Extracorporeal Membrane Oxygenation as a Postoperative Left Ventricle Conditioning Tool After Lung Transplantation in Patients With Primary Pulmonary Artery Hypertension: First Polish Experience

Tomasz Stącel[a], Remigiusz Antończyk[a,b], Magdalena Latos[a,b,*], Mirosław Nęcki[a], Piotr Przybyłowski[a,c], Marian Zembala[a,b], Marek Ochman[a,b], and Maciej Urlik[a]

[a]Silesian Center for Heart Diseases, Zabrze, Poland; [b]Department of Cardiac, Vascular and Endovascular Surgery and Transplantology, Medical University of Silesia, Katowice, Poland; and [c]First Chair of General Surgery Jagiellonian University, Medical College, Kraków, Poland

ABSTRACT

Background. Primary pulmonary hypertension can lead to hypertrophy of the right ventricle and ultimately to its insufficiency. Lung transplantation remains the only viable treatment for patients with certain forms of this disease. Usage of extracorporeal membrane oxygenation in veno-arterial form (VA-ECMO) after transplantation is both protective for left ventricle (enables adaptation to increased blood flow) and right ventricle (provides time to return to appropriate dimensions and in some cases to correct tricuspid regurgitaion).

Case Presentation. The case study describes 4 patients who were treated with VA-ECMO as a perioperative support. Three patients were diagnosed with idiopathic form of precapillary primary pulmonary hypertension. A fourth patient was a 49-year old woman diagnosed with hypoplastic pulmonary veins representing the postcapillary form of pulmonary hypertension. In all of the cases, VA-ECMO was introduced during the surgery (femoral vein/internal jugular vein and femoral artery) and maintained for several days after the transplantation. Regular echocardiographic and biochemical assessment in postoperative course revealed that cardiac function improved during and after such treatment among all patients. They were successfully weaned off ECMO and finally surgically explanted without any local complications. One patient was treated with awake ECMO protocol.

Conclusions. VA-ECMO was proved to be a useful tool during the transplantation and postoperative period. It helps to restore proper cardiac function, as well as prevent adverse effects of aforementioned pathologic changes of a heart.

PATIENTS suffering from an idiopathic form of pulmonary hypertension usually have an estimated 5-year survival of 57% [1]. Even though tremendous improvements have been achieved with pharmacologic therapy, the majority of patients will require lung transplantation, as it has been proved to be a higher up-front surgical-risk procedure to perform, but with excellent long-term survival and quality of life [2–4]. Significantly increased pulmonary artery pressure leads to a series of pathomorphological and functional changes in the heart. Poor outcome of idiopathic pulmonary arterial hypertension patients who have not undergone lung transplantation has been associated with high right atrial pressure, low cardiac index, and low venous saturation of oxygen [5]. If changes of the cardiac muscle are deemed reversible, lung transplantation can provide great long-term survival provided proper postoperative management is

*Address correspondence to Magdalena Latos MD, Medical University of Silesia, Silesian Centre for Heart Diseases ul. Marii Skłodowskiej-Curie 9 Pawilon C, 41-800 Zabrze, Poland. Tel: +48667288893. E-mail: latos.magdalena93@gmail.com

0041-1345/20
https://doi.org/10.1016/j.transproceed.2020.02.113

implemented. The heart conditioning after lung transplantation is particularly important, as certain pathophysiological changes must be diminished. Right ventricular hypertrophy with impaired systolic function can lead to right ventricle outflow tract obstruction despite proper fluid repletion. Sudden increase in the left ventricular cardiac output is to be expected, as pulmonary circulation regains proper vessels with low resistance by means of transplantation. However, as the left ventricle was not required to work with such preload for a long period of time before transplantation, it will certainly be dysfunctional after restoration of the proper pulmonary circulation [6]. All those things can lead to pulmonary edema and primary graft dysfunction unless, proper conditioning of the heart is implemented. Such thing can be achieved by concomitant intra- and postoperative use of veno-arterial mode of extracorporeal membrane oxygenation (VA-ECMO) [7]. Intraoperative use of this method was described to provide great results [8,9]. It is also reported that intraoperative use of this device is superior to standard cardiopulmonary bypass [8]. What is more, it was proved that this kind of intraoperative cardiac support presents decreased mortality of the patients when compared with transplantation without any extracorporeal support in this particular underlying disease [10]. What is even more important, prophylactic use of VA-ECMO in the postoperative period is associated with decreased mortality and favorable long-term results [8–13]. This type of treatment was originally proposed by lung transplant centers of Vienna [8,10–12] and Hannover [9,13] and then introduced into our practice. We present initial results of the first Polish experience with this method.

