

increase driving pressure if it decreases lung compliance (as in atelectasis), or increased tidal volume can decrease driving pressure if it increases lung compliance (as in recruitment). Therefore, reduction of tidal volume would decrease driving pressure until it reaches to the point where lung compliance starts to decrease. No study ever tested tidal volume in terms of driving pressure and it would be another interesting study subject. We think optimal tidal volume would be different in each individual if it is based on the lowest driving pressure.

We thank Dr. Amar for his careful review of our study.¹ As he said, lung resection and esophagectomy are two different surgeries. However, our hospital has many esophageal cancer surgeries (more than 300 cases per year). All included patients underwent the Ivor Lewis operation which usually takes only 4 to 5 h. All patients had no preoperative adjuvant chemoradiotherapy. We only studied complications until postoperative day 3, thus a lot of delayed complications (graft failure, aspiration pneumonia, among others) were not included. For this reason, we did not see inclusion of esophageal cancer surgery as a problem. The number of esophageal surgeries was small (control group $n = 12$ vs. driving pressure group $n = 16$) and the incidence of pulmonary complications diagnosed by Melbourne Group Scale was control group $n = 3$ and driving pressure group $n = 4$. Dr. Amar's other concern was the use of statistics. As he said, it is correct to use the Fisher exact test when expected frequencies are less than 5. Our concern was that the Fisher exact test runs an exact procedure especially for small-sized samples and is more conservative than the chi-square test. Our institutional statistician advised that acute respiratory distress syndrome (ARDS) is a small part of our primary outcome (pulmonary complications); therefore, showing the incidence itself is enough (ARDS: control group $n = 5$, driving pressure group $n = 0$). $P = 0.05$ cut is a consensus, some argue $P = 0.10$, or $P = 0.001$ is meaningful. Our P value by two different statistics was 0.025 versus 0.060, and the difference mostly came from small incidence of ARDS. Dr. Amar questioned why pneumonia occurred more frequently in both operated and nonoperated lungs in the control group. We think direct surgical injury and one-lung ventilation are associated with a profound inflammatory cytokine release because of abundant immune cells on the lung endothelium and alveolus.² Excessive neutrophils recruited in response to the proinflammatory cytokines increase pulmonary vascular permeability in both dependent and nondependent lungs.³ These reactions often precede systemic inflammatory response syndrome, ARDS, and pneumonia.⁴⁻⁶

Competing Interests

The authors report no conflicts of interest.

MiHye Park, M.D. and Hyun Joo Ahn, M.D. Samsung Medical Center, Sungkyunkwan University School of Medicine in Seoul, Korea (H.J.A.). hyunjooahn@skku.edu

DOI: 10.1097/ALN.0000000000002952

References

1. Park M, Ahn HJ, Kim JA, Yang M, Heo BY, Choi JW, Kim YR, Lee SH, Jeong H, Choi SJ, Song IS: Driving pressure during thoracic surgery: a randomized clinical trial. *ANESTHESIOLOGY* 2019; 130:385–93
2. de la Gala F, Pineiro P, Garutti I, Reyes A, Olmedilla L, Cruz P, Duque P, Casanova J, Rancan L, Benito P, Vara E: Systemic and alveolar inflammatory response in the dependent and nondependent lung in patients undergoing lung resection surgery: a prospective observational study. *Eur J Anaesthesiol* 2015; 32:872–80
3. Baudouin SV: Lung injury after thoracotomy. *Br J Anaesth* 2003; 91:132–42
4. Sugawara Y, Yamaguchi K, Kumakura S, Murakami T, Kugimiya T, Suzuki K, Nagaoka I, Inada E: The effect of one-lung ventilation upon pulmonary inflammatory responses during lung resection. *J Anesth* 2011; 25:170–7
5. Glynn P, Coakley R, Kilgallen I, Murphy N, O'Neill S: Circulating interleukin 6 and interleukin 10 in community acquired pneumonia. *Thorax* 1999; 54:51–5
6. Takenaka K, Ogawa E, Wada H, Hirata T: Systemic inflammatory response syndrome and surgical stress in thoracic surgery. *J Crit Care* 2006; 21:48–53; discussion 53–5

(Accepted for publication July 24, 2019.)

