

Interventional Therapies for Right Ventricular Failure Secondary to Precapillary Pulmonary Hypertension

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MECHANICAL SUPPORT FOR THE FAILING RIGHT VENTRICLE

Mechanical support for the right ventricle (RV) can address key mechanisms of right heart failure in the setting of pulmonary hypertension (PH), including: 1) reduction of RV preload, 2) reduction of RV afterload, and 3) provision of pump function. Moreover, lesser mechanisms contributing to ventricular failure can also be improved theoretically by mechanical support such as less tricuspid regurgitation secondary to ventricular dilatation¹ and improved left ventricular (LV) filling and function due to minor septal bowing.

One important concept to consider in the management of RV failure is that, although the RV is less adaptable to situations of pressure overload, it carries a substantial potential for recovery once its afterload is normalized. This particular scenario is well illustrated by RV recovery post-lung transplantation for PH.²

Although it is difficult to establish ideal timing for initiation of mechanical support for the failing RV, refractoriness to maximize pharmacological therapies should prompt the evaluation by a multidisciplinary team composed of an intensivist, respirologist/cardiologist, and cardiothoracic surgeon. It is crucial to consider the patient's bridging potential

Patients with pulmonary hypertension that progress to acute decompensation present high mortality rates. The main mechanism of death in this population is right ventricular failure. Once this scenario becomes refractory to optimized medical therapies, mechanical support is increasingly considered as either a bridge to recovery or, most often, as a bridge to definitive surgical treatment (such as lung transplantation, surgical embolectomy, or pulmonary endarterectomy). This review will focus on the existing evidence on mechanical support for the failing right ventricle, all in the context of precapillary pulmonary hypertension.

to avoid the futile initiation of extracorporeal life support (ECLS) at all costs. For patients with either acute massive pulmonary embolism (PE) or chronic thromboembolic pulmonary hypertension (CTEPH), the possibility of stabilization on ECLS for interventional embolectomy or pulmonary endarterectomy (PEA), respectively, should be considered. In patients with idiopathic pulmonary arterial hypertension (iPAH), candidacy for lung transplantation should have been assessed previously, although emergent evaluation may be considered on an individual basis. Another potential (but less likely) scenario is the use of ECLS as a bridge to recovery in iPAH patients that are either treatment-naïve or that are still not optimized on PH-targeted therapies.

Contraindications for mechanical support include: 1) irreversible neurological or end-organ damage; 2) intracranial bleeding or other major contraindication for anticoagulation; 3) inaccessible vessels for cannulation; 4) patients with irreversible cardiopulmonary failure not candidates for transplantation; and 5) septic shock.³⁻⁶

ECLS modes typically include a pump, an oxygenator, and the circuit tubing. Technological improvements have decreased the heating and thrombosis issues with earlier centrifugal

pumps, leading to less hemolysis.³ Modern oxygenators can now be used for prolonged periods and have significantly lower resistance compared to the older-generation ones.³ Moreover, heparin-coated tubing circuits are now widely available and require less systemic heparinization.³

MODES OF SUPPORT FOR RV FAILURE SECONDARY TO PH *Venovenous Extracorporeal Membrane Oxygenation*

Venovenous extracorporeal membrane oxygenation (VV-ECMO) for mechanical support for RV failure was successfully reported by the group from the University of Maryland in a 35-year-old female patient presenting with a pulmonary hypertensive crisis. Hemodynamic instability was observed at attempts to initiate milrinone and intravenous epoprostenol.⁷ Taking advantage of a large patent foramen ovale (PFO), they described the use of a dual-lumen single cannula with the outflow jet directed toward the left atrium through the PFO. This strategy allowed for PH-targeted medication titration, and the patient was successfully weaned from ECLS after 10 days. Except in particular circumstances in which patients have a large PFO or atrial septal defect (ASD), VV-ECMO is not considered an appropriate mode of support for RV failure due to the lack of hemodynamic support.

Another exceptional role for VV-ECMO support in patients with

Key Words—cardiopulmonary support; embolectomy; extracorporeal life support; mechanical support; ventricular failure

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Disclosure: Dr de Perrot has served as a speaker's bureau member for Bayer. He has also received institutional grant/research support from Bayer.

