

### Peripheral veno-arterial extracorporeal membrane oxygenation during lung transplantation with special reference to differential hypoxemia and vascular complications

#### Norihisa Shigemura, Hiromu Kehara, Yoshiya Toyoda

Division of Cardiovascular Surgery, Lewis Katz School of Medicine, Temple University Health System, Philadelphia, PA, USA Correspondence to: Norihisa Shigemura, MD, PhD. Division of Cardiovascular Surgery, Lewis Katz School of Medicine, Temple University Health System, N Broad Street, Philadelphia, PA 19140, USA. Email: Norihisa.Shigemura@tuhs.temple.edu.

Keywords: Lung transplantation; peripheral arterial disease (PAD); computed tomography scans of the abdomen and pelvis (CTAP); extracorporeal membrane oxygenation (ECMO); abdominal aortic aneurysm (AAA)

Submitted Oct 25, 2023. Accepted for publication Dec 19, 2023. Published online Jan 09, 2024.

View this article at: https://dx.doi.org/10.21037/jtd-23-1630

doi: 10.21037/jtd-23-1630

#### Introduction

In clinical lung transplantation, the role of intraoperative mechanical circulatory support (MCS) cannot be overemphasized, as it impacts transplant outcomes in multiple ways. Although it is difficult to conclude which MCS options are optimal without a randomized controlled trial with an intention-to-treat breakdown, robust data strongly support veno-arterial extracorporeal membrane oxygenation (VA ECMO) for MCS during lung transplantation (1,2).

As proponents of liberal VA ECMO use during lung transplant procedures at a high-volume transplant center, we believe that this option contributes to optimal allograft protection during the procedure and ultimately leads to improved posttransplant outcomes. The potential benefits of peripheral VA ECMO have been understated, and its potential pitfalls, which include differential hypoxemia and ECMO cannulation-associated peripheral vascular complications, have not been duly discussed. In this review, we detail our latest insights on the peripheral VA ECMO approach. Through presentation of our original data, we also highlight the solid strategy of using a peripheral VA ECMO approach for MCS combined with minimally invasive, antero-lateral thoracotomy surgical approach for lung transplant. This strategy is particularly useful for highrisk or elderly patients in light of the unique challenges and

limitations associated with geriatric lung transplantation.

#### **VA ECMO** as MCS during lung transplantation

Increasing evidence has demonstrated that VA ECMO is a superior modality to full cardiopulmonary bypass for intraoperative MCS during lung transplant procedures (3,4). Cannulation for VA ECMO can be performed centrally or peripherally. Central cannulation, which enables better blood drainage and avoids peripheral cannulation-related complications, has been preferred; however, bleeding complications from central cannulation sites are not negligible. In addition, in patients with suppurative lung diseases with extensive pleural and mediastinal involvement, such as complex cystic fibrosis, central cannulation should be avoided due to concerns that contamination of the cannulation sites and circuits may precipitate bacteremia or microaneurysm in immunosuppressed patients. In contrast, peripheral cannulation through the common femoral artery and femoral vein, separate and apart from chest exploration, can alleviate such concerns. Additionally, it may help surgeons focus on challenges in the chest with exposure that is not disturbed by cannulas or cannulationassociated complications, in particular when antero-lateral thoracotomy approach is routinely used for minimally invasive transplant as it is at our center, as these are safely established in the groin in a separate manner.

# Preoperative computed tomography (CT) assessment plays a key role in preventing peripheral vascular complications and determining optimal MCS approach during lung transplantation

The use of peripheral arterial access through groin for VA ECMO is increasing due in part to the recent advent of minimally invasive cardiac surgical interventions. In 2017, based on our extensive experience caring for older patients with end-stage lung disease who are often found to have concurrent peripheral arterial disease (PAD), we implemented a pretransplant assessment of PAD with CT scans of the abdomen and pelvis (CTAP) for all lung transplant candidates over 65 years of age and for younger candidates with outstanding cardiovascular or metabolic comorbidities. Our CTAP assessment for PAD utilizes a semi-quantitative 5-point scale to classify vascular calcifications over the distal aorta, common iliac artery, external iliac artery, and common femoral arteries, ranging from absent or minimal calcifications to severe diffuse calcification using criteria established previously (5). Then, we stratified the patients into two groups based on the vascular calcification scores: low calcification (score 1–2) and high calcification (score 3–5). Additionally, patients who had an abdominal aortic aneurysm (AAA) or an iliac artery aneurysm (IAA) were identified using the same CT images. AAA and IAA were defined as vessels with a maximal diameter of >30 mm for AAA and >20 mm for IAA in axial CT image slices.

