delivered ventilation during cardiopulmonary resuscitation. *Am J Respir Crit Care Med* [online ahead of print] 26 Sep 2018; DOI: 10.1164/rccm.201806-1111OC.
2. Chalkias A, Pavlopoulos F, Koutsovasilis A, d'Aloja E, Xanthos T. Airway pressure and outcome of out-of-hospital cardiac arrest: a prospective observational study. *Resuscitation* 2017;110:101–106.

Mechanical Ventilation during Extracorporal Support: The Relevance of V_T

To the Editor:

In cases in which pulmonary gas exchange is mainly guaranteed by extracorporeal support, the optimal ventilation strategy to protect the lung remains unclear. It is generally accepted that the ventilator should be set to prevent further ventilator-associated lung injury. Nevertheless, even a lung-protective approach with low V_Ts may still aggravate lung injury. Thus, an ultraprotective approach with very low V_Ts (<6 ml/kg) is frequently used in patients undergoing extracorporeal support to facilitate the healing of the injured lung (1). A very interesting concept is the reduction of the V_Ts to near apneic oxygenation, as done by Araos and colleagues (2). These researchers examined three different ventilation strategies in a swine acute respiratory distress syndrome model over the course of 24 hours, using extracorporeal membrane oxygenation to examine nonprotective, conventional, and near-apneic ventilation. The researchers found that histopathologic lung injury was lower in the conventional and especially the near-apneic group. However, wet-dry lung weight ratio and expression of most genes indicating fibroproliferation were not different between the groups. As remarked in the editorial by Fan (3), there was no comparison of ultraprotective strategies, and the three strategies differed not only in their V_Ts but also in positive end-expiratory pressure (PEEP) level and respiratory rate. Fan raised the question whether ventilation is needed at all during extracorporeal lung support. This was primarily described by Kolobow in an animal study (4).

Our group also conducted a study using a similar acute respiratory distress syndrome model (5). In the conventional group, protective mechanical ventilation with 6 ml/kg V_T was used. Unlike Araos and colleagues, we used arteriovenous extracorporeal lung assist to reduce V_Ts to 3 ml/kg body weight, and apneic oxygenation with V_Ts set to zero in further experimental groups. Moreover, an "open lung concept" was used in all groups by using PEEP levels above the lower inflection point of the lung. This strategy resulted in continuous airway pressure above 20 cm H_2O, even in the apneic group. Mean respiratory rate was similar in the 6 ml/kg and the 3 ml/kg group, with 20 and 17–18 breaths/min, respectively. After 24 hours, a histopathologic examination of the dependent lung showed more inflammation, alveolar exudation, and atelectasis with 3 ml/kg or no V_Ts. In contrast, alveolar overdistension was reduced with apneic oxygenation in the nondependent lung areas (5).

Hence, our study addressed several of the shortcomings of the data presented by Araos and colleagues and may help to answer the questions raised by Fan (3). Ventilation with protective V_Ts led to overdistension in the nondependent lung. Nevertheless, despite using high positive airway pressures, the dependent lung in the apneic group showed a worse lung injury score compared with protective V_Ts. Thus, the combination of both strategies as "near apneic ventilation with low respiratory rates" and higher PEEP levels might be very appealing. This strategy might prevent derecruitment of the dependent lung via repeated recruitment at a low rate set above higher PEEP levels. Overdistension of the nondependent lung may be prevented because of lower peak pressures and minimized shear stress resulting from a low respiratory rate. Another point is that using lower airway, and thus intrathoracic, pressures might reduce hemodynamic compromise. This is enabled by lower respiratory rates and lower V_Ts. Theoretically, a strategy with sufficient PEEP, low respiratory rates, and very low V_Ts individually adapted to the size of the residual nonconsolidated lung parts combined with prone positioning might be optimal to protect the lung during extracorporeal lung support.

We strongly agree with Fan that the optimal ventilator strategy during extracorporeal gas exchange should now be addressed in clinical studies. ■

Originally Published in Press as DOI: 10.1164/rccm.201810-1985LE on January 4, 2019

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

Markus Kredel, M.D.*
Christopher Lotz, M.D.
University of Würzburg
Würzburg, Germany

Caroline Rolfes, M.D.
Ralf Muellenbach, M.D.
Klinikum Kassel
Kassel, Germany

ORCID ID: 0000-0003-2183-033X (M.K.).

*Corresponding author (e-mail: kredel_m@ukw.de).

References

1. Marhong JD, Telesnicki T, Munshi L, Del Sorbo L, Detsky M, Fan E. Mechanical ventilation during extracorporeal membrane oxygenation: an international survey. *Ann Am Thorac Soc* 2014;11: 956–961.
2. Araos J, Alegria L, Garcia P, Cruces P, Soto D, Erranz B, *et al*. Near-apneic ventilation decreases lung injury and fibroproliferation in an ARDS model with ECMO. *Am J Respir Crit Care Med* [online ahead of print] 14 Sep 2018; DOI: 10.1164/rccm.201805-0869OC.
3. Fan E. "There is nothing new except what has been forgotten": the story of mechanical ventilation during extracorporeal support. *Am J Respir Crit Care Med* [online ahead of print] 3 Oct 2018; DOI: 10.1164/rccm.201809-1728ED.
4. Kolobow T, Gattinoni L, Tomlinson T, Pierce JE. An alternative to breathing. *J Thorac Cardiovasc Surg* 1978;75:261–266.