PH is in the context of respiratory failure following PEA for CTEPH. Ischemia-reperfusion injury and the pulmonary artery “steal” phenomenon can lead to severe respiratory failure secondary to ventilation/perfusion mismatch. The experience from the University of California, San Diego illustrates this application well, with 20 patients (from 1790 cases) requiring VV-ECMO after PEA. Six patients survived to hospital discharge and all of them were cannulated within 120 hours after PEA.⁸

Venoarterial ECMO

One of the most frequently utilized modes of support for patients with PH and RV failure is venoarterial (VA) ECMO. Vascular access is typically obtained peripherally, either percutaneously or through cut-down dissection of the femoral vessels. A multifenestrated inflow cannula in the femoral vein is advanced to the right atrium (RA) and the outflow cannula is inserted in the femoral artery. It has the advantage of implantation under local anesthesia for unstable patients too high risk for general anesthesia induction. Nevertheless, since the cannulae are positioned in the groin, patients cannot ambulate. Another disadvantage is that despite the possible insertion of a distal limb perfusion catheter, femoral VA-ECMO is prone to limb malperfusion and arterial complications. Moreover, since the arterial flow is retrograde with this configuration, patients are at risk for upper-body malperfusion, increased LV afterload, and poor oxygenation, especially if concomitant respiratory failure is present.

Additional cannulation sites include upper limb and central. Upper-limb cannulation is performed with access through dissection of the axillary vessels.⁹ This mode can be initiated under local anesthesia, but since a graft needs to be sewn end to side with the axillary artery (to prevent distal upper-limb malperfusion), it usually requires more time than femoral vessel cannulation. On the other hand, important advantages include ambulatory capability (there are no cannulae in the groin) and adequate perfusion/oxygenation to the upper body

in the event of respiratory dysfunction. Lastly, central cannulation is performed with the inflow cannula inside the RA and the outflow cannula in the ascending aorta. It requires general anesthesia and a sternotomy, but since the outflow is antegrade through the ascending aorta, there is optimal upper body and coronary artery perfusion/oxygenation.

Pulmonary Artery to Left Atrium ECLS

This mode of support consists of a membrane oxygenator (Novalung Interventional Lung Assist Device, Novalung, Germany) connected in parallel with the pulmonary circulation (pulmonary artery to left atrium). Due to its low oxygenator resistance, it can facilitate the bypass of approximately 50% of the cardiac output from the pulmonary circulation.¹⁰ A pump is not required since the blood flow is driven by the patient's own RV.¹¹ By creating a low-resistance circuit in parallel with the right heart, hemodynamic improvement by decreasing RV afterload is obtained. This mode of ECLS also provides carbon dioxide removal and oxygenation, although the inability to achieve higher flows due to the absence of a pump limits oxygenation capacity. Another advantage is that since the cannulation is central, patients can remain ambulatory for rehabilitation.

The drawback of pulmonary artery to left atrium (PA-LA) ECLS resides in the requirement of general anesthesia and a median sternotomy. Since patients tend to be hemodynamically unstable, peripheral cannulation for VA-ECMO initiation is usually performed under local anesthesia before induction of general anesthesia for a median sternotomy and central cannulation for the PA-LA ECLS.¹² It is important to highlight that in cases of combined intrinsic LV failure this pumpless mode will not provide adequate systemic hemodynamic support.

MECHANICAL SUPPORT AS A BRIDGE TO RECOVERY IN IPAHA

Even though mechanical support as a bridge to recovery for iPAH patients with RV failure seems unrealistic for most cases, there have been some recent reports of successful outcomes in very

well selected cases. In one by the group from Columbia University, a 48-year-old female still on submaximal PH-targeted therapy was supported with VA-ECMO when presenting with RV failure. Medications were optimized and she was decannulated after 6 days, surviving to hospital discharge.¹³ Another report describes 2 additional patients with iPAH who were supported with VA-ECMO.¹⁴ The first patient received an iPAH diagnosis at the moment of acute decompensation with RV failure, was then started on targeted therapy, and successfully weaned from the circuit after 16 days. The second patient already had known iPAH and presented with cardiogenic shock with no clear stressor. Dysfunction of multiple organs and systems followed and support was withdrawn after 13 days. This report emphasizes the role of patient selection and the higher potential of a favorable outcome with ECLS in patients with iPAH who are still not optimally treated.

