When the momentum has gone: what will be the role of extracorporeal lung support in the future?

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Purpose of review
There has been expanding interest in and use of extracorporeal support in respiratory failure concurrent with technological advances and predominantly observational data demonstrating improved outcomes. However, until there is more available data from rigorous, high-quality randomized studies, the future of extracorporeal support remains uncertain.

Recent findings
Outcomes for patients supported with extracorporeal devices continue to show favorable trends. There are several large randomized controlled trials that are in various stages of planning or completion for extracorporeal membrane oxygenation (ECMO) and extracorporeal carbon dioxide removal (ECCO2R) in the acute respiratory distress syndrome (ARDS) and chronic obstructive pulmonary disease (COPD), which may help clarify the role of this technology for these disease processes, and which stand to have a significant impact on a large proportion of patients with acute respiratory failure. Novel applications of extracorporeal lung support include optimization of donor organ quality through ex-vivo perfusion and extracorporeal cross-circulation, allowing for multimodal therapeutic interventions.

Summary
Despite the ongoing rise in ECMO use for acute respiratory failure, its true value will not be known until more information is gleaned from prospective randomized controlled trials. Additionally, there are modalities beyond the current considerations for extracorporeal support that have the potential to revolutionize respiratory failure, particularly in the realm of chronic lung disease and lung transplantation.

Keywords
acute respiratory distress syndrome, artificial lung, chronic obstructive pulmonary disease, extracorporeal carbon dioxide removal, extracorporeal membrane oxygenation, lung transplantation

INTRODUCTION

The role of extracorporeal gas exchange support in the management of both acute and chronic respiratory failure has evolved significantly since its first successful clinical application in the 1970s [1]. Despite initial failed attempts at demonstrating a benefit of extracorporeal membrane oxygenation (ECMO) and extracorporeal carbon dioxide removal (ECCO2R) over standard of care mechanical ventilation for severe acute respiratory distress syndrome (ARDS) in randomized controlled trials [2,3], advances in technology combined with improvements in conventional management strategies have led to reports of improved outcomes for ECMO in acute, severe hypoxemic respiratory failure [4–8]. The current literature offers a clue as to the short-term expectations for ECMO in severe ARDS, with a recently completed randomized controlled trial likely to further clarify its role [9]. Additional upcoming studies will help to inform the utility of ECCO2R in less severe forms of ARDS as a means of achieving lung-protective ventilation beyond the current standard of care [10,11]. Likewise, the use of ECCO2R to manage acute exacerbations of chronic obstructive pulmonary disease (COPD) has been shown to be feasible, and its role will likewise be better defined in upcoming trials [12].

The use of ECMO (or ECCO2R) as a means of supporting patients with end-stage respiratory

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KEY POINTS

- The results of a recently completed randomized controlled trial of ECMO for severe ARDS may help clarify its appropriate place among the various management strategies for ARDS.
- ECCO2R holds the promise of an even greater impact on acute respiratory failure than ECMO, given its potential role in facilitating minimization of invasive mechanical ventilation in both moderate ARDS and acute exacerbations of COPD, though positive results from current and future trials are needed before ECCO2R can be recommended for these indications outside of the research setting.
- Whereas ECMO as bridge to transplantation may help optimize select patients' lung transplant candidacy, there will likely be greater impact on maximization of successful lung transplantation through various ex-vivo means of optimizing donor lung quality.
- Organizations such as the International ECMO Network and Extracorporeal Life Support Organization aim to facilitate the development of rigorously designed trials in order to best inform the use of extracorporeal support in respiratory failure.

failure to lung transplantation (bridge to transplantation, BTT) has continued to expand, with favorable results from large observation studies encouraging further expansion of extracorporeal support as BTT, particularly as a means of facilitating mobilization and avoiding complications of invasive mechanical ventilation [13,14▪]. Further in the future, extracorporeal technology may expand beyond its more traditional roles of support, which to date have been limited to short-term use confined to the intensive care unit. Miniaturization, increased efficiency, novel antithrombotic coating technology, and improved durability of extracorporeal circuitry could lead to long-term, paracorporeal support, effectively the equivalent of a durable lung assist device or artificial lung. These and other advances, if ultimately achieved, would revolutionize the approach to both acute and chronic respiratory failure.

