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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Right Ventricular Failure Manifesting in COVID-19 ARDS: A Call to Transition from VV-ECMO to RVAD-ECMO

Sankalp P. Patel D.O. 1, Brian J. Solomon M.D. 2, Robert D. Pascotto, M.D. 2, Stephen E. D’Orazio M.D. 2, Elsy V. Navas M.D. 3, Robert J. Cubeddu M.D. 3, Gaston A. Cudemus M.D. 4

1. Department of Internal Medicine, Graduate Medical Education, NCH Healthcare System
2. Department of Cardiothoracic Surgery, Naples Heart Institute, NCH Healthcare System
3. Department of Cardiology, Naples Heart Institute, NCH Healthcare System
4. Department of Cardiovascular Critical Care, Director of ECMO program, Naples Heart Institute, NCH Healthcare System

Corresponding Author:
Sankalp P. Patel
Address: 311 9th St. N, Naples, FL 34102
Ph: (239) 624-0940
Fax: (239) 624-0941
Email: Sankalp.Patel@nchmd.org

Disclosures: The authors have nothing to disclose

Funding: No funding was provided for this report

Overview:

Often labeled the forgotten ventricle, the right ventricle’s (RV) importance has been magnified over the last two years as providers witness how SARS-CoV-2 infection has a predilection for exacerbating RV failure. Veno-venous extracorporeal membranous oxygenation (VV-ECMO) has become a mainstay treatment modality for a select patient population suffering from severe COVID-19 acute respiratory distress syndrome (ARDS). Concomitant early implementation of a right ventricular assist device with ECMO (RVAD-ECMO) may confer benefit in patient outcomes. The underlying mechanism of RV failure in COVID-19 has a multifactorial etiopathogenesis, nonetheless clinical evaluation of a patient necessitating RV support remains unchanged. Herein, we report a case of a critically ill patient who was transitioned from
Keywords: Right ventricular assist device, Extracorporeal Membranous Oxygenation, COVID-19, ProtekDuoTM, acute respiratory distress syndrome

Introduction

Approaching two years into the COVID-19 global pandemic, fatigued providers have been tasked with managing a seemingly insurmountable caseload of critically ill patients. Through utilization of a multi-disciplinary approach and adherence to standardized protocols, many institutions have demonstrated gradual improvement in outcomes as clinicians further understand the pathophysiologic basis of SARS-CoV-2 infection. The preponderance of right ventricular failure over left ventricular failure among severely infected patients stems from the elevated RV afterload with concurrent decrease in contractility, all presumably secondary to ARDS, thromboembolic disease, and direct viral penetration1. Advanced imaging modalities including cardiac magnetic resonance imaging (CMR) and echocardiography have also shown the incidence of RV failure exceeds LV failure in critically ill patients with COVID-192-3.

Timely recognition and intervention in the setting of right ventricular compromise is crucial, as these patients can decompensate rapidly. Upon identification of RV failure in a patient already on conventional VV-ECMO circuit, medical therapy in the form of offloading the RV through preload reduction, augmentation of contractility with inotropic agents, and initiation of inhaled pulmonary vasodilators should be optimized4. It is when medical therapy yields insufficient, and decompensation persists, that the option for further mechanical circulatory support be explored. With the advent of a dual-lumen single cannula such as the LivaNova® ProtekDuoTM, conventional VV-ECMO can be upgraded to further enhance RV support. This
report describes a case in which a patient receiving conventional VV-ECMO support for 6 weeks exhibited symptomatic congestive RV failure and underwent internal jugular venous cannula exchange with insertion of a ProtekDuo™ right ventricular assist device.

Case Report

A 53-year-old man unvaccinated against SARS-CoV-2 with medical history significant for anxiety, hypertension, and ARDS requiring mechanical ventilation 3 years ago due to substance overdose presented from outside facility to our institution for evaluation of VV-ECMO candidacy (height: 185 cm; weight 98 kg; BMI: 29.5 kg/m²).