Extracorporeal Membrane Oxygenation 1-yr Outcome: Comment

To the Editor:

Current trials published in medical literature, and especially the critical care literature, measure similar primary endpoints, namely, mortality. This measure is often an appropriate way of examining the effectiveness of some of our most novel and innovative treatments. Many trials also measure a number of other secondary endpoints, including time free from a ventilator or time spent in the hospital. But often these trials do not describe a patient's neurologic status or functional status after these interventions. Treatments for medical conditions once thought nonsurvivable have advanced rapidly in recent years. Patients can be kept alive in the face of complete failure of multiple organs, often for

extended periods of time. While mortality is an important endpoint, we applaud the recent publication by Grasselli *et al.*¹ for examining endpoints specifically related to a patient's quality of life.

An excellent example of quality of life–related outcomes research is in the cardiac arrest literature and the use of the modified Rankin scale to show neurologic outcomes after interventions.² Given that the incidence of the post–intensive care syndrome, or one of its three components, can be 25% or higher for patients *and* families or caregivers,³ we think the time is right to expand outcomes to examine a patient's functional status and quality of life after discharge from the intensive care unit. In a recent meta-analysis, only 48 studies out of 11,927 (0.4%) included health-related quality of life after discharge from the intensive care unit as an outcome measure.⁴

In a recent large trial of extracorporeal membrane oxygenation (extracorporeal membrane oxygenation for acute respiratory distress syndrome),⁵ 60-day mortality was not different between extracorporeal membrane oxygenation and conventional mechanical ventilation, but there was no information gathered on patients' quality of life after these interventions. Therefore, we were delighted to see Grasselli *et al.*'s¹ publication related to quality of life after extracorporeal membrane oxygenation and applaud them for including these measures in those who survived a very severe illness. The finding that those who underwent treatment with extracorporeal membrane oxygenation had less of an impact on health-related quality of life is especially important for such an invasive intervention. Could extracorporeal membrane oxygenation be a mechanism for helping people recover closer to their baseline functional status? Also, the fact that this intervention is often offered to a younger patient population (in this study, an average age of 54 yr)¹ makes us more hopeful that survivors of extracorporeal membrane oxygenation can have an acceptable quality of life for many years into the future.

We are hopeful that publications such as Grasselli *et al.*'s¹ are the beginning of a trend to new measures in the medical literature. Since “the ultimate goal of health care is to restore or preserve functioning and well-being related to health,”⁶ measures such as these may shed new light on treatments that allow our patients to be happier and more satisfied with their medical care.

Competing Interests

The authors declare no competing interests.

Thomas Phillips, D.O., Ryan J. Fink, M.D. Oregon Health and Science University, Portland, Oregon. phillith@ohsu.edu

DOI: 10.1097/ALN.0000000000002971

References

1. Grasselli G, Scaravilli V, Tubiolo D, Russo R, Crimella F, Bichi F, Corinna Morlacchi L, Scotti E, Patrini L, Gattinoni L, Pesenti A, Chiumello D: Quality of life and lung function in survivors of extracorporeal membrane oxygenation for acute respiratory distress syndrome. *ANESTHESIOLOGY* 2019; 130:572–80
2. Perkins GD, Ji C, Deakin CD, Quinn T, Nolan JP, Scomparin C, Regan S, Long J, Slowther A, Pocock H, Black JJM, Moore F, Fothergill RT, Rees N, O'Shea L, Docherty M, Gunson I, Han K, Charlton K, Finn J, Petrou S, Stallard N, Gates S, Lall R; PARAMEDIC2 Collaborators: A randomized trial of epinephrine in out-of-hospital cardiac arrest. *N Engl J Med* 2018; 379:711–21
3. Rawal G, Yadav S, Kumar R: Post-intensive care syndrome: An overview. *J Transl Int Med* 2017; 5:90–2
4. Gerth AMJ, Hatch RA, Young JD, Watkinson PJ: Changes in health-related quality of life after discharge from an intensive care unit: A systematic review. *Anaesthesia* 2019; 74:100–8
5. Combes A, Hajage D, Capellier G, Demoule A, Lavoué S, Guervilly C, Da Silva D, Zafrani L, Tirot P, Veber B, Maury E, Levy B, Cohen Y, Richard C, Kalfon P, Bouadma L, Mehdaoui H, Beduneau G, Lebreton G, Brochard L, Ferguson ND, Fan E, Slutsky AS, Brodie D, Mercat A; EOLIA Trial Group, REVA, and ECMONet: Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med* 2018; 378:1965–75
6. Fayers PM, Hays R, Hays RD. *Assessing quality of life in clinical trials: Methods and practice*: Oxford University Press, USA; 2005.