EXTRACORPOREAL MEMBRANE OXYGENATION FOR SEVERE ACUTE RESPIRATORY DISTRESS SYNDROME

The rationale for ECMO in severe ARDS stems from its ability to provide oxygenation and ventilation whenever invasive mechanical ventilation is either inadequate at supporting gas exchange or can do so only at the expense of excessive plateau airway pressures, contributing to ventilator-associated lung injury (VALI) with its associated morbidity and mortality [15]. The most recently published prospective randomized trial of ECMO versus conventional mechanical ventilation in severe ARDS remains the efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR) trial, now 8 years old, showing a significantly higher 6-month survival without severe disability in those referred for consideration of ECMO [5]. However, the pragmatic nature of the trial, without strict control of conventional management strategies and only consideration of ECMO in the intervention arm limit the ability to determine the effect of ECMO itself on survival. Subsequent matched pair analyses of ECMO versus conventional management in ARDS showed conflicting results of the impact of ECMO on outcomes [16,17]. Lack of consensus in the existing literature with ongoing debate about the efficacy of ECMO in severe ARDS has led to a multicenter, prospective randomized controlled trial of ECMO versus ongoing optimal standard of care conventional management [Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA)] [9], which includes low-tidal volume ventilation, neuromuscular blocking agents, and prone positioning, in patients with severe ARDS, the results of which are anticipated in early 2018. A result that favors the use of ECMO over the existing standard of care would justify an expanded role for ECMO in severe ARDS, though the nature of the study design would encourage putting ECMO in the context of a larger algorithm that incorporates other less invasive measures prior to the consideration of ECMO [18]. However, a negative study is unlikely to significantly curb enthusiasm for ECMO, given the rapid increase in usage that has already been occurring in the absence of convincing and rigorous, high-quality data. A recent epidemiological study from Germany demonstrated a marked increase in venovenous ECMO usage from 1 per 100 000 population in 2007 to 3 per 100 000 in 2012 [19▪▪]. However, this increase has also come with an unexpectedly high rate of mortality within the first 48 h of ECMO, suggesting either the potentially inappropriate use of ECMO in patients with excess predicted mortality independent of respiratory failure, or some combination of lack of experience and suboptimal technique. This study highlights the need for standardization of ECMO practices, including appropriate patient selection and optimization of lung protective ventilation strategies, though the optimal approach to invasive mechanical ventilation during ECMO support is unsettled and remains a target of ongoing investigations [20,21▪].

Regardless of the results and subsequent interpretations of the EOLIA trial, there will remain justifiable uses of ECMO in severe ARDS that are unlikely to be captured in randomized controlled trials [22]. These include the use of ECMO to facilitate safe transport of patient with severe ARDS from hospitals unable to provide adequate ARDS management to centers with sufficient experience and resources to provide optimal treatment strategies, including more advanced maneuvers such as prone positioning. With higher center-specific case volume associated with more favorable outcomes [23▪▪,24▪,25], and ECMO transport increasingly being demonstrated as safe (and safer than transport of the severe ARDS patient without ECMO support [5]), regionalization can certainly be justified, and even encouraged in the right clinical context [26,27▪,28]. Additionally, those patients too critically ill to tolerate a methodical, stepwise, algorithmic approach to ARDS management (e.g. severe hemodynamic instability or gas exchange impairment too severe to tolerate prone positioning) may benefit from the rapid institution of ECMO.

