3. Clemmer TP, Spuhler VJ, Berwick DM, Nolan TW. Cooperation: the foundation of improvement. *Ann Intern Med* 1998;128:1004–1009.
4. Collins FS. Re-engineering translational science: the time is right. *Sci Transl Med* 2011;3:1–6.
5. National Institutes of Health. The CRADA initiative [Internet; accessed 2011 Sept 15]. Available from: http://www.ott.nih.gov/cradas/model_agree.aspx
6. National Institutes of Health. The TRND initiative [Internet; accessed 2011 Sept 15]. Available from: http://trend.nih.gov/
7. Innovative Medicines Initiative [Internet; accessed 2011 Sept 15]. Available from: http://www.imi-europe.org/
8. Foundation for the NIH [Internet; accessed 2011 Sept 15]. Available from: http://www.fnih.org/support/foundation/research-partnership
9. Glass B. The ethical basis of science. *Science* 1965;150:1254–1261.
10. Hyatt HH. Protecting the medical commons: who is responsible? *N Engl J Med* 1975;293:235–241.
11. Petak SM, Coble YD, Duick DS, Gonzales-Campoy JM, Hodgson SF, Lefferts JD, Williams FA, Zeiger MZ. American Association of Clinical Endocrinologists and American College of Endocrinology: position statement on physician/industry relationships. *Endocr Pract* 2009;15:289.
12. Levinsky NG. Non-financial conflicts of interest in research. *N Engl J Med* 2002;347:759–761.
13. Beecher HK. Ethics and clinical research. *N Engl J Med* 1966;274:1354–1360.
14. MacIntyre A. After virtue: a study in moral theory, 3rd ed. Notre Dame, IN: University of Notre Dame Press; 2007.

Published 2012 by the American Thoracic Society
DOI: 10.1164/rccm.201110-1824ED

Extubation and the Myth of "Minimal Ventilator Settings"

Few interventions are more appreciated by a critically ill patient than the removal of an endotracheal tube. Extubation eliminates a major source of discomfort, eases communication, and expedites the path to recovery (1). Nonetheless, as many as 20% of patients require reinsertion of the endotracheal tube, although this is usually accomplished without complications (2). In a small proportion of patients, however, the need for rapid reintubation is lethal in its consequences.

I have been recently consulted about a number of patients who had been breathing comfortably at a low level of pressure support and positive end-expiratory pressure (PEEP) before extubation but, after extubation, developed immediate respiratory compromise followed by cardiorespiratory arrest and irreversible hypoxic brain injury. Analysis of these cases has motivated me to write this commentary.

The vast majority of patients can be successfully weaned from mechanical ventilation irrespective of whether this is executed by intermittent mandatory ventilation, pressure support, or T-tube trials. Randomized controlled trials have revealed differences in the relative speed with which weaning is accomplished by these techniques (3, 4), but the trials do not provide guidance on extubation—especially of the vulnerable patient. Some physicians find it convenient to extubate a patient once he or she can breathe comfortably on a pressure support of about 7 cm H_2O and PEEP 5 cm H_2O. Other physicians do not extubate patients until they are able to breathe on a T-tube circuit (without continuous positive airway pressure [CPAP]) for 30 to 60 minutes. From the perspective of extubation, the difference in endpoints appears unimportant because most patients reaching either target will tolerate tube removal.

But here's the rub. The challenge of clinical medicine is not about taking care of the great majority of patients who do well irrespective of the methods employed by their physicians. Instead, the goal is to take feasible steps that have a high likelihood of circumventing a catastrophe in a small number of instances.

At the point of extubation, a clinician needs to ask him or herself two questions: (*1*) will the patient be able to sustain spontaneous ventilation following tube removal? and (*2*) will the patient be able to protect his or her airway after extubation? My focus is solely on the first question. A patient's ability to successfully sustain spontaneous ventilation after extubation will depend on the mechanical load on the respiratory system secondary to resistance, elastance, and intrinsic PEEP, and how well a patient's respiratory muscles can cope with the imposed load (5). If there is any reason to fear that a patient might experience respiratory difficulties following extubation, it is incumbent on a physician to try and replicate the conditions that the patient will face after extubation—but to do so before removal of the endotracheal tube.