In brief, he presented to previous facility 9 days before transfer to our institution with hypoxic respiratory failure secondary to SARS-CoV-2 infection and was found to be saturating 85% on room air. Contrasted computed tomography of the chest was performed revealing expected diffuse bilateral groundglass opacities. He was subsequently placed on high-flow nasal cannula and encouraged to self-prone; however, the patient was non-compliant. Thereafter, non-invasive positive pressure ventilation (NIPPV) was provided in the form of bi-level positive airway pressure (BIPAP) with fraction of inspired oxygen (FiO2) set at 100%. The patient initially refused to be intubated, but after 3 days of worsening dyspnea evidenced through shallow, tachypneic respirations, he agreed to proceed. This occurred the day prior to transfer to our facility for VV-ECMO evaluation. Pertinent medical therapy given at outside facility included two doses of 400mg tocilizumab, 6mg dexamethasone daily for 9 days, completion of 5-day course of remdesivir, and treatment dose enoxaparin for a right axillary deep vein thrombus.
On arrival to our center, initial ventilator settings witnessed were set on volume-control continuous mandatory ventilation (VC-CMV), an FiO2 of 100%, tidal volume of 500mL, a respiratory rate (RR) of 15 breaths per minute, and a positive end-expiratory pressure (PEEP) at 18 cmH2O. The patient’s cardiopulmonary status remained tenuous, evidenced by his arterial blood gas (ABG) drawn on aforementioned ventilator settings showing signs of severe hypoxic and hypercapnic respiratory failure in the setting of ARDS shown here: pH of 7.22, PaO2 of 57.8 mmHg, PaCO2 of 61.4 mmHg, and low PaO2/FiO2 ratio of 57.8. He was receiving vasopressor support with norepinephrine at a fairly high dose of 20 mcg/min to prevent hypoperfusion. Cardiothoracic surgery had been notified and prompt percutaneous VV-ECMO was initiated. This was conducted with a dual cannula configuration involving one in the right femoral vein (25F) advanced into the abdominal inferior vena cava as the drainage cannula and the other in the right internal jugular vein (22F) as the return cannula with an initial flow rate of 4.5 L/min per protocol. Cannulas were secured in position and sterile dressings were applied; the procedure was uncomplicated and the patient was initiated on anticoagulation with a bivalirudin infusion with coagulation parameters in place. The rate of norepinephrine infusion, initially set at 20mcg/min, was titrated down to 2mcg/min an hour after ECMO initiation. Ventilator settings were appropriately adjusted in accordance to a lung protective ECMO strategy utilizing 4-6mL/kg tidal volume and RR of 10-15 breaths per minute per our protocol. Post-membrane ABG revealed adequate oxygenator performance with a PaO2/FiO2 ratio of 187. Transthoracic echocardiogram performed after cannulation revealed normal left ventricular ejection fraction (LVEF) 60-65%, normal RV size and function, and normal appearing tricuspid valve with trace regurgitation appreciated.
He continued supportive care while fine ventilator adjustments were made, and two weeks later, decision was made to transition from a two-cannula apparatus to a single dual-lumen 27Fr Crescent™ cannula configuration in the left subclavian vein with simultaneous tracheostomy, with plan to work with physical therapy and move towards rehabilitation. The transition was performed without complication, and aside from bleeding which was controlled intraoperatively due to the patient being anticoagulated for 2 weeks, he returned to the cardiovascular intensive care unit (CVICU) in hemodynamically stable condition. We attempted to wean ECMO on multiple occasions; nonetheless, the patient was unable to tolerate a sweep < 4L/min due to hypercapnia and his CT scan revealing diffusely severe lung disease (Figure 2). He continued undergoing supportive care, physical therapy, and daily awakening. Given significant volume influx through multiple infusions required for sedation, anticoagulation, and inflow from VV-ECMO, the patient was intermittently on loop diuretic infusions as well; however, our focus led to the elimination of multiple infusions with time and implementing oral medications to prevent volume overload.

One morning, a transient bout of hypotension and worsening hypoxia was encountered, and the patient underwent a point-of-care bedside echocardiogram, unveiling septal-D flattening (+McConnell sign) and severely reduced RV function consistent with RV volume overload. Aggressive diuresis was trialed along with pulmonary vasodilator therapy with epoprostenol, and his course was concomitantly complicated by a suspected nosocomial fungal infection corroborated by a markedly profound leukocytosis and sputum cultures (+) for Candida Albicans. The patient was placed on micafungin therapy with gradual intermittent improvement observed and was noted to be awake, alert, and oriented but extremely weak. Medical therapy for RV failure was pursued until the patient decompensated again 6 weeks into his hospital course.
experiencing a recurrent bout of hypotension and hypoxia in conjunction with marked elevation in liver function tests and rise in creatinine (Table 1). Medications administered included diuresis with furosemide and initiation of inhaled epoprostenol. At this time, a repeat transthoracic echocardiogram was performed and elucidated just how severe the RV failure was. RVSP was noted to be 51mmHg, the right ventricle appeared severely enlarged, moderate tricuspid regurgitation and elevated pulmonary artery systolic pressure also now accompanied septal flattening visualized 2 weeks prior (Figure 1). At that juncture, a joint decision among all providers was made to exchange the current VV-ECMO Medtronic® Crescent™ dual-lumen cannula for a LivaNova® ProtekDuo™ dual-lumen RVAD cannula given the severe pulmonary dysfunction evidenced by CT scan and noted lack of reserve.