5. Johannes A, Kredel M, Zollhoefer B, Schlegel N, Von Kirschbaum C, Brederlau J, *et al*. Influence of apneic oxygenation and minimal tidal volumes on ventilator-associated lung injury. *Minerva Anestesiol* 2014;80:526–536.

Reply to Kredel *et al.*

From the Authors:

We appreciate the editorial by Fan (1) and the letter by Kredel and colleagues regarding our recent publication (2). Both compare the near-apneic ventilation strategy we applied, associated with high-flow veno-venous extracorporeal membrane oxygenation (ECMO), with near-apneic strategies applied in association with low-flow extracorporeal CO_2 removal systems ($ECCO_2R$). We think this comparison overlooks a fundamental difference. In the original experience in patients with acute respiratory distress syndrome (ARDS) reported by Gattinoni and coworkers (3), intermittent sighs to peak airway pressures of 35–45 cm H_2O and high positive end-expiratory pressure (PEEP) levels from 15 to 25 cm H_2O were applied. In Johannes and colleagues' study (4), PEEP levels above 20 cm H_2O were used after a recruitment maneuver in an experimental model of ARDS. In contrast, our near-apneic strategy kept PEEP at 10 cm H_2O and maximal airway pressures at 20 cm H_2O. Although the decreases in $\dot{V}_E$ were of similar magnitude to our study, airway pressures differ markedly. As $ECCO_2R$ does not contribute to oxygenation, very high airway pressures have to be applied in severe ARDS to maintain oxygenation, so that static stress and strain remain high, and eventually right ventricular function and hemodynamics may be compromised. This potential risk has become more apparent after the negative results of the OSCILLATE (Oscillation for ARDS Treated Early) and ART (Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial) trials (5, 6). In contrast, in our study, we could keep significantly lower mean and driving airway pressures, avoiding both static and dynamic stress and strain. We believe this is the fundamental reason why our results differ from those of Johannes and colleagues (4), who found no positive effect of decreasing V_T to 3 or even 0 ml/kg on lung tissue inflammation. In fact, we have recently presented in abstract form the results of a study evaluating 3 different airway pressures (low: PEEP 0 cm H_2O–peak inspiratory pressure [PIP] 10 cm H_2O; moderate: PEEP 10 cm H_2O–PIP 20 cm H_2O; high: PEEP 20 cm H_2O–PIP 30 cm H_2O) applied during a near-apneic protocol in the same model of ARDS supported by venovenous ECMO (7). We found that low and high airway pressures were associated with increased lung water and higher histologic scores, respectively, compared with a near-apneic protocol using moderate airway pressures (which is the same protocol used in the near-apneic group of the present study).

The issue of mechanical ventilation during ECMO has been poorly studied. Most studies published up to now have been surveys (8), observational descriptive studies (9), and noncontrolled studies to assess feasibility or physiologic effects of certain interventions (10). Our study is one of the first efforts to compare different ventilatory strategies during ECMO in a controlled design. The study was planned as a proof of concept regarding the value of resting the lungs by minimizing the energy imposed. We believe the results provide significant evidence in favor of the lung rest concept. The fact that not all the measured variables were modified by the ventilator strategy is completely expected in a 24-hour experimental model comparing clinically relevant strategies. However, histologic lung injury, which is a major component of ARDS, was clearly improved by near-apneic ventilation.

In the recently published EOLIA, the largest randomized clinical trial to date on venovenous ECMO for severe ARDS, patients assigned to the ECMO group had a reduction in their mechanical power by 2.5 times in relation to the control group (conventional protective protocol) (11). Although this is a significant reduction, if our experimental near-apneic protocol would have been in place, the reduction in mechanical power compared with the control group would have been in the order of 18 times. It is uncertain whether this would have resulted in better clinical outcomes; however, based on our data, we think this should be assessed in future trials.

We fully agree with Fan (1) and Kredel and colleagues (2) that several uncertainties remain about the role of prone position, spontaneous breathing, or specific ventilatory variables to achieve the ideal lung rest. While we wait for clinical studies in this area, we will continue addressing these questions via an experimental approach.

The story of prone position has taught us that we should not give up sound concepts only because they are old or we have not been able to find their place. Instead, we must learn from our mistakes, refresh the valuable old concepts with new perspectives, and challenge our current approaches. We think that our study, despite all the limitations of an experimental design, is a significant step in that direction. ■

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

Joaquin Araos, D.V.M., Ph.D.
Alejandro Bruhn, M.D., Ph.D.*
Pontificia Universidad Católica de Chile
Santiago, Chile

ORCID ID: 0000-0001-8034-1937 (A.B.).

*Corresponding author (e-mail: alejandrobruhn@gmail.com).

Originally Published in Press as DOI: 10.1164/rccm.201812-2258LE on January 4, 2019

References

1. Fan E. "There is nothing new except what has been forgotten": the story of mechanical ventilation during extracorporeal support. *Am J Respir Crit Care Med* [online ahead of print] 03 Oct 2018; DOI: 10.1164/rccm.201809-1728ED.