EXTRACORPOREAL CARBON DIOXIDE REMOVAL FOR LESS SEVERE ACUTE RESPIRATORY DISTRESS SYNDROME

Whether or not severe, refractory hypoxemia remains a reasonable indication for extracorporeal support in ARDS, one could make a strong case for its use to minimize VALI, which is the more common risk for morbidity and mortality in ARDS, a risk that is present even in milder forms of ARDS whenever oxygenation is relatively well preserved [29]. Animal models, posthoc analyses of randomized trials, and observational data all suggest that reductions in tidal volumes and airway pressures below the current standard of care could further reduce ARDS mortality [30–32]. However, achieving very low tidal volume, low pressure ventilation – as well as low respiratory rates – whenever trying to limit the total exposure of the lung to excess energy [33▪], is inherently limited by intolerable levels of hypercapnia and acidemia, especially in the context of reduced respiratory system compliance from ARDS. Prospective studies with surrogate outcomes have indicated a protective effect whenever invasive mechanical ventilation is reduced to very low (beyond standard of care) tidal volumes, airway pressures, or respiratory rates, whenever coupled with ECCO2R to manage ventilation [34–36]. As carbon dioxide removal is achievable with lower blood flow rates than for oxygenation [37], ECCO2R can be accomplished with smaller cannulae, which may translate into a lower risk profile than ECMO. If the physiological benefit of ECCO2R translates into a significant impact on major clinical outcomes, the impact could have far greater reach than ECMO for severe hypoxemia given that moderate ARDS is much more commonly encountered than severe ARDS (46.6 versus 23.4% as per the prospective cohort LUNG SAFE study) [38▪▪].

At the current time, ECCO2R remains an experimental technique for maximizing lung protective ventilation [39]. Its acceptance and broad application for use within the ARDS population hinges on ongoing and future studies that will better define its role and bring clarity to the risk–benefit profile associated with its use [10,11].

EXTRACORPOREAL CARBON DIOXIDE REMOVAL FOR ACUTE HYPERCAPNIC RESPIRATORY FAILURE

Much in the way ECCO2R can facilitate minimization of invasive mechanical ventilation in ARDS, it can likewise be used to minimize or avoid invasive mechanical ventilation in patients with acute exacerbations of COPD, who are either failing noninvasive ventilation (NIV) or already receiving invasive mechanical ventilation, a scenario that is otherwise associated with high morbidity and mortality owing to dynamic hyperinflation, ventilator-associated injury and pneumonia, and consequences of immobility, among others [40]. This feasibility has been demonstrated repeatedly in predominantly small, observational studies [41–44]. Perhaps the best indicator to date of a benefit of ECCO2R over conventional management in COPD exacerbations can be found in a cohort study of patients failing NIV who received ECCO2R, matched to historical controls managed conventionally [45]. NIV paired with ECCO2R had a 12% intubation rate, compared with 33% in the historical control group. However, the potential risks associated with such an intervention are highlighted by a 52% rate of adverse events related to ECCO2R, which illustrates both the need for prospective randomized data to understand the net clinical effect of ECCO2R for COPD exacerbations and the importance of device selection and management. A prospective randomized controlled trial is currently underway, evaluating the role of ECCO2R in both those failing NIV and those already intubated in the context of COPD exacerbations [12]. If this and other prospective studies show a favorable risk–benefit profile for ECCO2R in acute exacerbations of COPD, there is potential for widespread application of the technology in the clinical realm, especially with the development of devices that require minimal expertise beyond that needed for the initiation and management of renal dialysis

circuits. However, until such time as this technology is shown to be superior to conventional management, it should be reserved only for research purposes. If clinical efficacy is established, cost-effectiveness should also be rigorously explored and may determine, in large part, how widespread the technology becomes. Any benefit found in the COPD population would potentially translate to other forms of acute hypercapnic respiratory failure as well, including severe cases of status asthmaticus.