#### PAD

When PAD was quantified in 130 lung transplant patients over 70 years of age who underwent lung transplantation at our center between January 2018 and December 2020, 44% of the patients (57/130) had high vascular calcification scores, and the remaining 73 patients (56%) had low calcification scores. When comparing baseline clinical characteristics between the two groups (*Table 1*), lung transplant recipients with high calcification scores exhibited a higher prevalence of coronary artery disease (42.1% vs. 16.4%, P<0.05), a history of smoking (89.5% vs. 75.3%, P<0.05), and coexisting AAA or IAA (15.8% vs. 2.7%, P<0.05). Survival in high score group 1, and 3 years was 78.8%±5.4%, and 60.7%±8.0%, respectively, and the corresponding survival in low score group was 90.3%±3.5%, and 65.6%±7.5%, respectively. The 1-year survival was remarkably worse in

the high score group than in the low score group, however, survival conditional on hospital survivor appears to be comparable between the two groups. Of note, PAD with a high calcification score was identified as a significant risk factor associated with 1-year mortality following lung transplantation in this patient cohort. Thus, our findings with this newly implemented evaluation process using CTAP reaffirmed the importance of stratifying risks associated with PAD that can negatively impact outcomes after a lung transplant.

Although peripheral VA ECMO access through groin using the common femoral artery and femoral vein is less invasive and more common than central VA ECMO, literature addressing procedure-associated complications and the potentially detrimental effects of peripheral VA ECMO on the eventual surgical outcomes is scarce (6). An objective assessment using CTAP images and a vascular calcification scoring system helps identify patients at highrisk for such complications and more importantly, helps us minimize the risks by preemptively avoiding peripheral access and proactively choosing safer sites for ECMO or cardiopulmonary bypass cannulation. We avoided peripheral cannulation for MCS during the lung transplant procedure in the three patients in this study with pre-existing severe PAD noted on CTAP to reduce the associated risks. Because all enrolled patients underwent CTAP assessment in this study, we could not formally determine the impact of preoperative CT assessment on the outcomes where the differences between patients with high calcification scores and patients with low scores were smaller than expected. This might be attributed to the contribution of the CTAP assessment to avoiding procedure-associated risks and selecting the best approach for each lung transplant procedure.

In basic science studies, remote ischemic preconditioning is a well-established mechanism that can attenuate injuries associated with ischemia and reperfusion (7,8). In solid organ transplantation, this concept has been eagerly applied for therapeutic purposes to mitigating ischemia-reperfusion injury in organ allografts (9,10). Although one might expect that the pre-existing ischemia associated with PAD may decrease the incidence of primary graft dysfunction after lung transplantation, our data do not support this expectation, and we have observed poorer lung allograft function in patients with severe PAD than in other patients. We speculate that atherosclerotic occlusive diseases, such as PAD, give rise to chronic tissue ischemia/hypoxia and upregulation of proangiogenic factors, such as vascular

Table 1 Recipient characteristics with low vs. high calcification scores among those with PAD

Variables	Low calcification (n=73)	High calcification (n=57)	P value
Age (years)	73 [70–80]	72 [70–79]	0.363
Sex			0.797
Male	51 (69.9)	41 (71.9)	
Female	22 (30.1)	16 (28.1)	
Body mass index (kg/m²)	28.0 [18.8–35.4]	27.3 [18.0–34.4]	0.589
Diabetes mellitus	9 (12.3)	10 (17.5)	0.404
Coronary artery disease	12 (16.4)	24 (42.1)	0.001
Smoking history	55 (75.3)	51 (89.5)	0.039
Baseline creatinine (mg/dL)	0.86 [0.23–1.63]	0.90 [0.30–1.59]	0.634
Diagnosis			0.069
Chronic obstructive pulmonary disease	15 (20.5)	21 (36.8)	
Idiopathic pulmonary fibrosis	55 (75.3)	32 (56.1)	
Other	3 (4.1)	4 (7.0)	
O <sub>2</sub> support (L/min)	4 [0–60]	4 [0–40]	0.352
Ventilator	1 (1.4)	1 (1.8)	>0.99
ECMO	0	0	-
6-minute walk distance (feet)	787 [0–2,000]	787 [0–1,771]	0.749
Mean pulmonary artery pressure (mmHg)	24 [0–55]	25 [0–60]	0.213
Lung allocation score	36.5 [30.0–87.9]	35.2 [26.9–87.0]	0.397
Prednisone ≥10 mg	25 (34.2)	14 (24.6)	0.232
AAA or IAA	2 (2.7)	9 (15.8)	0.011