With the patient receiving VV-ECMO through a single dual-lumen cannula, the complexity of decannulation and substitution with ProtekDuo™ RVAD device was not straightforward. A multidisciplinary approach led by the ECMO team was implemented, with all in agreement with establishing drainage through the right femoral vein intraoperatively, while concomitantly positioning the Crescent™ cannula into the subclavian vein to continue inflow. The challenge here encountered was attempting to simultaneously fit two 32Fr cannulas within the superior vena cava. After accessing the right femoral vein, a dilator kit was utilized to dilate from 8Fr to 24Fr, until a 25Fr long venous cannula was inserted to the IVC. The line was subsequently clamped. The Crescent™ cannula was then clamped, with the drainage remaining attached to the middle port. Under fluoroscopic guidance, the cannula was repositioned into the subclavian vein. VV-ECMO ensued successfully thereafter, and this approach opened adequate room in the SVC for the placement of the ProtekDuo™ RVAD. Ultrasound-guided access was obtained with a J-wire and exchanged for a 6Fr sheath. A Swan-Ganz catheter was inserted into
the right pulmonary artery (PA) thereafter. An extra-stiff Amplatz™ wire was placed through the Swan-Ganz catheter into the right PA in preparation for dilation. Upon dilation to 26Fr under fluoroscopy, a 31Fr ProtekDuo™ cannula was inserted. After successful insertion without complications, the RVAD cannula was attached to a separate circuit. This circuit had a Quadrox-i® oxygenator linked to a LifeSPARC® pump. The patient’s saturation increased to 100% and flow was initiated at 4.5L at a rate of 7500 RPM. The patient maintained stability for 15 minutes with isolated RVAD-ECMO configuration saturating >99% SpO2. This was when subclavian-femoral VV-ECMO was decannulated and removed with adequate pressure maintained to prevent bleeding along with 3 separate compressive sutures tied with the aid of cardiothoracic surgery. He was transferred back to the CVICU hemodynamically stable for further supportive care. In only 24 hours, a significant improvement was observed in renal function, with near complete resolution of hepatic dysfunction following 2 weeks thereafter. Approximately 1-month post-placement of the ProtekDuo™ dual-lumen single RVAD cannula (Fig 1), the patient demonstrated resounding improvement in hemodynamic stability and complete resolution of congestive hepatopathy and renal failure as well (Table 1).

Discussion:

Much of the data encompassing the cardiovascular complications of COVID-19 has mainly focused on arrhythmias, myocardial dysfunction, and myocardial injury involving the left heart. A recent meta-analysis revealed almost one out of five patients infected with SARS-CoV-2 exhibit right ventricular dysfunction, with a threefold higher likelihood of all-cause death in comparison to subjects without RV failure. The RV is the link between our systemic venous circulation and the pulmonary circuit. Lesser dense myofibrils (~1/3 density compared to LV) provide a chamber with increased compliance, permitting fluctuations in venous return. Well
known, the RV exudes a complex physiological relationship between rhythm, preload, contractility, afterload, and interdependence with the LV. The supposed mechanism of RV failure in patients with COVID ARDS is likely secondary to dense lung fibrosis leading to increased RV afterload and pulmonary arterial pressures causing eventual cor pulmonale\(^7\).

Though there is likely a multifactorial pathogenesis at play in the setting of COVID, one fact about RV failure irrespective of underlying cause, is how rapidly patients can decompensate. The medical management of RV failure involves optimization of preload and mitigating factors which may increase pulmonary vascular resistance. Once inhaled pulmonary vasodilators have been started, a patient’s cardiopulmonary status is likely very precarious. This is when discussion is initiated regarding extracorporeal life support, and whether a patient is an optimal candidate\(^8\).