CASE PRESENTATION

This study presents 4 patients with primary pulmonary hypertension. Three patients received double lung transplantations owing to idiopathic pulmonary arterial hypertension. Remaining patient underwent double lung transplantation owing to congenital hypoplasia of pulmonary veins. Among all recipients except patient 3, VA-ECMO was established in the same manner: outflow cannula (venous) was inserted through femoral vein whereas inflow cannula (arterial) was introduced by femoral artery. Peripheral leg perfusion with additional arterial cannula of the lower limb was also implemented as a bypass from arterial cannula to distal part of femoral artery. In case of the first 3 patients, sedation and mechanical ventilation after procedure was maintained for 2 to 3 days during VA-ECMO therapy. Proper fluid repletion, hemostatic control aiming at ACT of 160 to 180 seconds, constant supervision of red blood cells and platelets count (aiming at hematocrit exceeding 35% and platelet count exceeding 100,000 /mL at all times), were crucial during the ECMO treatment.

Patient Number 1

A 48-year-old woman was qualified to be a double lung recipient owing to primary pulmonary hypertension in the course of congenital hypoplasia of the pulmonary veins. Her medical history was significant as she underwent 2 thromboembolic incidents (lower extremity deep vein thrombosis and pulmonary veins thrombosis), as well as such were present among multiple members of her family. Despite pharmacologic treatment, her postcapillary pulmonary hypertension caused a development of right ventricle heart failure. At qualification process, transthoracic echocardiography revealed paradoxical movement of the interventricular septum, right ventricle systolic pressure (RVSP) at 63 mm Hg, tricuspid valve regurgitation, and acceleration time (AcT) of 72 ms. Her right heart catheterization revealed the following: pulmonary artery pressure 59/22/37 mm Hg, mean pulmonary capillary wedge pressure of 23 mm Hg, and pulmonary vascular resistance 3.2 Wood units. She underwent double lung transplantation without any complications. The patient was admitted into the intensive care unit (ICU) sedated, mechanically ventilated, and on VA-ECMO with pump flow support of 3.6 L/min (80% of cardiac output). Twenty-four hours after procedure, ECMO flow was constantly being reduced 0.5l/min every 12 hours as permitted by daily evaluations done during routine echocardiography. ECMO was explanted 3 days after lung transplantation. Full mental capacity was restored 3 days after final weaning off. Three days of such treatment temporarily took a toll on her mental status. Even though she was conscious, it was difficult for her to initiate and maintain verbal contact, as well as her allopsychiatric orientation was disturbed. We assume that constant blood flow provided by ECMO combined with full sedation for several days do not work in the patient's favor. The patient's heart was assessed daily after explantation of VA-ECMO. Three weeks after such treatment, echocardiography was performed in order to assess the cardiac function. Previously described mild tricuspid valve regurgitation subsided. Ejection fraction of the left ventricle (LVEF) was 56% and it was comparable with preoperative echocardiographic assessment. Overall cardiac function was assessed as proper. She was discharged in general good condition. The patient still remains under care of our facility and so far has reached 12-month survival.

