Get Fit for Lung Transplant With Ambulatory Extracorporeal Membrane Oxygenation!

Organ allocation for lung transplant is currently determined by severity of disease and predicted post-transplant survival.[1] Unfortunately, due to a shortage of organs, some lung transplant candidates become so critically ill that they require invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO) while on the waiting list. Management of these patients is a major clinical, economic, and ethical challenge. In fact, although severity of disease calls for prioritization, the post-transplant benefit for this subgroup of recipients has traditionally been poor, with potential waste of organs.[2-4]

Pathophysiology of critical illness suggests that several factors can be modified in the management of the bridge phase to reduce risks of lung transplant candidates who significantly deteriorate. Use of minimal sedation, avoidance of intubation, and early delivery of physical and occupational therapy diminish the incidence of delirium, ventilator-associated pneumonia, diaphragm dysfunction, and neuromuscular deconditioning and can thus improve outcome.[5,6] If this is valid also for the most fragile lung transplant candidates, then maintaining them awake, spontaneously breathing, and actively performing some physical therapy, even when they require the ICU, will probably be of benefit.

Growing evidence suggests that ECMO with minimal (if any) sedation and no intubation should be preferred over traditional mechanical ventilation for bridging critically ill patients to lung transplant.[7] Active rehabilitation during awake ECMO should probably be the next step.[8]

Rehder et al[9] previously reported in Respiratory Care their initial positive experience with ambulatory ECMO as a bridge to lung transplant. They reviewed the medical records of 9 consecutive subjects treated with veno-venous ECMO before surgery. The first 4 subjects were deeply sedated and mechanically ventilated; they did not perform active rehabilitation. The following 5 subjects were kept awake, with or without ventilator support; they actively exercised with the aim of standing and walking as soon as possible, while receiving ECMO. Of note, some of these subjects were considered appropriate candidates for lung transplant only after a few days of active rehabilitation.[8] All 9 subjects finally underwent lung transplantation, and 1-y survival was 100% in both groups. Ambulatory, compared with non-ambulatory, ECMO was associated with longer pre-transplant stay in the ICU (because listing was delayed until subjects could stand and walk) but shorter post-transplant stay in the ICU and in the hospital. As a result, the mean total (before and after transplant) stay in the ICU fell from 49 to 27 d ($P = .01$), and hospital stay fell from 98 to 49 d ($P = .01$).[9] In the current issue of Respiratory Care, Bain et al[10] compare the costs of treatment between those same 2 subgroups of subjects. Ambulatory ECMO was associated with nonsignificantly higher median pre-transplant costs ($88,137 vs $52,124, $P = .08$) but significantly lower post-transplant costs ($38,468 vs $143,407, $P = .01$). The individual cost of total (before and after transplant) hospital stay diminished by approximately $60,000. In other terms, clinical and economic benefits of active rehabilitation largely exceeded the increased pre-transplant resource utilization. This conclusion is rather convincing even if the study is very small, single-center, and retrospective.

See the Original Study on Page 1

Along with these benefits, awake and ambulatory ECMO carries some risks, especially if treatment is prolonged.[7,11] Some patients require urgent intubation because of worsening respiratory failure, ineffective clearance of secretions, dyspnea, and anxiety. Others suffer from major bleeding or develop sepsis and multi-organ failure and are finally delisted. Fatal decannulation is possible. For all of these reasons, implementation of awake and ambulatory ECMO requires a substantial commitment of personnel,[9] expertise, and experience.