EXTRACORPOREAL SUPPORT AS BRIDE TO TRANSPLANTATION

Pretransplant extracorporeal support has traditionally been associated with poor outcomes, often attributed to complications of the device, poor timing of implementation, and inappropriate patient selection. However, recent cohort studies have demonstrated markedly improved outcomes whenever ECMO (or ECCO2R) is initiated as a means of maximizing patients' pretransplant conditioning and transplant eligibility, which involves the prioritization of early mobilization and removal or avoidance of invasive mechanical ventilation, whenever feasible [14▪,46–48]. Upper body cannulation strategies may maximize the chance of achieving both of these goals, including patients with primary or secondary pulmonary hypertension who require venoarterial ECMO [49,50,51▪,52]. Favorable outcomes have also been linked to ECMO case volume, with lower mortality rates associated with higher volume centers [24▪,25]. Given the current trends in posttransplant mortality for patients bridged with ECMO, there will likely be ongoing, steady use of ECMO as BTT, without the possibility of a randomized controlled trial to prove a benefit over conventional management given the nature of the patient population. However, we encourage careful patient selection to minimize the possibility of patients being delisted while dependent on ECMO, a so-called 'bridge to nowhere', especially whenever those patients are alert and interactive, bound to the ICU but unable or unwilling to be disconnected from extracorporeal support [53].

NOVEL USES OF EXTRACORPOREAL LUNG SUPPORT

The expansion of lung transplantation ultimately depends much more on sufficient donor lung availability than it does on the successful use of ECMO as BTT, as the number of individuals awaiting lung transplantation greatly exceeds the available number of organs, many of which are deemed unsuitable for transplantation prior to or during procurement (https://http://www.unos.org/data/). Novel strategies to improve donor lung quality have revolved around ex-vivo lung maintenance, affording the opportunity to optimize lung function prior to transplantation. The most commonly cited approach has been ex-vivo lung perfusion, which uses an acellular normothermic perfusate to prolong the time period for assessment of lung quality and potentially improve the function of impaired lungs during the same timeframe [54,55]. A competing system uses normothermic whole blood perfusate [56]. Unfortunately, both systems are limited to several hours, which may be inadequate to achieve sufficient lung recovery, especially for more grave injuries such as aspiration or contusion. A recently reported technique that may overcome these limitations is cross-circulation between potential donor lungs and a transplant recipient [57▪▪]. Through the use of an extracorporeal system that maintains a durable physiologic homeostatic environment, this swine model demonstrates the feasibility of maintaining organ viability for days, which allows for a natural reparative process in injured lungs. The durability of the system creates the opportunity to use strategies to improve lung function, such as stem cell-based therapies, that would previously have been infeasible with only a few hours of ex-vivo support [58].

Although extracorporeal systems may significantly expand the number of suitable donor organs for lung transplantation, it is unlikely to completely satisfy the unmet needs of patients awaiting lung transplantation.

Ultimately, patients with chronic and acute on chronic respiratory failure are in need of a durable device capable of providing gas exchange on the order of months to years, either as bridge to transplantation or destination device therapy, comparable with ventricular assist devices for end-stage heart failure. Such devices are currently under development and being studied in short-term animal models [59▪], though human-based, long-term application of these devices likely remains years away. Finally, the suggestion that chronic COPD could be treated with intermittent 'lung dialysis' via ECCO2R in stable, advanced COPD patients, much the way chronic kidney disease is treated with chronic kidney dialysis, is being explored with increasing urgency. Whether such a strategy will be efficacious or feasible has yet to be determined.