Continuous variables are shown as median [range]; categorical variables are shown as absolute n (%). PAD, peripheral arterial disease; ECMO, extracorporeal membrane oxygenation; AAA, abdominal aortic aneurysm; IAA, iliac artery aneurysm.

endothelial factor (11,12), which may contribute to graft dysfunction by strongly inducing vascular permeability in the lungs (13).

#### AAA and IAA

Routine CTAP assessment revealed higher incidental findings of AAA among patients with preexisting PAD. According to current recommendations for AAA treatment, patients with an AAA with a maximum diameter >54 mm and patients with outstanding symptoms should be considered for aneurysm repair surgery. Surveillance is recommended for patients with smaller aneurysms (14). In addition to maximum diameter, other factors, such as saccular shape (15), rapid expansion (16), and PAD (17)

have been identified as risk factors for aneurysm rupture. In the context of lung transplantation, anesthesia management during the procedure is challenging due to unavoidable hypotension caused by reperfusion after implanting the donor lung allografts. This necessitates the subsequent use of vasopressors and inotropes that may lead to rebound hypertension (18,19). Major concerns remain as to whether these blood pressure swings place an excessive burden on the aneurysmal wall.

In our series, 2 of the 11 patients identified with AAA or IAA on CTAP died due to aneurysm rupture and hemorrhagic shock during hospital admission. Notably, both had PAD, as indicated by high vascular calcification scores, and were asymptomatic preoperatively with aneurysm sizes of 40 mm (AAA) and 26 mm (IAA). Their

**Table 2** Differential hypoxemia during lung transplantation with peripheral VA ECMO and that severity

Differential hypoxemia with VA ECMO	Value (n=78)	
No	49 [63]	
Yes <sup>†</sup>	29 [37]	
Mild (SpO $_2$ <80% and duration <10 min)	18 [23]	
Moderate (40%≤ SpO <sub>2</sub> <80% and duration ≥10 min)	7 [9]	
Severe (SpO₂ <40% and duration ≥10 min)	4 [5]	

Values are presented as n [%].  $^{\dagger}$ , differential hypoxemia was defined as the lowest SpO<sub>2</sub> value at right upper extremity is less than 80%. The duration of the SpO<sub>2</sub> is less than 80% was also recorded. VA ECMO, veno-arterial extracorporeal membrane oxygenation; SpO<sub>2</sub>, saturation of peripheral oxygen.

initial postoperative course was uneventful until they experienced acute onset hemodynamic compromise leading to shock, then died immediately despite all cardiopulmonary resuscitation attempts including urgent bedside VA ECMO institution. Our experience in patients with PAD and concurrent AAA strongly advocates that, although pre-existing AAA may not be prohibitive for a life-saving lung transplant, the potential for complications should not be underestimated. These patients should undergo transplantation at an experienced center equipped to duly handle their potentially complicated recovery. Additionally, there are many reports describing the rapid growth of AAAs after solid organ transplantation (20-22). Immunosuppressive drugs may play a role in the rapid growth of an aneurysm posttransplant, and regular followup is necessary after any organ transplant.

## Differential hypoxemia (Harlequin syndrome) during lung transplantation

Differential hypoxemia, also widely known as Harlequin syndrome or north-south syndrome is a more recently recognized clinical problem associated with VA ECMO but has been rarely reported or debated in the context of lung transplantation. Harlequin syndrome is hypoxemia of the upper body due to low oxygenation of the blood from the lungs while the lower body is well perfused through peripheral ECMO from the femoral artery (23-25). In the intensive care unit (ICU), this unique phenomenon is often witnessed when the heart recovers from cardiogenic shock with VA ECMO support while the lungs remain compromised with poor gas exchange (25). It is also often

recognized among patients in the Intensive care units (ICUs) with advanced lung disease who have normal left ventricular function on VA ECMO.

