Bridging Children to Lung Transplantation Using Extracorporeal Membrane Oxygenation

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Bridging patients to lung transplant with mechanical ventilatory support has been a long-standing practice, albeit one with an established risk of increased mortality compared with those bridged without support (1). Extracorporeal membrane oxygenation (ECMO) as an alternative bridge to transplant was generally avoided because of poor outcomes (2), but in 2005 the Lung Allocation Score (LAS) was adopted for children 12 years and older, reducing the potential waiting time, such that ECMO as a bridge became more feasible (3). Coupled with the development of double-lumen catheters and ambulatory ECMO strategies, venovenous ECMO has become an accepted tool to bridge adult candidates to lung transplant (4). Previous work reviewing data from the Organ Procurement and Transplantation Network (OPTN) registry did not identify a difference in survival among children (<18 yr old) (5) or adolescents (12–17 yr old) (6) bridged to lung transplant with ECMO compared with those receiving a lung transplant without ECMO as a bridge.

In this issue of *AnnalsATS*, Thompson and colleagues (pp. 415–423) report the outcomes of children who received ECMO as a bridge to lung transplant (7). The study was a retrospective analysis of the OPTN registry that reported 1- and 5-year survival for children <21 years old who received a lung transplant between 2004 and 2019 (7). Outcomes were compared among three groups: those bridged to lung transplant with ECMO support (with or without mechanical ventilation), mechanical ventilation (without ECMO), or neither (7).

The authors reported that, although at hospital discharge patients bridged to lung transplant with ECMO had an associated increased risk of mortality, long-term survival of children receiving ECMO as a bridge to lung transplant was comparable to those who required neither ECMO nor ventilatory support (7). The 1-month Kaplan-Meier estimated survival after lung transplant was 88% (95% confidence interval [CI], 78–94%) for children bridged to transplant with ECMO compared with 97% (95% CI, 96–98%) among children not requiring ECMO or mechanical ventilation. At 1 year, a stable difference in survival persisted between the two groups: 84% (95% CI, 72–91%) among ECMO-supported patients versus 92% (95% CI, 90–94%) among patients not requiring life support. At 5 years post-transplant, both groups had an estimated survival of approximately 50%. This suggests that children bridged to lung transplant with ECMO initially have a higher pretransplant severity of illness that confers a short-term risk of increased mortality, but over the medium to long term the difference stabilizes and then dissipates. This is further supported by the authors' finding that children who were bridged to lung transplant with mechanical ventilation (but without ECMO) had comparable survival at 1 month, 1 year, and 5 years post lung transplant to children bridged to lung transplant with ECMO.

Over the 15-year course of the study, only 68 children (6.7%) received ECMO as a bridge to transplant, but approximately 80% were adolescents or young adults and 31 (46%) were between 18 and 21 years old. Nonetheless, the proportion of children receiving ECMO as a bridge to transplant increased from 0% in 2004 to 16.7% in 2018, similar to adult lung transplant patients (8). Although the rarity of ECMO as a bridge to lung transplant and its relative growth is expected, the very limited number of patients in a national registry reinforces the importance of multicenter collaborative research to assist lung transplant centers in identifying candidates for ECMO bridging to lung transplant.

Some of the limitations of the current work also serve as a reminder that existing lung transplant registries (e.g., OPTN Database or the International Society for Heart and Lung Transplantation Registry) are missing key data elements to inform the best strategies of ECMO support in bridge to lung transplantation. For example, the present study did not report on ECMO cannulation strategies, which may considerably affect the risk and outcome profile, or what proportion of patients who

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received ECMO were awake and active. One of the benefits of ECMO as a bridge to lung transplant is that it can enable the cessation of sedation, removal of the endotracheal tube, and active rehabilitation (1, 9). Many of these gaps could be addressed by merging transplant and ECMO registries, as has been previously done for pediatric heart transplantation (10). Future studies should also consider cannulation strategies that are most likely to facilitate active rehabilitation and potentially reduce complications while awaiting transplantation. Some examples might include dual-lumen right internal jugular cannulas that drain blood from the right atrium and reinfuse it into the pulmonary artery, thus providing mechanical right ventricular support as well as extracorporeal gas exchange; tunneling the ECMO cannula to reduce the risk of infection; or surgically implanting a paracorporeal oxygenator (11).

Also, because lung transplant registries naturally only include patients who receive lung transplants, it is difficult to know what might happen to similar patients who did not receive transplants. Future work with combined lung transplant and ECMO registries may help address the urgent need to identify candidates who are most likely to be successfully bridged to transplant.