(Accepted for publication August 12, 2019.)

Extracorporeal Membrane Oxygenation 1-yr Outcome: Reply

In Reply:

We thank Drs. Phillips and Fink for their interest in our work¹ and we completely agree with all their observations. Through the years, we have assisted with continuous

significant advancements in the care of critically ill patients. Better management of mechanical ventilation and sepsis, advanced monitoring techniques, and more recently, extracorporeal life support techniques, all contributed to improve the rate of survival of critical illness. There is also a tendency to admit older patients with more comorbidities to intensive care units (ICU). At the same time, however, we are realizing that being discharged alive from ICU might not be “the last stage of the journey,” but rather, the beginning of an even longer and potentially more painful ordeal. Indeed, ICU survivors experience not only the direct consequences of the critical illness, but also significant long-term outcomes including physical weakness, neurocognitive impairment, and psychiatric disorders that, in turn, significantly affect their quality of life.² Moreover, families and caregivers are also at increased risk for psychologic sequelae, particularly posttraumatic stress disorder. Hence, in critical patients, long-term mortality, morbidity, and quality of life may be considered more meaningful outcomes than short-term mortality.³

In our study,¹ acute respiratory distress syndrome survivors had almost full recovery of lung function, but severe impairment of quality of life, and stress, anxiety, depression, and posttraumatic stress disorder occurred with alarming frequency. Interestingly, patients treated with extracorporeal membrane oxygenation had a better health-related quality of life than those receiving conventional treatment. We acknowledge that the generalizability of our results is limited, since they come from a single-center study with significant methodologic limitations,⁵ conducted in a highly specialized tertiary referral center. For these reasons, our data do not prove that extracorporeal membrane oxygenation is “a mechanism for helping people recover closer to their baseline functional status,” but they provide a hypothesis for future research. We strongly believe that larger, multicenter, well-designed trials are necessary to understand the actual impact of extracorporeal membrane oxygenation support upon long-term outcomes. Moreover, from a clinical perspective, we believe that specialized multidisciplinary follow-up programs⁵ may allow the early recognition and treatment of physical and/or psychologic sequelae and can play a crucial role to improve the quality of life of patients recovering from critical illnesses.

Competing Interests

Dr. Grasselli received payment for lectures from ThermoFisher (Waltham, Massachusetts) and Pfizer Pharmaceuticals (New York, New York) and travel, accommodation, and congress registration support from Biotest (Dreieich, Germany; all these relationships are unrelated with the current work). The other authors declare no competing interests.

Giacomo Grasselli, M.D., Vittorio Scaravilli, M.D., Davide Chiumello, M.D. Fondazione IRCCS Ca' Granda Policlinico Hospital, and the University of Milan, Milan, Italy. giacomo.grasselli@unimi.it

DOI: 10.1097/ALN.0000000000002970

References

1. Grasselli G, Scaravilli V, Tubiolo D, Russo R, Crimella F, Bichi F, Corinna Morlacchi L, Scotti E, Patrini L, Gattinoni L, Pesenti A, Chiumello D: Quality of life and lung function in survivors of extracorporeal membrane oxygenation for acute respiratory distress syndrome. *ANESTHESIOLOGY* 2019; 130:572–80
2. Inoue S, Hatakeyama J, Kondo Y, Hifumi T, Sakuramoto H, Kawasaki T, Taito S, Nakamura K, Unoki T, Kawai Y, Kenmotsu Y, Saito M, Yamakawa K, Nishida O: Post-intensive care syndrome: Its pathophysiology, prevention, and future directions. *Acute Med Surg* 2019; 6:233–46
3. Adhikari NK, Fowler RA, Bhagwanjee S, Rubenfeld GD: Critical care and the global burden of critical illness in adults. *Lancet* 2010; 376:1339–46
4. Hodgson CL, Brodie D: Comparing apples to oranges? *ANESTHESIOLOGY* 2019; 130:528–9
5. Dinglas VD, Chessare CM, Davis WE, Parker A, Friedman LA, Colantuoni E, Bingham CO, Turnbull AE, Needham DM: Perspectives of survivors, families and researchers on key outcomes for research in acute respiratory failure. *Thorax* 2018; 73:7–12

(Accepted for publication August 12, 2019.)