Although this phenomenon is well-documented in the ICU, it is not well-studied in the operating room, because peripheral VA ECMO is not the standard MCS for any elective cardiac or thoracic procedures. Cardiac anesthesiologists who do not routinely manage lung transplantation may be overwhelmed by this phenomenon, leading to suboptimal management (24).

Because VA ECMO is more frequently used for MCS during lung transplantation at our institution, we analyzed the incidence of differential hypoxemia during lung transplant surgery. Among our 78 patients who underwent lung transplantation with peripheral VA ECMO, 37% of the patients developed differential hypoxemia during the procedure, whereas 63% remained stable without hypoxemic episodes meeting the standardized diagnostic criteria (Table 2). Among patients who developed differential hypoxemia, hypoxemia was mild in most patients (62%); 7 patients (24%, 7/29) were classified as having moderate hypoxemia and 4 (14%, 4/29) had severe hypoxemia. It should be noted that no serious neurological consequences resulted from the incidents of differential hypoxemia, and all the patients, including those with severe differential hypoxemia during transplant, were discharged from hospital uneventfully following lung transplantation. Because there have been no prior studies of differential hypoxemia during lung transplant or any other cardiothoracic surgical procedures, this 37% incidence of differential hypoxemia when using VA ECMO as intraoperative MCS awaits further validation with additional data from other centers.

# The ultimate impact of minimally invasive surgery and selection of MCS on long-term outcomes after lung transplantation

When combined with a minimally invasive surgical approach using antero-lateral thoracotomy, MCS with VA ECMO can help minimize the surgical burden during lung transplantation procedures. The indications for MCS using VA ECMO can be further extended, particularly in elderly and high-risk patients. While peripheral VA ECMO is an effective option for intraoperative MCS during lung transplantation, the pitfalls detailed in this review should be well understood. Geriatric lung transplantation presents unique challenges because pre-existing comorbidities in older patients must be considered where our transplant

program is currently working to strive for further progress in the future of lung transplantation (26). Some challenges can be primarily attributed to post-transplant management, in particular those associated with the current immunosuppression regimen including renal and metabolic toxicities. Thus, minimizing the surgical burden in elderly patients may not necessarily lead to optimal surgical outcomes. Further studies are warranted to unveil the interplay between lung transplantation and the aging process.

#### **Acknowledgments**

We thank Ashley Johnson Whiting from Temple University Hospital for collecting data and Shannon Wyszomierski for editing the manuscript. *Funding*: None.

#### **Footnote**

Provenance and Peer Review: This article was commissioned by the editorial office, Journal of Thoracic Disease. The article has undergone external peer review.

*Peer Review File*: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1630/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1630/coif). N.S. serves as an unpaid editorial board member of Journal of Thoracic Disease from September 2023 to August 2025. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work and ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was reviewed by the Temple University Institutional Review Board on January 3, 2022 (protocol number: 29028), and the requirement for individual consent for this retrospective analysis was waived.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-

commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

#### References

- Expert Consensus Panel; Hartwig M, van Berkel V, et al.
   The American Association for Thoracic Surgery (AATS)
   2022 Expert Consensus Document: The use of mechanical circulatory support in lung transplantation. J Thorac
   Cardiovasc Surg 2023;165:301-26.
- Hoetzenecker K, Schwarz S, Muckenhuber M, et al.
   Intraoperative extracorporeal membrane oxygenation and the possibility of postoperative prolongation improve survival in bilateral lung transplantation. J Thorac Cardiovasc Surg 2018;155:2193-2206.e3.
- Biscotti M, Yang J, Sonett J, et al. Comparison of extracorporeal membrane oxygenation versus cardiopulmonary bypass for lung transplantation. J Thorac Cardiovasc Surg 2014;148:2410-5.
- Machuca TN, Collaud S, Mercier O, et al. Outcomes of intraoperative extracorporeal membrane oxygenation versus cardiopulmonary bypass for lung transplantation. J Thorac Cardiovasc Surg 2015;149:1152-7.
- Lockhart ME, Robbin ML, McNamara MM, et al. Association of pelvic arterial calcification with arteriovenous thigh graft failure in haemodialysis patients. Nephrol Dial Transplant 2004;19:2564-9.
- Wong JK, Melvin AL, Joshi DJ, et al. Cannulation-Related Complications on Veno-Arterial Extracorporeal Membrane Oxygenation: Prevalence and Effect on Mortality. Artif Organs 2017;41:827-34.
- 7. Wolfrum S, Schneider K, Heidbreder M, et al. Remote preconditioning protects the heart by activating myocardial PKCepsilon-isoform. Cardiovasc Res 2002;55:583-9.
- 8. Kharbanda RK, Mortensen UM, White PA, et al. Transient limb ischemia induces remote ischemic preconditioning in vivo. Circulation 2002;106:2881-3.
- Farooqui W, Pommergaard HC, Rasmussen A. Remote ischemic preconditioning of transplant recipients to reduce graft ischemia and reperfusion injuries: A systematic review. Transplant Rev (Orlando) 2018;32:10-5.
- 10. Lin E, Snell GI, Levvey BJ, et al. Safety, feasibility, and effect of remote ischemic conditioning in patients undergoing lung transplantation. J Heart Lung Transplant 2014;33:1139-48.