Regarding candidacy, only 10% (7/68) with ECMO support as a bridge to lung transplant had pneumonia or acute respiratory distress syndrome (ARDS) (7), but this may become increasingly relevant as a result of the coronavirus disease (COVID-19) pandemic. There have been early reports in COVID-19 of using ECMO as a bridge to lung transplant (12). A difficult question in acute lung disease, such as ARDS, is when to transition the goal of ECMO from a bridge to recovery to a bridge to transplant. It is unknown which children will recover after prolonged ECMO support (13). Children requiring ECMO support for ARDS likely have an in-hospital mortality risk of 30–40%, but most who survive to hospital discharge are anticipated to have long-term survival (14). Conversely, none of the 7 children receiving a lung transplant for pneumonia or ARDS died before hospital discharge, but the mortality at 5 years after transplant was 50% (7). The most common cause of death beyond the first year after pediatric lung transplant is chronic lung allograft dysfunction (15). Expectant waiting for recovery may also carry attendant risks, because increasing ECMO support days are associated with increasing complications (16), although Thompson and colleagues were unable to demonstrate an association between the duration of ECMO (per day or in patients with >30 d of ECMO) and death at hospital discharge after lung transplant (7). Nonetheless, it is important to note that although the LAS makes access to donor organs in 2–4 weeks feasible for adolescents and adults on ECMO in the United States, for children <12 years old the LAS does not apply, which can lead to much longer waitlist times. These prolonged waitlist times may contribute to the low transplant numbers observed in preadolescent children.

This study reinforces both that ECMO can bridge children to lung transplant with long-term outcomes that are comparable to lung transplant without ECMO and that early mortality remains higher because the patients are critically ill at the time of lung transplant. As the authors indicate, this study also highlights the need to better understand how patients should be selected and cared for when considering ECMO as bridge to transplant. That research will undoubtedly require large multicenter collaborative research and will be most efficient if it can rely on merging existing registries. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1 Fuehner T, Kuehn C, Hadem J, Wiesner O, Gottlieb J, Tudorache I, *et al.* Extracorporeal membrane oxygenation in awake patients as bridge to lung transplantation. *Am J Respir Crit Care Med* 2012;185:763–768.

2 Puri V, Epstein D, Raithel SC, Gandhi SK, Sweet SC, Faro A, *et al.* Extracorporeal membrane oxygenation in pediatric lung transplantation. *J Thorac Cardiovasc Surg* 2010;140:427–432.

3 Lancaster TS, Miller JR, Epstein DJ, DuPont NC, Sweet SC, Eghtesady P. Improved waitlist and transplant outcomes for pediatric lung transplantation after implementation of the lung allocation score. *J Heart Lung Transplant* 2017;36:520–528.

4 Gulack BC, Hirji SA, Hartwig MG. Bridge to lung transplantation and rescue post-transplant: the expanding role of extracorporeal membrane oxygenation. *J Thorac Dis* 2014;6:1070–1079.

5 Hayes D Jr, McConnell PI, Tobias JD, Whitson BA, Preston TJ, Yates AR, *et al.* Survival in children on extracorporeal membrane oxygenation at the time of lung transplantation. *Pediatr Transplant* 2015;19:87–93.

6 Sainathan S, Ryan J, Sharma M, Harano T, Morell V, Sanchez P. Outcome of bridge to lung transplantation with extracorporeal membrane oxygenation in pediatric patients 12 years and older. *Ann Thorac Surg* 2021;112:1083–1088.

7 Thompson K, Staffa SJ, Nasr VG, Zalieckas JM, Fynn-Thompson F, Boyer D, *et al.* Mortality after lung transplantation for children bridged with extracorporeal membrane oxygenation. *Ann Am Thorac Soc* 2022;19:415–423.

8 Mason DP, Thuita L, Nowicki ER, Murthy SC, Pettersson GB, Blackstone EH. Should lung transplantation be performed for patients on mechanical respiratory support? The US experience. *J Thorac Cardiovasc Surg* 2010;139:765–773.e1.

9 Rehder KJ, Turner DA, Hartwig MG, Williford WL, Bonadonna D, Walczak RJ Jr, *et al.* Active rehabilitation during extracorporeal membrane oxygenation as a bridge to lung transplantation. *Respir Care* 2013;58:1291–1298.

10 Almond CS, Singh TP, Gauvreau K, Piercey GE, Fynn-Thompson F, Rycus PT, *et al.* Extracorporeal membrane oxygenation for bridge to heart transplantation among children in the United States: analysis of data from the Organ Procurement and Transplant Network and Extracorporeal Life Support Organization Registry. *Circulation* 2011; 123:2975–2984.

11 Hoganson DM, Gazit AZ, Boston US, Sweet SC, Grady RM, Huddleston CB, *et al.* Paracorporeal lung assist devices as a bridge to recovery or lung transplantation in neonates and young children. *J Thorac Cardiovasc Surg* 2014;147:420–426.

12 Bharat A, Machuca TN, Querrey M, Kurihara C, Garza-Castillon R Jr, Kim S, *et al.* Early outcomes after lung transplantation for severe COVID-19: a series of the first consecutive cases from four countries. *Lancet Respir Med* 2021;9:487–497.