The indications for initiating ECMO in COVID-19 patients have been described by Mikkelsen et al., who recommended consideration in patients with PaO2/FiO2 < 50mmHg for >3 hours, PaO2/FiO2 < 80mmHg for >6 hours, or arterial pH lower than 7.25 with PaCO2 of >60mmHg for 6 hours. Our patient met those criteria on arrival to our facility, and RV failure persisted on VV-ECMO, thus demanding need for isolated RV mechanical circulatory support.

The ProtekDuo\(^{TM}\) had its first-in-man use in 2016, in conjunction with rising popularity of the left-ventricular assist device (LVAD) with primary complications of this device being RV failure\(^9\). Similar to conventional VV-ECMO, the ProtekDuo\(^{TM}\) operates through centrifugal flow, and can provide a flow of up to 4.5L/min. Upon insertion within the right internal jugular vein, there is a proximal return cannula which remains in the RA, while the remainder distal drainage lumen is fed (usually over Swan Ganz catheter) directly into the main pulmonary artery creating an RA-PA bypass tract passing the RV\(^10\). The advantage of the ProtekDuo\(^{TM}\) cannula, in comparison to its competitors, is the insertion within the right IJ vein, permitting full ambulation...
within recipients. RVAD-ECMO with the ProtekDuo™ in patients with COVID-19 in comparison to mechanical ventilation alone has been to show to reveal no increase in secondary end-organ damage, with higher in-hospital and 30-day survival in the RVAD-ECMO cohort, leading to a conclusion to prioritize RV support in these patients. RVAD-ECMO configuration with the ProtekDuo™ single dual-lumen cannula, in comparison to conventional Crescent™ VV-ECMO circuit in severely ill COVID-19 patients has not yet been studied, though our case showcases there appears to be a benefit through addition of right ventricular support.

**Conclusion/Follow-Up:**

We present herein a case of remarkable hemodynamic improvement status post mechanical circulatory support implementation with the LivaNova® ProtekDuo™ device. Our patient is currently alert, awake, and oriented to person, place and situation and is working with physical and occupational therapy regularly. He is off mechanical ventilation, tolerating regular diet, and our plan remains to have him placed at a lung transplant institution once able to walk 100-200 feet.

**Conflicts of Interest**
No conflicts of interest to disclose

**References**

1. Lan Y, Liu W, Zhou Y. Right Ventricular Damage in COVID-19: Association Between Myocardial Injury and COVID-19. *Front Cardiovasc Med.* 2021;8:606318. Published 2021 Feb 16. doi:10.3389/fcvm.2021.606318
2. Argulian E, Sud K, Vogel B, Bohra C, Garg VP, Talebi S, et al. Right ventricular dilation in hospitalized patients with COVID-19 infection. *JACC Cardiovasc Imaging.* (2020) 13:2459–61. 10.1016/j.jcmg.2020.05.010
3. Huang L, Zhao P, Tang D, Zhu T, Han R, Zhan C, et al. Cardiac involvement in patients recovered from COVID-2019 identified using magnetic resonance imaging. *JACC Cardiovasc Imaging.* (2020). 10.1016/j.jcmg.2020.05.004
4. Grant C Jr, Richards JB, Frakes M, Cohen J, Wilcox SR. ECMO and Right Ventricular Failure: Review of the Literature. *J Intensive Care Med.* 2021 Mar;36(3):352-360. doi: 10.1177/0885066619900503. Epub 2020 Jan 22. PMID: 31964208.
5. Tajbaksh A, Gheibi Hayat SM, Taghizadeh H, et al. COVID-19 and cardiac injury: clinical manifestations, biomarkers, mechanisms, diagnosis, treatment, and follow up. *Expert Rev Anti Infect Ther.* 2021;19(3):345-357. doi:10.1080/14787210.2020.1822737
6. Corica, B., Marra, A.M., Basili, S. *et al.* Prevalence of right ventricular dysfunction and impact on all-cause death in hospitalized patients with COVID-19: a systematic review and meta-analysis. *Sci Rep* **11**, 17774 (2021). https://doi.org/10.1038/s41598-021-96955-8

7. Arrigo M, Huber LC, Winnik S, Mikulicic F, Guidetti F, Frank M, Flammer AJ, Ruschitzka F. Right Ventricular Failure: Pathophysiology, Diagnosis and Treatment. Card Fail Rev. 2019 Nov 4;5(3):140-146. doi: 10.15420/cfr.2019.15.2. PMID: 31768270; PMCID: PMC6848943.

