Editorial Commentary

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

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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 high-risk 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 cannulation-associated 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 high-risk 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/m^2)	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_2 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[†]	29 [37]
Mild (SpO_2 <80% and duration <10 min)	18 [23]
Moderate (40%≤ SpO_2 <80% and duration ≥10 min)	7 [9]
Severe (SpO_2 <40% and duration ≥10 min)	4 [5]

Values are presented as n [%]. [†], differential hypoxemia was defined as the lowest SpO_2 value at right upper extremity is less than 80%. The duration of the SpO_2 is less than 80% was also recorded. VA ECMO, veno-arterial extracorporeal membrane oxygenation; SpO_2, 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 follow-up 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.

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