- Findley CM, Mitchell RG, Duscha BD, et al. Plasma levels of soluble Tie2 and vascular endothelial growth factor distinguish critical limb ischemia from intermittent claudication in patients with peripheral arterial disease. J Am Coll Cardiol 2008;52:387-93.
- 12. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. Nat Med 2003;9:669-76.
- Zhou W, Liu K, Zeng L, et al. Targeting VEGF-A/ VEGFR2 Y949 Signaling-Mediated Vascular Permeability Alleviates Hypoxic Pulmonary Hypertension. Circulation 2022;146:1855-81.
- Chaikof EL, Dalman RL, Eskandari MK, et al. The Society for Vascular Surgery practice guidelines on the care of patients with an abdominal aortic aneurysm. J Vasc Surg 2018;67:2-77.e2.
- Vorp DA, Raghavan ML, Webster MW. Mechanical wall stress in abdominal aortic aneurysm: influence of diameter and asymmetry. J Vasc Surg 1998;27:632-9.
- Limet R, Sakalihassan N, Albert A. Determination of the expansion rate and incidence of rupture of abdominal aortic aneurysms. J Vasc Surg 1991;14:540-8.
- 17. Crawford JD, Chivukula VK, Haller S, et al. Aortic outflow occlusion predicts rupture of abdominal aortic aneurysm. J Vasc Surg 2016;64:1623-8.
- Miranda A, Zink R, McSweeney M. Anesthesia for lung transplantation. Semin Cardiothorac Vasc Anesth 2005;9:205-12.
- 19. Kachulis B, Mitrev L, Jordan D. Intraoperative anesthetic

Cite this article as: Shigemura N, Kehara H, Toyoda Y. Peripheral veno-arterial extracorporeal membrane oxygenation during lung transplantation with special reference to differential hypoxemia and vascular complications. J Thorac Dis 2024;16(1):798-803. doi: 10.21037/jtd-23-1630

- management of lung transplantation patients. Best Pract Res Clin Anaesthesiol 2017;31:261-72.
- 20. Lokanathan R, Taylor DC. Abdominal aortic aneurysm after pulmonary transplantation: a case report. J Vasc Surg 2000;31:585-8.
- 21. Dasari T, Heroux A, Peyton M, et al. Abdominal aortic aneurysms (AAA) post heart transplantation: a systematic review of literature. Ann Transplant 2011;16:147-52.
- Machado R, Antunes I, Oliveira P, et al. Impact of Endovascular Aortic Aneurysm Repair in a Renal Transplantation Program. Ann Vasc Surg 2016;36:290. e15-23.
- 23. Rupprecht L, Lunz D, Philipp A, et al. Pitfalls in percutaneous ECMO cannulation. Heart Lung Vessel 2015;7:320-6.
- Ghalayini M, Brun PY, Augustin P, et al. Esmolol Corrects Severe Hypoxemia in Patients with Femoro-Femoral Venoarterial Extracorporeal Life Support for Lung Transplantation. J Extra Corpor Technol 2016;48:113-21.
- Prisco AR, Aguado-Sierra J, Butakoff C, et al. Concomitant Respiratory Failure Can Impair Myocardial Oxygenation in Patients with Acute Cardiogenic Shock Supported by VA-ECMO. J Cardiovasc Transl Res 2022;15:217-26.
- Shigemura N, Toyoda Y. Elderly patients with multiple comorbidities: insights from the bedside to the bench and programmatic directions for this new challenge in lung transplantation. Transpl Int 2020;33:347-55.