As described above, VV-ECMO with a dual-lumen single cannula was used in the context of a PFO to support a treatment-naïve patient presenting with decompensated RV failure. ECLS was discontinued after 10 days and the patient successfully transitioned to targeted therapy.⁷ Again, the reversibility of this scenario by initiation of PH-targeted therapy is closely linked to the favorable outcome achieved.

In our experience, one additional situation where VA-ECMO has been integral to recovery was the development of severe pulmonary edema related to undiagnosed pulmonary venous obstructive disease after the introduction of pulmonary vasodilative therapy.

MECHANICAL SUPPORT AS A BRIDGE TO LUNG TRANSPLANTATION FOR IPAHA

Although management of PH has improved substantially, it is still not possible to predict treatment response and, more importantly, how fast a patient will deteriorate once he or she becomes refractory. Given that expert panel recommendations for lung transplant referral include patients with New York Heart Association class III or IV during

escalating therapy; rapidly progressive disease; and use of parenteral targeted therapy,¹⁵ lung transplant programs are often left with a narrow window of opportunity that should encompass patient assessment, enlistment, and a wait for a suitable donor to become available. This clinical scenario, along with the fact that iPAH patients are often young and experience excellent outcomes conditional to 1-year survival after lung transplantation,¹⁶ makes it logical to consider advanced bridging strategies to support this population when they present with RV failure.

The PA-LA ECLS constitutes an adequate mode for bridging iPAH patients to lung transplantation because of several key features: 1) enables active rehabilitation while on the wait-list; 2) can be utilized for prolonged time, such as cases described with 175 and 69 days¹⁷; and 3) has been used successfully in the pediatric population.¹⁷ According to early reports, this mode of support began being used clinically as a bridge to lung transplant by 2005.^{10,18}

Schmid et al reported a 38-year-old female with RV failure secondary to iPAH who was initially supported with central VA-ECMO. With progressive deterioration and inability to wean, authors got approval to use the PA-LA ECLS. The patient improved, was weaned from the ventilator, and became ambulatory while waiting for lung transplantation. After 62 days on the device, she received a successful double-lung transplant.

Subsequently, 4 PH patients were bridged to either double-lung or heart-lung transplant in the combined experience of the Toronto and the Hannover lung transplant programs.¹⁸ The PA-LA ECLS was used from 8 to 30 days until the patients received a transplant with favorable early outcomes. These authors also reported that although the circuit may become dysfunctional due to fibrin deposition, it could be easily exchanged. Moreover, another important lesson involved the benefit of preparation for peripheral VA-ECMO cannulation under local anesthesia for patients at high risk of cardiocirculatory collapse at induction. Once stabilized on VA-ECMO, the

team can safely proceed with general anesthesia, median sternotomy, and PA-LA ECLS cannulation. The VA-ECMO can then be weaned at the end of the procedure.

Subsequent contributions by the group from Hannover focused on the concept of awake ECLS as a bridge to transplant.¹⁹ Most recently, they reported 26 such patients, including 7 iPAH patients supported with femoral VA-ECMO initiated under local anesthesia.²⁰ Most of these patients remained extubated until transplantation or death on ECLS. In an intention-to-treat analysis, authors reported 62% survival at 6 months. Of note, the outcomes were significantly better in the awake bridge population than in the intubated and mechanically ventilated one. Likewise, this was also true in the comparison between those patients remaining awake versus those initially on awake ECMO but eventually requiring intubation.

The impact of ECLS as a bridge to transplant in patients with iPAH is highlighted by the study from de Perrot and coworkers from the University of Toronto.¹² When comparing an early 1997-2005 listed cohort with a more recent 2006-2010 listed cohort (the second one aggressively managed with availability of ECLS as bridge to transplant), the wait-list mortality significantly decreased from 22% to 0%. Importantly, this higher risk profile in the recipient population has not compromised outcomes: the 30-day mortality went from 16.5% to 9.5%. The authors note, however, that this strategy may be associated with a longer post-transplant ICU stay.