Patient Number 2

A 39-year-old woman with advanced form of idiopathic pulmonary arterial hypertension was qualified to be treated by means of lung transplantation. At qualification her mean pulmonary artery pressure during right heart catheterization was 57.3 mm Hg, despite pharmacologic treatment consisting of maximal tolerable doses of prostanoids administered via Hickman catheter and oral therapy of endothelin receptor antagonists and phosphodiesterase 5 inhibitors. During that hospitalization the patient's echocardiography revealed dilated right heart with akinetic interventricular septum, RVSP of 80 mm Hg, tricuspid annular plane systolic excursion (TAPSE) of 11 mm, moderate tricuspid valve regurgitation with annulus of 47 mm wide, as well as excessive fluid in the pericardial sac. She also presented hepatosplenomegaly and systolic murmur over tricuspid valve. Biochemical tests pointed out the significantly elevated NTproBNP (2208 ng/mL), impaired liver function, and thrombopenia. Echocardiography performed at admission for lung transplantation demonstrated findings similar to those at qualification. Furthermore, function of the left heart was also impaired (LVEF 46%). The patient underwent the procedure with intraoperative VA-ECMO. She was admitted to the ICU with VA-ECMO support. Her early postoperative course was complicated with bleeding, which required right re-thoracotomy owing to hematoma of the pleural cavity. In following days, support was gradually weaned off according to daily echocardiographic findings until explantation after 3 days. The patient was sedated and mechanically ventilated during the postoperative ECMO treatment. She regained the full mental capacity after a

week since weaning off. Her neurologic symptoms were similar to those observed in Patient 1. Her cardiac function was assessed daily. Echocardiography performed 3 weeks after the procedure at discharge demonstrated LVEF 50%, normokinesis with improved movement of the interventricular septum, and trace of fluid in the pericardial sac. Tricuspid regurgitation also subsided. She was discharged in general good condition. She remains in our care, and so far she has reached 12-month survival in good general condition. Her late post-transplant course was complicated with bronchial stenoses, which were treated with bronchoscopic interventions. No bronchial stenting was needed.

Patient Number 3

A 40-year old man with advanced form of idiopathic pulmonary arterial hypertension was treated with maximal tolerable doses of endothelin receptor antagonists, prostanoids phosphodiesterase 5 inhibitors. Before admission to lung transplant facility, he was hospitalized for several weeks owing to exacerbation of underlying disease, which required catecholamines as part of the treatment. At admission for lung transplantation, he presented features of severe right heart failure, such as massive ascites, edema of the lower extremities, and central cyanosis. Echocardiography performed the day before transplantation revealed excessive fluid in the pericardial sac, generalized hypokinesis of the left heart with LVEF 40% with RVSP 115 mm Hg, TAPSE 9, diameter of the tricuspid valve annulus 50 mm with central massive regurgitation, and lack of cusps' coaptation. AcT was 54 ms. Right ventricle ejection fraction was also severely impaired. The patient underwent one complex procedure consisting of tricuspid valve plasty using Carpentier-Edwards Classic ring 36 mm followed by double lung transplantation. It should be noted that in order to perform such complex procedure cardiopulmonary bypass circuit (CPB) was implemented into ECMO system, which in this case was enriched with additional venous cannula introduced through right jugular vein and connected with another one coming from femoral vein. A day after the procedure the patient was reoperated on because of significant postoperative bleeding from right pleural cavity. It was the consequence of right internal jugular vein dissection owing to improper percutaneuos introduction of ECMO inflow cannula. VA-ECMO was maintained as a tool of heart conditioning for 6 days after the operation. While on postoperative ECMO, the patient was mechanically ventilated and sedated. Weaning off VA-ECMO itself was uneventful, as well as it was guided by daily echocardiographic evaluation. However, after cessation of sedation the patient presented symptoms of flaccid tetraplegia. Computed tomography and magnetic resonance imaging assessment performed 15 and 45 days after operation respectively, revealed focal lesions of pons and cerebellum, as well as edema of the spinal cord. His neurologic status only slightly improved despite wide spectrum of pharmacologic treatment and extensive physiotherapy. Routine echocardiographic examinations were performed daily. Three weeks after the procedure his LVEF was 36%. General hypokinesis with akinesis of the interventricular septum persisted, whereas the right ventricle had narrow, fissured lumen with significant hypokinesis of the free wall. Severe tricuspid valve regurgitation subsided into a trace. Coexisting infections caused rapid deterioration of his state. He died 85 days after lung transplantation and 79 days after VA-ECMO explantation. This case prompted authors to conduct so-called "awake" ECMO after lung transplantation, aiming to avoid neurologic complications and detect them early.