Some physicians claim that application of pressure support of 5 to 10 cm H_2O simply overcomes the resistance engendered by an endotracheal tube (6). Thus, if a patient is able to sustain ventilation at this ventilator setting, he or she should be able to breathe without difficulty following extubation. This claim ignores the inflammation and edema that develops in the upper airways after an endotracheal tube has been in place for a day or more. On removal of the tube, the mucosal swelling produces an increase in upper airway resistance. Straus and colleagues (7) demonstrated experimentally that the respiratory work dissipated against the supraglottic airway after extubation is almost identical to the work dissipated against an endotracheal tube before extubation. Thus, applying any level of pressure support causes physicians to underestimate the respiratory resistance a patient will encounter after extubation. The addition of a small amount of pressure support produces surprisingly large reductions in inspiratory work in ventilated patients: 5 cm H_2O decreases inspiratory work by 31 to 38%, and 10 cm H_2O decreases work by 46 to 60% (8, 9). Nonetheless, most—but not all—patients can tolerate a 30 to 60% increase in inspiratory load at the point of extubation.

Some clinicians believe that insertion of an endotracheal tube leads to the loss of "physiologic PEEP," which is thought to result from intermittent narrowing of the vocal cords (10). The concept of physiologic PEEP, however, is a myth. Lung volume at end-expiration generally approximates the relaxation volume of the respiratory system, which is determined by the static balance between the opposing elastic recoil of the lung and chest wall (11, 12). Accordingly, static recoil pressure of the respiratory system is zero at end-expiration in a healthy adult. The addition of 5 cm H_2O of PEEP can decrease work of breathing by as much as 40% in ventilated patients (9). PEEP also produces a substantial increase in cardiac output in patients with left-ventricular failure (13). In patients with heart or lung disease, the elimination of PEEP at the moment of extubation can lead to rapid cardiopulmonary decompensation. As when assessing patients on low levels of pressure support, observing a patient breathe on CPAP 5 cm H_2O hampers the ability of a physician to predict the patient's capacity to handle an increase in cardiorespiratory load following extubation.

The expression "minimal ventilator settings" has become a commonplace, suggesting that pressure support of 5 cm H_2O or CPAP 5 cm H_2O provides little assistance to a patient. This cliché is oxymoronic, analogous to saying that a woman can be minimally pregnant. The increase in cardiorespiratory load engendered by a switch from pressure support of 5 cm H_2O or CPAP 5 cm H_2O to zero assistance at the point of extubation is enough to precipitate a lethal cataclysm in some patients. Because it is difficult to foretell which patients will be unable to cope with an increased cardiorespiratory load after extubation, I check that patients are able to breathe without respiratory distress for about thirty minutes on a T-piece without CPAP before removing an endotracheal tube (1). (Although less than ideal, an equivalent assessment can be performed through the use of Flow-by—provided that pressure support and CPAP are both set at zero.)

Taking simple steps to prevent infrequent occurrences that lead to a clinical catastrophe should dictate the practice of medicine, rather than employing approaches that are convenient to physicians and successful in most patients.

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

Acknowledgment: The author thanks Laurent Brochard, M.D., for comments on an earlier version of the manuscript.