Recently, 2 large series reinforced the positive outcomes observed previously. The combined report from the University of Kentucky/University of California, San Francisco included 31 patients bridged to lung transplant with ECLS, with 13 of them presenting with RV failure and requiring VA-ECMO or PA-LA ECLS.²¹ Outcomes were excellent, with 1-year survival of 93%. The second study describes the experience from the University of Pittsburgh.²² Out of 31 patients, 9 were bridged with VA-ECMO for RV failure. With a 1-year survival of 74%,

this series pointed to a high incidence of primary graft dysfunction in bridged patients: 13 of the 24 patients actually transplanted required postoperative ECLS due to primary graft dysfunction. Recently, one interesting algorithm for managing unstable candidates for lung transplantation reinforced the interchangeable nature of the support modes, always targeting the least invasive one able to provide ambulatory status while patients await donor lungs.

Since peripheral groin cannulation prevents patients from being ambulatory and able to pursue a more aggressive rehabilitation while on the wait-list, the use of upper-extremity cannulation may be advantageous and deserves further consideration.^{23,24}

As described above, another support mode that assists the ambulatory status is the VV-ECMO with a dual-lumen single cannula in patients with large ASD. Ideal positioning includes the direction of the outflow jet toward the defect, providing oxygenated blood to the left heart through the right atrium. This mode of support has been tested in animal models and translated to clinical use.^{7,13,25,26} Since the use of balloon septostomy has been successfully described as a palliative measure for PH patients presenting with RV failure,^{27,28} whether this strategy coupled with the benefits of dual-lumen single-cannula VV-ECMO providing not only optimal RV unloading but also adding oxygenated blood through the newly created right-to-left shunt could be superior than the VA-ECMO or PA-LA ECLS modes remains to be studied.

Lastly, another potential application for VA-ECMO is as bridge to recovery for patients with ventricular dysfunction following lung transplantation. Some programs indeed have described its routine use in the early post-transplant period for patients with iPAH.^{29,30}

ADDITIONAL ECLS APPLICATIONS IN RV FAILURE SECONDARY TO PH

Besides the growing use of ECLS for patients with iPAH, there have been interesting reports focusing on its use for patients with CTEPH and patients with acute massive PE. VA-ECMO can be

considered in very well selected patients with CTEPH and RV failure as a bridge to PEA, as reported by Mydin et al.³¹ Another application is as a bridge to recovery post-PEA, when VA-ECMO can be lifesaving for patients with persistent PH and/or airway hemorrhage. This clinical scenario is well illustrated in the study of Berman et al, describing the Papworth Hospital experience with 7 patients (from a total of 127) requiring VA-ECMO for cardiopulmonary support post-PEA.³² All patients presented with persistent PH and RV failure post-PEA, with 5 being successfully decannulated and 4 achieving hospital discharge.

For patients with RV failure secondary to massive PE, ECLS has been utilized as either a bridge to recovery or bridge to embolectomy. Since massive PE is a reversible condition and a previously healthy RV will likely fail once submitted to overwhelming increases in afterload, the use of VA-ECMO for temporary cardiopulmonary support seems adequate. The group from the University of Michigan has reported a total of 43 patients initially referred for ECLS consideration due to massive PE.³³ Ultimately, 19 were placed on VA-ECMO and 2 on VV-ECMO, with the remainder not meeting criteria due to the following reasons: too stable (n=7); prolonged cardiopulmonary resuscitation with irreversible damage (5); age >70 years (4); weight above the air transportation limit (3); prolonged mechanical ventilation (3). Of the 13 patients surviving to hospital discharge (62%), 4 of them were treated with embolectomy, while the remaining were treated with anticoagulation/thrombolytics.

Similar to other previously described situations, the RV has a remarkable potential to recover in post-cardiovascular surgery scenarios (post-cardiotomy, post-heart transplant, post-LVAD insertion). In this setting, Cheung et al have reported a 78% successful RVAD explantation rate.³⁴ Nevertheless, while these devices can be considered as rescue therapy in RV failure post-cardiotomy, post-heart transplant, and post-LVAD implantation, they should not be considered appro-

priate therapy in cases of unresolved severe PH since they do not address the main pathophysiological mechanism of RV failure (pressure overload).³⁵

CONCLUSION

ECLS strategies can be lifesaving for patients with precapillary PH presenting with RV failure refractory to medical therapies. It is crucial that the multidisciplinary team establishes each patient's true bridging potential (to recovery or to surgical therapy) and avoids futile ECLS initiation. For lung transplant candidates, recent literature favors the use of ambulatory modes that enable active rehabilitation and spontaneous breathing during the waiting period.

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