CONCLUSION

Despite the ongoing rise in ECMO use for severe ARDS, it's future impact will not be fully understood until more information is obtained from prospective

randomized controlled trials with a focus on moderate ARDS and acute exacerbations of COPD. Enrichment of study populations by selecting those most likely to benefit from ECMO and ECCO2R may help to optimize trial design [60▪▪], and organizations such as the International ECMO Network (ECMONet) and the Extracorporeal Life Support Organization (ELSO) may further help to facilitate the development of rigorously designed trials, thereby maximizing the quality of evidence for the use of such technology(http://www.internationalecmonetwork.org; http://www.elso.org). Additionally, there are novel potential considerations for extracorporeal support beyond the usual indications that have the potential to revolutionize the management of chronic respiratory failure and lung transplantation. However, substantial work remains before such approaches will be ready for clinical application.

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Conflicts of interest

D.B. is currently on the medical advisory boards of ALung Technologies and Kadence. All compensation for these activities is paid to Columbia University. D.A. and M.B. have no conflicts of interest to report. This manuscript includes discussion of unlabeled and investigational uses of ECMO and ECCO2R.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Hill JD, O'Brien TG, Murray JJ, *et al.* Prolonged extracorporeal oxygenation for acute posttraumatic respiratory failure (shock-lung syndrome). Use of the Bramson membrane lung. N Engl J Med 1972; 286:629–634.
2. Zapol WM, Snider MT, Hill JD, *et al.* Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. JAMA 1979; 242:2193–2196.
3. Morris AH, Wallace CJ, Menlove RL, *et al.* Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO2 removal for adult respiratory distress syndrome. Am J Respir Crit Care Med 1994; 149(2 Pt 1):295–305.
4. Patroniti N, Zangrillo A, Pappalardo F, *et al.* The Italian ECMO network experience during the 2009 influenza A(H1N1) pandemic: preparation for severe respiratory emergency outbreaks. Intensive Care Med 2011; 37:1447–1457.
5. Peek GJ, Mugford M, Tiruvoipati R, *et al.* Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet 2009; 374:1351–1363.
6. Abrams D, Brodie D. Extracorporeal membrane oxygenation for adult respiratory failure: 2017 update. Chest 2017; 152:639–649.
7. Davies A, Jones D, Bailey M, *et al.* Extracorporeal membrane oxygenation for 2009 Influenza A (H1N1) acute respiratory distress syndrome. JAMA 2009; 302:1888–1895.
8. Davies A, Jones D, Gattas D. Extracorporeal membrane oxygenation for ARDS due to 2009 Influenza A (H1N1): reply. JAMA 2010; 303:941–942.
9. Assistance Publique - Hôpitaux de Paris. Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2011- [cited 27 Aug 2017]. Available from: http://clinicaltrials.gov/ct2/show/NCT01470703 (NLM Identifier: NCT01470703).
10. Belfast Health and Sociual Care Trust. Protective Ventilation with Veno-venous Lung Assist in Respiratory Failure (REST). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2016- [cited 27 Aug 2017]. Available from: http://clinicaltrials.gov/ct2/show/NCT02654327 (NLM Identifier: NCT02654327).
11. European Society of Intensive Care Medicine. Strategy of Ultraprotective Lung Ventilation with Extracorporeal CO2 Removal for New-Onset Moderate to Severe ARDS (SUPERNOVA). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014- [cited 2017 Aug 27]. Available from: http://clinicaltrials.gov/ct2/show/NCT02282657 (NLM Identifier: NCT02282657).
12. Alung Technologies. Extracorporeal CO2 Removal with the Hemolung RAS for Mechanical Ventilation Avoidance During Acute Exacerbation of COPD (VENT-AVOID). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2017- [cited 2017 Aug 27]. Available from: http://clinicaltrials.gov/ct2/show/NCT03255057 (NLM Identifier: NCT03255057).
13. Abrams D, Brodie D, Arcasoy S. Extracorporeal life support in lung transplantation. Clin Chest Med 2017. [Epub ahead of print]
14. ▪ Biscotti M, Gannon WD, Agerstrand C, *et al.* Awake extracorporeal membrane oxygenation as bridge to lung transplantation: a 9-year experience. Ann Thorac Surg 2017; 104:412–419.

