ventilation, mechanical circulatory support, and longer total hospital stay. However, these findings did not reach statistical significance (see Table 4).

Table 4
Outcome data as related to presence or absence of significant RV dysfunction.

Outcomes	Total, n = 33	No RV Dysfunction, n = 19	RV Dysfunction, n = 14	P Value
Survival to discharge %	39.4%	42.1%	35.7%	0.466
Mean Duration of mechanical ventilation (days)	36.3	32.4	41.7	0.182
Mean Duration of mechanical circulatory support (days)	27.3	20.9	35.9	0.062
Mean Duration of Total Hospital Stay (days)	54.9	47.0	65.6	0.153

Discussion

RV injury, dilation and dysfunction as a result of COVID-19 pneumonia is a well-recognized complication of this condition[7] and previous studies have objectively examined this phenomenon through echocardiography[12] and magnetic resonance imaging (MRI)(13). It has been demonstrated that presence of RV dysfunction is a significant adverse prognostic indicator in severely ill patients with COVID-19 [10, 13–15]. We identified that an overwhelming majority (78.8%) of the patients admitted needing VV ECMO for COVID-19 were of non-white ethnic background. This is significant in the WWAMIO region with predominantly white population. However, higher incidence and higher morbidity and mortality rates in the non-white ethnic minorities from COVID-19 is a well reported phenomenon that could possibly be explained by socioeconomic disparities and lack of access to health care[16, 17].

In this study of COVID-19 patients on VV ECMO, 42% of cohort demonstrated echocardiographic evidence of clinically significant RV dysfunction. This is remarkable as it confirms the previously shown high incidence of RV dysfunction within patients with ARDS secondary to COVID-19 reported by other studies [18–20]. Additionally, we identified that pre-existing chronic lung disease increases the risk of RV dysfunction by nearly 3-fold. As such these patients should be more attentively monitored for evidence of RV dysfunction using TTE, particularly with TAPSE and RV FAC measurements. A previous study by Lan et al[10], demonstrated elevation in serum markers of D-Dimer and C-Reactive Protein (CPR) as surrogates of RV dysfunction. In this study, we identified that serum Troponin I and BNP were strong indicators of RV dysfunction. Our data showed troponin I elevation was 6-fold and BNP elevation was 4-fold higher in the RV dysfunction cohort as compared to the non-RV dysfunction cohort. Indicating that up-trending levels of these two markers should prompt physicians to monitor patients for RV dysfunction using TTE. However, we recommend that any patient who requires VV ECMO due to COVID-19 should get a baseline and a follow-up TTE to monitor RV function.

Furthermore, we report survival to hospital discharge of 39% amongst our COVID-19 patients who required VV ECMO. Our study could not further confirm findings by previous studies that reported higher mortality rates in patients with RV dysfunction. However, our study did demonstrate a trend towards increased length of hospitalization, as well as duration on mechanical and circulatory support in the RV dysfunction cohort. It is unknown whether RVAD support of patients with RV failure due to COVID ARDS improves mortality, and furthermore unknown if RVAD rescue of patients on VV ECMO with a failing RV is a viable option. This question is ripe for further study as some preliminary data suggest impressively high rates of survival in patients supported using RVADs. Furthermore, since the completion of this study, in a more recent case of a previously fit and healthy, unvaccinated 32-year-old man with severe COVID pneumonia, VV ECMO was transitioned to percutaneous RVAD to support RV failure. However, we found that since institution of RVAD support, he developed precipitously worsening fibrotic lung transformation to the extent that he was made a lung transplant candidate. Upon continuation of RVAD support, he developed paradoxical venous and liver congestion, leading to multiple deep venous thrombotic events and massive hepatosplenomegaly despite adequate anticoagulation, a well-functioning extra-corporeal pump and good drainage. The cause for this is not immediately apparent. However, we postulate release of vascular inflammatory mediators in response to extra-corporeal support and COVID infection could be potential factors. We would recommend transitioning to VAV ECMO as a fallback strategy in cases where the patients are under supported with an RVAD or there is a malfunction with the RVAD device/circuit.

Based on the findings presented in this study we devised a flowchart algorithm (see Fig. 1) for evaluation, monitoring and management of COVID-19 patients on VV ECMO with respect to RV dysfunction.

Figure 1: Flow chart for early diagnosis and management of right ventricular dysfunction in COVID-19 patients who require VV ECMO.

Conclusions

In conclusion, we identified that a significant proportion of patients with COVID-19 infection requiring VV ECMO develop RV dysfunction. There is significant predilection of this phenomenon for ethnic minorities. Troponin I and BNP were identified as early biomarkers of RV dysfunction. We recommend baseline and serial TTE in these critically ill COVID-19 patients on VV ECMO, in order to trend RV function and institute appropriate therapies including inotropic and percutaneous RVAD support.