13 Nelson-McMillan K, Vricella LA, Stewart FD, Young J, Shah AS, Hibino N, *et al.* Recovery from total acute lung failure after 20 months of extracorporeal life support. *ASAIO J* 2020;66:e11–e14.

14 Barbaro RP, Xu Y, Borasino S, Truemper EJ, Watson RS, Thiagarajan RR, *et al.*; RESTORE Study Investigators. Does extracorporeal membrane oxygenation improve survival in pediatric acute respiratory failure? *Am J Respir Crit Care Med* 2018;197: 1177–1186.

15 Hayes D Jr, Cherikh WS, Chambers DC, Harhay MO, Khush KK, Lehman RR, *et al.*; International Society for Heart and Lung Transplantation. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: twenty-second pediatric lung and heart-lung transplantation report-

2019; Focus theme: donor and recipient size match. *J Heart Lung Transplant* 2019;38:1015–1027.
16 Dalton HJ, Reeder R, Garcia-Filion P, Holubkov R, Berg RA, Zuppa A, *et al.*; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network. Factors associated with bleeding and thrombosis in children receiving extracorporeal membrane oxygenation. *Am J Respir Crit Care Med* 2017;196:762–771.

Give the Kidneys a Good Night of Sleep

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Chronic kidney disease is a growing public health problem that affects 9.1% of the world population (1), including 37 million people in the United States (2). Chronic kidney disease is predominantly diagnosed and classified based on estimated glomerular filtration rate and urine albumin excretion (3). Albuminuria may be the first clinical manifestation of chronic kidney disease, and in glomerular diseases such as diabetic kidney disease, albuminuria usually presents before the reduction in glomerular filtration rate (4). Furthermore, albuminuria is associated with underlying hypertension and obesity and is a well-established risk factor for chronic kidney disease progression and cardiovascular events (3).

Over the past two decades, there have been significant advances in our understanding of mechanisms associated with the progression of chronic kidney disease, including genetic, behavioral, metabolic, and other novel risk factors (5). However, despite the high prevalence of sleep disorders among patients with chronic kidney disease, the association between sleep disorders and early markers of kidney disease such as albuminuria remains understudied. In the general population, the prevalence of sleep disordered breathing is estimated to be 10%. Among patients with chronic kidney disease, prevalence estimates are much higher, ranging from 25% in patients with early stages of kidney disease to 70% among patients with end-stage kidney disease. Of note, this finding does not seem to be explained by known factors such as age, body mass index (BMI), or other comorbidities (6). Therefore, there is a critical need to better understand the association between sleep disorders and chronic kidney disease.

Prior studies have reported significant associations between prevalent sleep disordered breathing and albuminuria in diverse community-based cohorts (7, 9, 10), as well as among patients with diabetes (6) and hypertension (7). In this issue of *AnnalsATS*, Murase and colleagues (pp. 451–461) report the results of a large community-based (8), cross-sectional study evaluating the association between sleep disordered breathing, blood pressure, and albuminuria. They evaluated more than 6,000 individuals enrolled in the Nagahama study who wore a wrist actigraph for at least 5 days and a pulse oximeter for at least 2 days and provided a spot urine sample for measurement of urine albumin to creatinine ratio. In addition, a subset of participants (5,313) underwent daytime and nighttime home blood pressure measurements to evaluate blood pressure as a potential mediator of the association between sleep disordered breathing and albuminuria. Patients with end-stage kidney disease, those with active malignancy, and those receiving treatment for sleep disordered breathing were excluded from the study. Sleep disordered breathing was defined using the actigraphy-modified 3% oxygen desaturation index (ODI) and the cumulative percentage of sleep time with oxygen saturation $<90\%$. At study entry, the mean age of participants was 58 years, 67% were women, 35% had hypertension, 6.5% had diabetes, and the mean BMI was 22 kg/m^2.

In this study, moderate to severe sleep disordered breathing (defined as ODI ≥ 15) was found in 12.4% of participants, and moderately increased albuminuria (defined as urine albumin to creatinine ratio 30–299 mg/g) in 7.0%. Albuminuria was higher among individuals with moderate to severe sleep disordered breathing compared with those with mild (ODI 5 to <15) or no sleep disordered breathing (ODI < 5). After adjusting for the presence of obesity, hypertension, and diabetes, individuals with moderate to severe sleep disordered breathing had higher odds of albuminuria (odds ratio, 1.90; 95% confidence interval [CI], 1.36–2.65). Furthermore, mediation analysis revealed that systolic blood pressure (measured in the morning and during sleep) explained 28.3% (95% CI, 14.9–41.7%) of the association between sleep disordered breathing and albuminuria, suggesting that other mechanistic pathways might be involved.

Interestingly, Murase and colleagues did not find a significant association between the cumulative percentage of sleep time with oxygen saturation less than 90% and

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