The complexity of the dynamic interaction between artificial (ECMO) and native (patient) lungs in clearing whole-body carbon dioxide (CO_2) production deserves one final comment. Almost 40 y ago, Kolobow et al[12] reported that in healthy and spontaneously breathing sheep, increasing artificial lung ventilation (sweep gas flow) and extra-

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corporeal CO_2 removal resulted in a proportional decrease in native lung ventilation (spontaneous breathing frequency and tidal volume), down to apnea. As a result, arterial pH and CO_2 remained unchanged.[12] These findings were recently replicated in sheep with or without ARDS[13] and in humans with COPD.[14] Our own preliminary observations suggest that patients with end-stage pulmonary disease (awaiting lung transplant) do the same. By contrast, those with severe ARDS can respond in a less predictable manner, with some of them breathing too fast and/or too hard even when sweep gas flow is very high. Nonetheless, as a general rule, excessive extracorporeal support causes hypoventilation and reduced clearance of secretions, with secondary pulmonary atelectasis, hypoxemia, and, eventually, right heart dysfunction. Insufficient extracorporeal support produces respiratory distress, additional lung injury, systemic overinflammation, and muscular exhaustion.

In conclusion, muscle strength is a major determinant of lung transplant outcome;[15] therefore, lung transplant candidates, even those who are critically ill, should "get fit" for it. Ambulatory ECMO can turn the bridge period from a risky waiting time into an opportunity to actively rehabilitate, for achieving the best outcome (and saving some money).

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REFERENCES

1. Egan TM, Murray S, Bustami RT, Shearon TH, McCullough KP, Edwards LB, et al. Development of the new lung allocation system in the United States. Am J Transplant 2006(5 Pt 2);6:1212-1227.
2. Mason PD, Thuita L, Nowicki ER, Murthy SC, Pettersson GB, Blackston EH. Should lung transplantation be performed for patients on mechanical respiratory support? The US experience. J Thorac Cardiovasc Surg 2010;139(3):765-773.
3. Singer JP, Blanc PD, Hoopes C, Golden JA, Koff JL, Leard LE, et al. The impact of pretransplant mechanical ventilation on short- and long-term survival after lung transplantation. Am J Transplant 2011; 11(10):2197-2204.
4. Inci I, Klinzing S, Schneiter D, Schuepbach RA, Kestenholz P, Hillinger S, et al. Outcome of extracorporeal membrane oxygenation as a bridge to lung transplant: an institutional experience and literature review. Transplantation 2015;99(8):1667-1671.
5. Antonelli M, Conti G, Rocco M, Bufi M, De Blasi RA, Vivino G, et al. A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. N Engl J Med 1998;339(7):429-435.
6. Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet 2009;373(9678):1874-1882.
7. 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(7):763-768.
8. Turner DA, Cheifetz IM, Rehder KJ, Williford WL, Bonadonna D, Banuelos SJ, et al. Active rehabilitation and physical therapy during extracorporeal membrane oxygenation while awaiting lung transplantation: a practical approach. Crit Care Med 2011;39(12):2593-2598.
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(8):1291-1298.
10. Bain JC, Turner DA, Rehder KJ, Eisenstein EL, Davis RD, Cheifetz IM, Zaas DW. Economic outcomes of extracorporeal membrane oxygenation with and without ambulation as a bridge to lung transplantation. Respir Care 2016;61(1):1-7.
11. Crotti S, Iotti GA, Lissoni A, Belliato M, Zanierato M, Chierichetti M, et al. Organ allocation waiting time during extracorporeal bridge to lung transplant affects outcome. Chest 2013;144(3):1018-1025.
12. Kolobow T, Gattinoni L, Tomlinson T, Pierce JE. An alternative to breathing. J Thorac Cardiovasc Surg 1978;75(2):261-266.
13. Langer T, Vecchi V, Belenkiy SM, Cannon JW, Chung KK, Cancio LC, et al. Extracorporeal gas exchange and spontaneous breathing for the treatment of acute respiratory distress syndrome: an alternative to mechanical ventilation? Crit Care Med 2014;42(3):e211-e220.
14. Crotti S, Lissoni A, Tubiolo D, Azzari S, Tarsia P, Caspani L, Gattinoni L. Artificial lung as an alternative to mechanical ventilation in COPD exacerbation. Eur Respir J 2012;39(1):212-215.
15. Maury G, Langer D, Verleden G, Dupont L, Gosselink R, Decramer M, Troosters T. Skeletal muscle force and functional exercise tolerance before and after lung transplantation: a cohort study. Am J Transplant 2008;8(6):1275-1281.