Abbreviations

ECMO: extra-corporeal membrane oxygenation

RVAD: Right ventricular assist device

RV: right ventricle

CT: computed tomography

MCS: mechanical circulatory support

ABG: Arterial blood gas

ARDS: Acute respiratory distress syndrome

CRP: C-Reactive Protein

BNP: Brain natriuretic peptide

TAPSE: Tricuspid annular plane systolic excursion

FAC: Fractional area change

PAP: Pulmonary artery pressures

TTE: Transthoracic echocardiogram

WWAMIO: Washington, Wyoming, Alaska, Montana, Idaho, and Oregon

IRB: Institution review board

Declarations

Ethics approval and consent to participate: This was a retrospective study hence there were no participants involved and no consent was not required from any subjects. The University of Washington Human Subjects Division and Ethics committee, evaluated the institution review board (IRB) application and approved the study for data collection and subsequent publication of outcomes. All methods were performed in accordance with guidelines and regulations as outlined by declaration of Helsinki.

Consent for publications: Included in IRB approval. Retrospective study

Availability of data and materials: All can be obtained from the corresponding author mkhors@uw.edu

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Figures

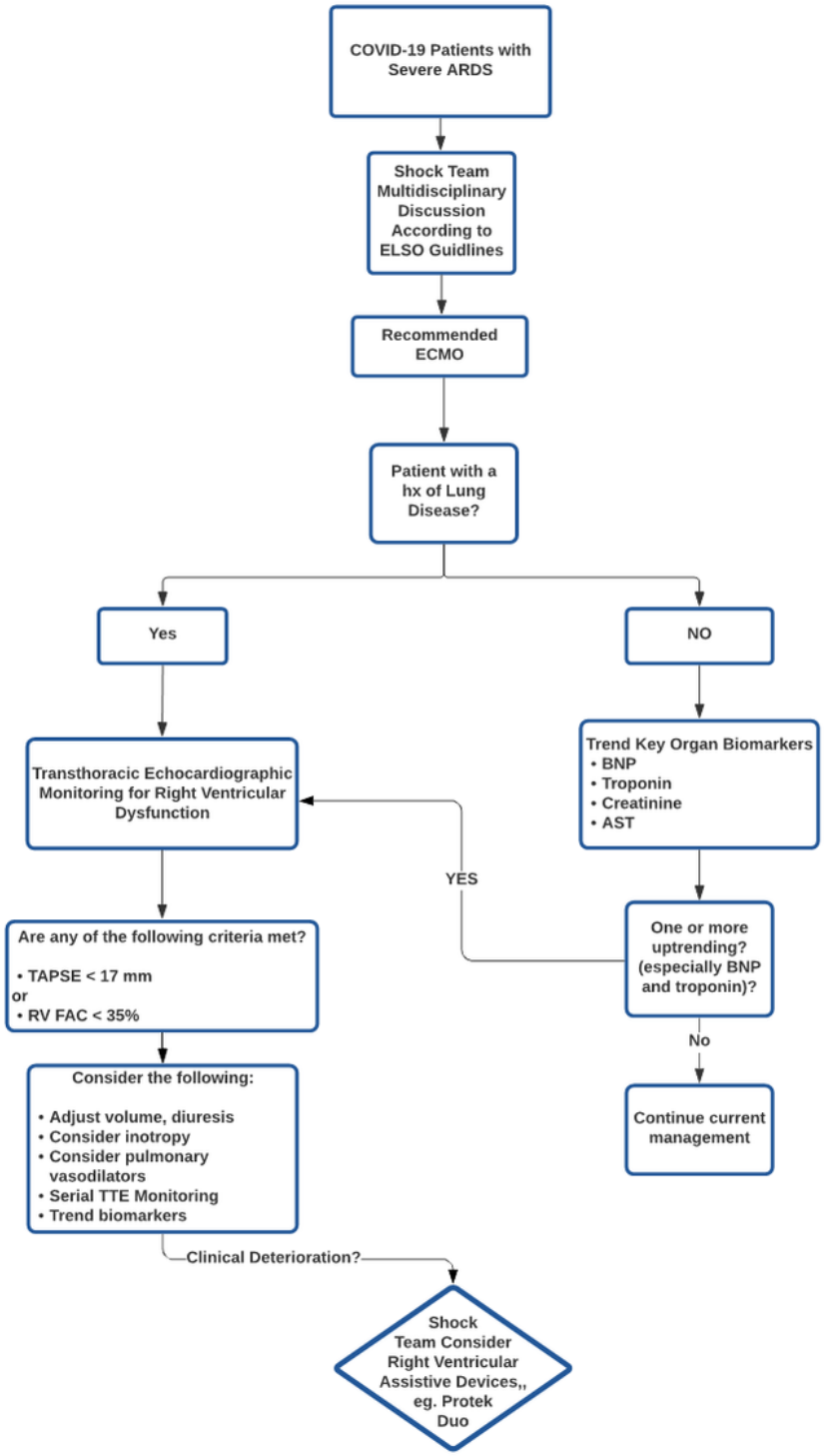

Figure 1

Flow chart for early diagnosis and management of right ventricular dysfunction in COVID-19 patients who require VV ECMO.