Patient Number 4

A 20-year-old man with advanced idiopathic pulmonary arterial hypertension was admitted in order to begin qualification process for lung transplantation. Despite maximal tolerable doses of intravenous prostanoid and oral forms of endothelin receptor antagonists and phosphodiesterase 5 inhibitors, the patient presented symptoms of right heart failure such as ascites and central cyanosis. Echocardiography revealed impaired function of the left ventricle (LVEF 47%) with general hypokinesis and dyskinesis of the interventricular septum. There was a trace of mitral valve regurgitation, as well as massive central tricuspid valve regurgitation with lack of cusps' coaptation. Annulus of this valve was 50 mm. However, taking into consideration the patient's height (almost 200 cm), we did not consider performing valvuloplasty during lung transpalntation. RVSP was 100 mm Hg, TAPSE 14 mm, and AcT 54 ms. A significant amount of excessive fluid was depicted in the pericardial sac. Right ventricle was significantly dilated, and its systolic function was defected. Owing to his height it was difficult to find donor lungs. Almost a year after qualification, the patient was admitted as a matching donor was available. At admission, initial echocardiography the day before lung transplantation did not differ much from the aforementioned one from qualification. The patient was fully oxygen dependent and presented dyspnea at the slightest activity. The patient underwent lung transplantation with VA-ECMO as the cardiorespiratory support of choice. During the procedure, there was significant blood loss owing to hypertrophic bronchial arteries and considerable venous blood stasis. The patient was admitted to the ICU with postoperative ECMO while sedated and mechanically ventilated but with intention of rapid implementation of "awake ECMO protocol." A few hours after admission to the ICU, the patient regained consciousness almost immediately after cessation of Propofol. He was extubated a few hours later. He was closely monitored for the possibility of the Harlequin syndrome. In the morning of the second day on VA-ECMO, it was noticeable that oxygen saturation measured on the right hand showed several short moments of desaturation. Immediate chest radiograph and echocardiography revealed the beginning of the pulmonary edema owing to acute mitral valve regurgitation as a result of the widening of its annulus in course of increased preload of the left ventricle. The patient was intubated again and treated accordingly. His consciousness was maintained as small doses of dexmedetomidine were administered to facilitate the presence of the endotracheal tube. During ECMO therapy daily neurologic and echocardiographic checks were performed. Initial ECMO support was 5.2 L/min, which was calculated to be the patient's entire cardiac output. After this event, it was decided to diminish this parameter and to start intravenous infusion of adrenaline in small doses. This decision led to subsiding mitral valve regurgitation, as well as gradual increase of LVEF. Further weaning was carried out under daily echocardiographic evaluation (twice a day) at the average rate of 1 L/min during first day and 0.5 L/min in the remaining days, and was uneventful (except one episode of bleeding from the place of cannulation). VA-ECMO was explanted 6 days after its introduction at support of 2 L/min without complication and with satisfactory cardiac function. Three weeks after transplantation, echocardiography evaluated left ventricle function as satisfactory (LVEF 45%) with general normokinesis and slight mitral regurgitation. Right heart function was also assessed as satisfactory with RVSP of 30 mm Hg. Six weeks after transplantation, the patient's left ventricle systolic function is proper (LVEF 51%), as well as reduction of tricuspid ring's

diameter is present with no tricuspid regurgitation, which justifies our original decision not to correct this valve (see above). Hickman catheter was removed 3 days prior to discharge, at which point the patient presented good tolerance of exercise with no symptoms of cardiac or respiratory dysfunction.