8. Ventetuolo CE, Klinger JR. Management of acute right ventricular failure in the intensive care unit. Ann Am Thorac Soc. 2014 Jun;11(5):811-22. doi: 10.1513/AnnalsATS.201312-446FR. PMID: 24828526; PMCID: PMC4225807.

9. Aggarwal V, Einhorn BN, Cohen HA. Current status of percutaneous right ventricular assist devices: First-in-man use of a novel dual lumen cannula. *Catheter Cardiovasc Interv.* 2016;88(3):390-396. doi:10.1002/ccd.26348

10. Nicolais, C. D., Suryapalam, M., O’Murchu, B., Bashir, R., O’Neill, B. P., Alvarez, R., … Aggarwal, V. (2018). USE OF PROTEK DUO TANDEM HEART FOR PERCUTANEOUS RIGHT VENTRICULAR SUPPORT IN VARIOUS CLINICAL SETTINGS: A CASE SERIES. *Journal of the American College of Cardiology*, 71(11), A1314.doi:10.1016/s0735-1097(18)31855-2

11. Cain MT, Smith NJ, Barash M, et al. Extracorporeal Membrane Oxygenation with Right Ventricular Assist Device for COVID-19 ARDS. *J Surg Res.* 2021;264:81-89. doi:10.1016/j.jss.2021.03.017

![Fig. 1 Quadrox i® oxygenator attached to LifeSPARC® console with ProtekDuo™ cannulas seen (left); cannula tip seen entering right PA under fluoroscopy (middle); Echocardiogram image of septal-D flattening (+McConnell Sign) demanding RVAD (right)](image1)

**Figure 2. Severely Diffuse Dense Pulmonary Fibrosis secondary to SARS-CoV-2 infection. Left shows Crescent™ cannula with dual lumen cannulas seen on patient’ left-side. Right shows ProtekDuo™ cannula with worsened fibrotic changes with dual lumen cannulas on patient’s right-side.**

| Baseline Labs | Values on Arrival | Values day before ProtekDuo™ | Values 1 month after ProtekDuo™ | Normal Values |
|---------------|-------------------|-----------------------------|---------------------------------|---------------|
| WBC           | 15.9              | 25.5                        | 8.8                             | 4.2-10.8 th/ul|
| Hgb           | **10.7**          | 7.6                         | **11.0**                        | 14-18 gm/dL   |
| Platelet      | 158               | 73                          | 91                              | 130-450 th/ul |
| Bicarbonate   | 22                | 25                          | 30                              | 21-32 mmol/L  |
| BUN           | 20                | 79                          | 10                              | 7-18 mg/dL    |
| Creatinine    | 0.6               | 1.1                         | 0.5                             | 0.6-1.3 mg/dL |
| Lactate       | **3.8**           | **5.9**                     | 1.1                             | 0.4-2.0 mmol/L|
| Troponin I    | 0.13              | (-)                         | (-)                             | < 0.15 ng/mL  |
| NT-proBNP     | 801               | **18,189**                  | -                               | 0-125 pg/ml   |
| Albumin       | **2.1**           | 3.6                         | 3.2                             | 3.4-5.0 gm/dL |
| Total bilirubin| 0.5              | **3.1**                     | 0.4                             | 0.2-1.0 mg/dL |
| Protein       | 5.2               | 7.9                         | 7.5                             | 6.4-8.2 gm/dL |
| Alkaline Phosphatase | 116      | **435**                     | 87                              | 50-136 IU/L   |
| ALT (SGPT)    | 37                | **3,630**                   | 50                              | 12-78 IU/L    |
| AST (SGOT)    | 35                | **4,536**                   | 46                              | 15-57 IU/L    |

*Table 1. Pertinent Laboratory Studies; note that blue-colored text reveals elevated values whereas red-colored text denotes decreased levels.*
Figure 1 Quadrox-i™ oxygenator attached to LifeSPARC™ console with ProtekDuo™ cannulas seen (left); cannula tip seen entering right PA under fluoroscopy (middle). Echocardiogram image of septal D flattening (+McConnell Sign) demanding RVAD (right).

Figure 2 Severely Diffuse-Dense Pulmonary Fibrosis secondary to SARS-CoV-2 infection. Left shows Crescent™ cannula with dual lumen cannulas seen on patient’s left-side. Right shows ProtekDuo™ cannula with worsened fibrotic changes with dual lumen cannulas on patient’s right-side.