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References

1. Tobin MJ. Mechanical ventilation. *N Engl J Med* 1994;330:1056–1061.
2. Thille AW, Harrois A, Schortgen F, Brun-Buisson C, Brochard L. Outcomes of extubation failure in medical intensive care unit patients. *Crit Care Med* 2011;39:2612–2618.
3. Brochard L, Rauss A, Benito S, Conti G, Mancebo J, Rekik N, Gasparetto A, Lemaire F. Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. *Am J Respir Crit Care Med* 1994;150:896–903.
4. Esteban A, Frutos F, Tobin MJ, Alía I, Solsona JF, Valverdú I, Fernández R, de la Cal MA, Benito S, Tomás R, *et al.* A comparison of four methods of weaning patients from mechanical ventilation. *N Engl J Med* 1995;332:345–350.
5. Jubran A, Tobin MJ. Pathophysiologic basis of acute respiratory distress in patients who fail a trial of weaning from mechanical ventilation. *Am J Respir Crit Care Med* 1997;155:906–915.
6. Mohsenifar Z, Hay A, Hay J, Lewis MI, Koerner SK. Gastric intramural pH as a predictor of success or failure in weaning patients from mechanical ventilation. *Ann Intern Med* 1993;119:794–798.
7. Straus C, Louis B, Isabey D, Lemaire F, Harf A, Brochard L. Contribution of the endotracheal tube and the upper airway to breathing workload. *Am J Respir Crit Care Med* 1998;157:23–30.
8. Jubran A, Van de Graaff WB, Tobin MJ. Variability of patient-ventilator interaction with pressure support ventilation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995;152:129–136.
9. Sassoon CS, Light RW, Lodia R, Sieck GC, Mahutte CK. Pressure-time product during continuous positive airway pressure, pressure support ventilation, and T-piece during weaning from mechanical ventilation. *Am Rev Respir Dis* 1991;143:469–475.
10. Sagana R, Hyzy RC. Positive end-expiratory pressure (PEEP). UpToDate, Waltham, MA, version 19.3: September 2011
11. Vinegar A, Sinnett EE, Leith DE. Dynamic mechanisms determine functional residual capacity in mice, *Mus musculus. J Appl Physiol* 1979; 46:867–871.
12. Martin JG, De Troyer A. The thorax and control of function residual capasit. In: Roussos C, Macklem PT, editors. The thorax: part B. Vol 29 of Lung biology in health and disease. New York: Marcel Dekker; 1985. pp. 899–921.
13. Pinsky MR. Effect of mechanical ventilation on heart-lung interactions. In: Tobin MJ, editor. Principles and practice of mechanical ventilation. New York: McGraw-Hill; 2006. pp. 729–757.

DOI: 10.1164/rccm.201201-0050ED

Activin A: A Mediator Governing Inflammation, Immunity, and Repair

Acute respiratory distress syndrome (ARDS), the most severe form of acute lung injury (ALI), is a major cause of morbidity and mortality in intensive care units (1). It represents a common clinical disorder characterized by alveolar epithelial and endothelial injury, apoptosis, and necrosis. Additional features include the development of pulmonary edema and inflammatory cell accumulation. These functional and structural alterations of the lung finally cause acute respiratory failure. A reparative response mediated by cytokines and growth factors is responsible for the resolution of the injury, but an uncontrolled response may mount into a fibroproliferative disorder (2). Therapies targeting selected proximal proinflammatory mediators that were successful in animal models failed to improve survival in patients. Thus the current treatment of patients lacks molecular- and pathophysiology-based strategies and remains supportive, resulting in an unacceptably high mortality (1, 2).

Proinflammatory cytokines as tumor necrosis factor (TNF)-α and growth factors including transforming growth factor (TGF)-β have been identified as playing a key role in the pathogenesis of ALI (2). Activin A, a member of the TGF-β superfamily, is a homodimeric protein that is bound and thereby inactivated by its endogenous inhibitor follistatin (recently reviewed in Reference 3; *see* Figure 1). It has been discovered to be a mediator in acute and chronic inflammatory diseases such as asthma, sepsis, and inflammatory bowel disease. Activin A exhibited potent proinflammatory actions such as the release of proinflammatory cytokines, synthesis of nitric oxide, and generation of eicosanoids (3). In addition, it has been shown to be a modulator of immunity based on antiinflammatory effects in activated monocytes and lymphocytes. It inhibited the maturation of dendritic cells and the activation and proliferation of T and B lymphocytes, and induced the development of $Foxp3^+$ regulatory T cells (Treg) (3–6).

The study by Apostolou and coworkers in this issue of the *Journal* (pp. 382–391) elucidated the impact of activin A on ALI using a murine adenovirus-mediated overexpression model (7). Overexpression of activin A led to an acute and prolonged lung injury over more than 8 weeks. Typical characteristics such as alveolar epithelial cell (AEC) apoptosis, proinflammatory cytokine release, invasion of leukocytes, hyaline membrane formation, reduced pulmonary compliance, and even a systemic procoagulant state were detectable during the early phase of ALI. In the later phase of the prolonged time course, inordinate repair as well as structural changes occurred, including honeycomb-like

Supported by Excellence Cluster Cardio-Pulmonary System (ECCPS), Transregio (TR 84) "Innate Immunity of the Lung" (Deutsche Forschungsgemeinschaft), and International Research Training Group (IRTG) 1062, "Signalling Mechanisms in Lung Physiology and Disease" (Deutsche Forschungsgemeinschaft).