DISCUSSION

Our findings are consistent with the work of Hannover, Vienna, and Toronto centers and confirm that lung transplant recipients owing to severe pulmonary primary hypertension require intraoperative and postoperative prolonged VA-ECMO support [8–13]. An article published by Wisser et al has already described its benefits among patients of the Lung Transplant Program of Vienna in 2001 [14]. Furthermore, the study published by Pereszlenyi et al revealed that the Viennese way of ECMO support concomitant with mechanical ventilation of fully sedated patients has its benefits as well as risks [11]. Four out of 17 patients in their study required re-thoracotomy owing to hemostatic complications of VA-ECMO. We recognized that such problem also was present among our patients. Available literature suggests that up to 50% of patients may experience bleeding events, as well as a smaller percentage might encounter some form of thrombosis [15,16]. According to those studies, targeting a specified activated partial thromboplastin time plays a key role. An Austrian study by Moser et al demonstrated that patients with prolonged VA-ECMO support after bilateral lung transplantation benefit from such strategy in comparison to those, who have ECMO explanted immediately after the procedure [8]. Such finding is supported by a more recent study from the same facility by Hoetzenecker et al [10]. Such treatment provides excellent results with 1-year survival of lung transplant recipients owing to severe pulmonary hypertension exceeding 90%, as reported by Hoeper et al [12]. Austrian experience uses VA-ECMO as prolonged mean of heart conditioning along with mechanical ventilation and sedation. The first 3 patients of our work were also treated this way. As it was described by the authors, certain neurologic aspects of this treatment made us rethink our postoperative ECMO strategy. The German lung transplant facility of Hannover also emphasizes benefits of ECMO, with notable differences being lack of sedation while on ECMO and extubation as soon as possible [9,13]. Such strategy allows for early detection of neurologic complications and does not burden the cerebral function with adverse effects of long-time sedation. Patient number 4 was treated this way with great outcome. Survival rates at 3 and 12 months of patients described by Tudorache et al were 100% and 96%, respectively [13]. Furthermore, other results published from the same German center revealed that proper awake postoperative ECMO management among patients with severe primary pulmonary hypertension produces 5-year survival rates comparable to recipients owing to other underlying diseases [9]. The aforementioned study by Salman et al also presents results suggesting that their strategy also favors achievement of normal cardiac function after lung transplantation.

Tricuspid valve regurgitation among patients with severe pulmonary hypertension can occur in the course of the disease. Its severity correlates with severity of pulmonary arterial hypertension, as well as it is a significant predictor of long-term mortality [17]. Influence of lung transplantation without tricuspid valve plasty on right ventricle function was assessed by Gorter et al [18]. Right ventricular recovery was confirmed by cardiac magnetic resonance imaging. Favorable changes in ejection fraction and muscle mass of both ventricles were noted. The area of the tricuspid valve annulus decreased significantly, as well as no patient experienced this valve regurgitation after lung transplantation. This finding indicates that tricuspid valve plasty is not always necessary among such patients. On the other hand, the study by Shigemura et al assessed that combined tricuspid valve plasty and bilateral lung transplantation were successfully performed without an increase in morbidity or mortality and contributed to decreased primary graft dysfunction [19].

CONCLUSION

This study describes the first Polish experience with consecutive intra- and postoperative prolonged VA-ECMO as a tool of heart conditioning. The first 3 patients were managed in accordance with Viennese protocol (sedated and mechanically ventilated during VA-ECMO). Owing to neurologic complications, the fourth patient was treated with awake ECMO protocol as led by Hannover's example. Lung transplant recipients owing to severe pulmonary primary hypertension undeniably require intraoperative and, what is of utmost importance, postoperative prolonged VA-ECMO support, preferably as they are awake and extubated.

REFERENCES

[1] Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, McGoon MD. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. Chest 2012;142:448–56.

[2] Yusen RD, Christie JD, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, et al. International Society for Heart and Lung Transplantation. The Registry of the International Society for Heart and Lung Transplantation: thirtieth adult lung and heart-lung transplant report–2013; focus theme: age. J Heart Lung Transplant 2013;32:965–78.

[3] Keshavjee S. Lung transplantation for idiopathic pulmonary arterial hypertension: steps in the right direction. Circulation 2013;127:2470–1.

[4] Hill C, Maxwell B, Boulate D, Haddad F, Ha R, Afshar K, et al. Heart-lung vs double-lung transplantation for idiopathic pulmonary arterial hypertension. Clin Transplant 2015;29:1067–75.

[5] Nickel N, Golpon H, Greer M, Knudsen L, Olsson K, Westerkamp V, et al. The prognostic impact of follow-up assessments in patients with idiopathic pulmonary arterial hypertension. Eur Respir J 2012;39:589–96.