This study demonstrates the favorable posttransplant outcomes that can be achieved whenever pretransplant ECMO is combined with an awake, extubated strategy that prioritizes early mobilization.

15. Brodie D, Bacchetta M. Extracorporeal membrane oxygenation for ARDS in adults. N Engl J Med 2011; 365:1905–1914.
16. Pham T, Combes A, Roze H, *et al.* Extracorporeal membrane oxygenation for pandemic Influenza A(H1N1)-induced acute respiratory distress syndrome: a cohort study and propensity-matched analysis. Am J Respir Crit Care Med 2013; 187:276–285.
17. Noah MA, Peek GJ, Finney SJ, *et al.* Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). JAMA 2011; 306:1659–1668.
18. Brodie D, Guerin C. Rescue therapy for refractory ARDS should be offered early: no. Intensive Care Med 2015; 41:926–929.
19. ▪▪ Karagiannidis C, Brodie D, Strassmann S, *et al.* Extracorporeal membrane oxygenation: evolving epidemiology and mortality. Intensive Care Med 2016; 42:889–896.

This epidemiological study reveals a significant rise in the use of venovenous ECMO in German ICUs from 2007 to 2014. Venovenous ECMO was associated with higher than expected mortality within the first 48 h of use, calling into question the appropriate utilization of this technology.

20. Marhong JD, Munshi L, Detsky M, *et al.* Mechanical ventilation during extracorporeal life support (ECLS): a systematic review. Intensive Care Med 2015; 41:994–1003.
21. ▪ Serpa Neto A, Schmidt M, Azevedo LC, *et al.* Associations between ventilator settings during extracorporeal membrane oxygenation for refractory hypoxemia and outcome in patients with acute respiratory distress syndrome: a pooled individual patient data analysis: mechanical ventilation during ECMO. Intensive Care Med 2016; 42:1672–1684.

This individual patient data meta-analysis of ARDS patients receiving ECMO identifed driving pressure as the only ventilatory parameter during ECMO support that was independently associated with in-hospital mortality. Older age, male sex, and lower body mass index were also found to be independently associated with mortality.

22. Abrams D, Brodie D. ECMO is first-line therapy for ARDS. Crit Care Med 2017. [Epub ahead of print]
23. ▪▪ Barbaro RP, Odetola FO, Kidwell KM, *et al.* Association of hospital-level volume of extracorporeal membrane oxygenation cases and mortality. Analysis of the extracorporeal life support organization registry. Am J Respir Crit Care Med 2015; 191:894–901.

This study demonstrates that higher annual hospital ECMO volume is associated with lower in-hospital mortality.

24. ▪ Hayes D Jr, Tobias JD, Tumin D. Center volume and extracorporeal membrane oxygenation support at lung transplantation in the lung allocation score era. Am J Respir Crit Care Med 2016; 194:317–326.

This study highlights the relationship between center-specific lung transplant volume and the effect of pretransplant ECMO on posttransplant mortality, with ECMO associated with higher posttransplant mortality at low volume centers and no adverse effect at high volume centers.

25. George TJ, Beaty CA, Kilic A, *et al.* Outcomes and temporal trends among high-risk patients after lung transplantation in the United States. J Heart Lung Transplant 2012; 31:1182–1191.

26. Wallace DJ, Angus DC, Seymour CW, *et al.* Geographic access to high capability severe acute respiratory failure centers in the United States. PLoS One 2014; 9:e94057.

27. ■ Biscotti M, Agerstrand C, Abrams D, *et al.* One hundred transports on extracorporeal support to an extracorporeal membrane oxygenation center. Ann Thorac Surg 2015; 100:34–40.
This study demonstrates the feasibility and safety of ECMO for interhospital transport at a high volume ECMO center.

28. Salina M, Biscotti M, Agerstrand C, *et al.* Management of surge in extracorporeal membrane oxygenation transport. Ann Thorac Surg 2017. (in press).

29. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. N Engl J Med 2014; 370:980.

30. Frank JA, Gutierrez JA, Jones KD, *et al.* Low tidal volume reduces epithelial and endothelial injury in acid-injured rat lungs. Am J Respir Crit Care Med 2002; 165:242–249.

31. Hager DN, Krishnan JA, Hayden DL, Brower RG. Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. Am J Respir Crit Care Med 2005; 172:1241–1245.

32. Needham DM, Colantuoni E, Mendez-Tellez PA, *et al.* Lung protective mechanical ventilation and two year survival in patients with acute lung injury: prospective cohort study. BMJ 2012; 344:e2124.

33. ■ Gattinoni L, Tonetti T, Cressoni M, *et al.* Ventilator-related causes of lung injury: the mechanical power. Intensive Care Med 2016; 42:1567–1575.
This mathematical model attempts to estimate the relative contribution of individual ventilator parameters to ventilator-related lung injury.

34. Terragni PP, Del Sorbo L, Mascia L, *et al.* Tidal volume lower than 6 ml/kg enhances lung protection: role of extracorporeal carbon dioxide removal. Anesthesiology 2009; 111:826–835.

35. Bein T, Weber-Carstens S, Goldmann A, *et al.* Lower tidal volume strategy (approximately 3 ml/kg) combined with extracorporeal CO(2) removal versus 'conventional' protective ventilation (6 ml/kg) in severe ARDS: The prospective randomized Xtravent-study. Intensive Care Med 2013; 39:847–56.

36. Grasso S, Stripoli T, Mazzone P, *et al.* Low respiratory rate plus minimally invasive extracorporeal Co2 removal decreases systemic and pulmonary inflammatory mediators in experimental Acute Respiratory Distress Syndrome. Crit Care Med 2014; 42:e451–e460.

37. Pesenti A, Patroniti N, Fumagalli R. Carbon dioxide dialysis will save the lung. Crit Care Med 2010; 38:S549–S554.

38. ■■ Bellani G, Laffey JG, Pham T, *et al.* Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA 2016; 315:788–800.
This prospective international cohort study reveals that ARDS is under-recognized, undertreated, and associated with a higher than expected mortality, indicating the opportunity for improvements in the management of patients with ARDS.

39. Morelli A, Del Sorbo L, Pesenti A, *et al.* Extracorporeal carbon dioxide removal (ECCO2R) in patients with acute respiratory failure. Intensive Care Med 2017; 43:519–530.

40. Chandra D, Stamm JA, Taylor B, *et al.* Outcomes of noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease in the United States, 1998-2008. Am J Respir Crit Care Med 2012; 185:152–159.

41. Abrams DC, Brenner K, Burkart KM, *et al.* Pilot study of extracorporeal carbon dioxide removal to facilitate extubation and ambulation in exacerbations of chronic obstructive pulmonary disease. Ann Am Thorac Soc 2013; 10:307–314.

42. Burki NK, Mani RK, Herth FJ, *et al.* A Novel extracorporeal co_2 removal system: results of a pilot study of hypercapnic respiratory failure in patients with COPD. Chest 2013; 143:678–686.

43. Roncon-Albuquerque R Jr, Carona G, Neves A, *et al.* Venovenous extracorporeal CO_2 removal for early extubation in COPD exacerbations requiring invasive mechanical ventilation. Intensive Care Med 2014; 40:1969–1970.

44. Kluge S, Braune SA, Engel M, *et al.* Avoiding invasive mechanical ventilation by extracorporeal carbon dioxide removal in patients failing noninvasive ventilation. Intensive Care Med 2012; 38:1632–1639.

45. Del Sorbo L, Pisani L, Filippini C, *et al.* Extracorporeal CO_2 removal in hypercapnic patients at risk of noninvasive ventilation failure: a matched cohort study with historical control. Crit Care Med 2014; 43:120–127.