[6] Vigneswaran WT, Garrity ER Jr, Odell JA. Lung transplantation for pulmonary hypertension. In: Collaud S, De Perrot M,

editors. Lung transplantation (principles and practice). CRC Press Boca Raton, FL: Taylor and Francis Group; 2016. p. 213–22.

[7] Machuca TN, Collaud S, Mercier O, Cheung M, Cunningham V, Kim SJ, et al. Outcomes of intraoperative extracorporeal membrane oxygenation versus cardiopulmonary bypass for lung transplantation. J Thorac Cardiovasc Surg 2015;149:1152–7.

[8] Moser B, Jaksch P, Taghavi S, Muraközy G, Lang G, Hager H, et al. Lung transplantation for idiopathic pulmonary arterial hypertension on intraoperative and postoperatively prolonged extracorporeal membrane oxygenation provides optimally controlled reperfusion and excellent outcome. Eur J Cardiothorac Surg 2018;53:178–85.

[9] Salman J, Ius F, Sommer W, Siemeni T, Kuehn C, Avsar M, et al. Mid-term results of bilateral lung transplant with postoperatively extended intraoperative extracorporeal membrane oxygenation for severe pulmonary hypertension. Eur J Cardiothorac Surg 2017;52:163–70.

[10] Hoetzenecker K, Schwarz S, Muckenhuber M, Benazzo A, Frommlet F, Schweiger T, et al. Intraoperative extracorporeal membrane oxygenation and the possibility of postoperative prolongation improve survival in bilateral lung transplantation. J Thorac Cardiovasc Surg 2018;155. 2193-206.e3.

[11] Pereszlenyi A, Lang G, Steltzer H, Hetz H, Kocher A, Neuhauser P, et al. Bilateral lung transplantation with intra- and postoperatively prolonged ECMO support in patients with pulmonary hypertension. Eur J Cardiothorac Surg 2002;21:858–63.

[12] Hoeper MM, Benza RL, Corris P, de Perrot M, Fadel E, Keogh AM, et al. Intensive care, right ventricular support and lung transplantation in patients with pulmonary hypertension. Eur Respir J 2019;53.

[13] Tudorache I, Sommer W, Kühn C, Wiesner O, Hadem J, Fühner T, et al. Lung transplantation for severe pulmonary hypertension–awake extracorporeal membrane oxygenation for postoperative left ventricular remodelling. Transplantation 2015;99:451–8.

[14] Wisser W, Marta G, Senbaklavaci O, Neuhauser P, Mares P, Klepetko W. BLTX with intra- and postoperatively prolonged ECMO in patients with pulmonary hypertension: beneficial effect on initial organ function. J Heart Lung Transplant 2001;20:224–5.

[15] Mazzeffi M, Greenwood J, Tanaka K, Menaker J, Rector R, Herr D, et al. Bleeding, transfusion, and mortality on extracorporeal life support: ECLS working group on thrombosis and hemostasis. Ann Thorac Surg 2016;101:682–9.

[16] Sklar MC, Sy E, Lequier L, Fan E, Kanji HD. Anticoagulation practices during venovenous extracorporeal membrane oxygenation for respiratory failure. A systematic review. Ann Am Thorac Soc 2016;13:2242–50.

[17] Chen L, Larsen CM, Le RJ, Connolly HM, Pislaru SV, Murphy JG. The prognostic significance of tricuspid valve regurgitation in pulmonary arterial hypertension. Clin Respir J 2018;12:1572–80.

[18] Gorter TM, Verschuuren EAM, van Veldhuisen DJ, Hoendermis ES, Erasmus ME, Bogaard HJ, et al. Right ventricular recovery after bilateral lung transplantation for pulmonary arterial hypertension. Interact Cardiovasc Thorac Surg 2017;24:890–7.

[19] Shigemura N, Sareyyupoglu B, Bhama J, Bonde P, Thacker J, Bermudez C, et al. Combining tricuspid valve repair with double lung transplantation in patients with severe pulmonary hypertension, tricuspid regurgitation, and right ventricular dysfunction. Chest 2011;140:1033–9.