46. Biscotti M, Sonett J, Bacchetta M. ECMO as bridge to lung transplant. Thorac Surg Clin 2015; 25:17–25.

47. Mohite PN, Sabashnikov A, Reed A, *et al.* Extracorporeal Life Support in 'Awake' Patients as a Bridge to Lung Transplant. Thorac Cardiovasc Surg 2015; 63:699–705.

48. Abrams D, Javidfar J, Farrand E, *et al.* Early mobilization of patients receiving extracorporeal membrane oxygenation: a retrospective cohort study. Crit Care 2014; 18:R38.

49. Biscotti M, Bacchetta M. The 'sport model': extracorporeal membrane oxygenation using the subclavian artery. Ann Thorac Surg 2014; 98: 1487–1489.

50. Biscotti M, Vail E, Cook KE, *et al.* Extracorporeal membrane oxygenation with subclavian artery cannulation in awake patients with pulmonary hypertension. ASAIO J 2014; 60:748–750.

51. ■ Chicotka S, Rosenzweig EB, Brodie D, Bacchetta M. The 'Central Sport Model': extracorporeal membrane oxygenation using the innominate artery for smaller patients as bridge to lung transplantation. ASAIO J 2016; 63:e39–e44.
Internal jugular venous drainage coupled with innominate arterial reinfusion via an end-to-side graft is a novel configuration for upper body venoarterial oxygenation, and may be well suited for those whose peripheral vessels are too small to accommodate cannulation or grafting.

52. Rosenzweig EB, Brodie D, Abrams DC, *et al.* Extracorporeal membrane oxygenation as a novel bridging strategy for acute right heart failure in group 1 pulmonary arterial hypertension. ASAIO J 2014; 60:129–133.

53. Abrams DC, Prager K, Blinderman CD, *et al.* Ethical dilemmas encountered with the use of extracorporeal membrane oxygenation in adults. Chest 2014; 145:876–882.

54. Cypel M, Yeung JC, Hirayama S, *et al.* Technique for prolonged normothermic ex vivo lung perfusion. J Heart Lung Transplant 2008; 27:1319–1325.

55. Cypel M, Yeung JC, Liu M, *et al.* Normothermic ex vivo lung perfusion in clinical lung transplantation. N Engl J Med 2011; 364:1431–1440.

56. Warnecke G, Moradiellos J, Tudorache I, *et al.* Normothermic perfusion of donor lungs for preservation and assessment with the Organ Care System Lung before bilateral transplantation: a pilot study of 12 patients. Lancet 2012; 380:1851–1858.

57. ■■ O'Neill JD, Guenthart BA, Kim J, *et al.* Cross-circulation for extracorporeal support and recovery of the lung. Nat Biomed Eng 2017; 1:0037. doi:10.1038/s41551-017-0037.
This study describes a novel extracorporeal, cross-circulation approach to supporting donor lungs within a durable physiologic homeostatic environment for days, allowing for an extended duration of time to optimize donor lung function prior to transplantation.

58. Huang SX, Islam MN, O'Neill J, *et al.* Efficient generation of lung and airway epithelial cells from human pluripotent stem cells. Nat Biotechnol 2014; 32:84–91.

59. ■ Skoog DJ, Pohlmann JR, Demos DS, *et al.* Fourteen day in vivo testing of a compliant thoracic artificial lung. ASAIO J 2017; 63:644–649.
This study demonstrates the feasibility of a novel compliant artifical lung to support gas exchange in an animal model as bridge to lung transplantation.

60. ■■ Goligher EC, Amato MBP, Slutsky AS. Applying precision medicine to trial design using physiology: extracorporeal CO_2 removal for ARDS. Am J Respir Crit Care Med 2017; 196:558–568.
The use of physiology to predict patients most likely to benefit from very lung protective ventilation strategies can help enrich study populations and optimize results of prospective clinical trails.