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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.

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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

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technology-driven procrastination to creep into clinical decision-making.

As the US data confirm, high-volume centers are best placed for such decision-making, being associated with a 20% improvement in absolute survival rates.[5] It is therefore difficult for Dr Trudzinski and colleagues to justify their criticisms of our experience in candidate selection. According to national registries, our center has performed 2.5-fold more LTx procedures (n = 1,010) in the last 10 years than the respective centers of the corresponding authors combined (www.dso.de, https://optn.transplant.hrsa.gov/data/view-data-reports/center-data/). In addition, we have published a series of pioneering articles regarding mechanical support in LTx, including novel bridging strategies[4] and the largest single-center study on LTx candidates on mechanical support.[6]

The published recommendations are compatible with the consensus from the International Society of Heart and Lung Transplantation.[7] This document is recommended to the authors, giving more balance than personal opinion of critical care physicians in a low-volume center. Should the authors wish to better understand their social and ethical commitments toward future candidates, we encourage visiting a high-volume program.

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CHEST-ATS Guidelines on Weaning/Extubation Ignore Scientific Principles

To the Editor:

The new American College of Chest Physicians/American Thoracic Society guidelines on ventilator weaning/extubation[1-3] fail to take into account well-proven principles of diagnostic testing and basic pulmonary physiology. I invite the committee's response to four points.

1. The committee states "weaning predictors…lack sufficient positive and negative predictive value to make them routinely useful." The assertion is unreferenced. The previous guidelines reached the same conclusion based on a meta-analysis that contained 15 major methodological errors.[4] No error has been defended. Members of the previous committee were contacted repeatedly by the Editor in Chief of *Critical Care Medicine* but refused to respond.[5] The committee chair merely repeated assertions.[5] On what data does the committee base its assertion?

Bayesian principles pivot around the importance of pretest probability and form the bedrock for the evaluation of any clinical/diagnostic test.[6] Ignoring these principles when rendering recommendations is irresponsible.

2. The committee recommends initiating the weaning process with a spontaneous breathing trial (SBT). To begin weaning with a confirmatory test (SBT) rather than a screening test (weaning predictors) goes against every principle of diagnostic testing.[6,7] Any unnecessary delay in commencing an SBT will cause prolongation of mechanical ventilation. Weaning predictors are not done to forecast a failed SBT; their primary purpose is to alert a physician that a patient

might tolerate an SBT sooner than he/she otherwise thinks and move that SBT to an earlier time. By waiting until caregivers have decided to undertake a 30- to 120-min confirmatory test, as opposed to a 1- to 2-min screening test, the committee is axiomatically prolonging the duration of ventilation.

3. The committee makes explicit recommendations for weaning/extubation based on the sensitivity/specificity of SBTs. The committee fails to inform readers that such data do not exist and are unobtainable. Collection of such data would require extubating all patients in whom an SBT fails and counting the number who require reintubation—a patently unethical study.
4. Randomized trials comparing postextubation outcome following pressure support vs T-tube trials reveal no statistical difference in mortality. But these trials (in aggregate) do not come even remotely close to possessing sufficient statistical power to detect differences in death or catastrophe following extubation. Numerous experimental studies show that work of breathing at pressure support of 5 to 8 cm H_2O is approximately 40% less than at pressure support of 0 cm H_2O.[8] Ignoring the mathematical difference in the two settings leads to patient deaths.[8]

The new American College of Chest Physicians/American Thoracic Society guidelines risk unnecessary deaths because they ignore the scientific basis of weaning/extubation: Bayesian foundation and physiological principles.

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Response

To the Editor:

Regarding Dr Tobin's first point, he correctly notes that we did not reference our statement "Moreover, weaning predictors such as maximal inspiratory pressure, static respiratory system compliance, and rapid/shallow breathing index lack sufficient positive and negative predictive value to make them routinely useful for judging patients' ability to wean."[1] We do so now in the work by Meade et al.[2] In support of our statement, we also reference a study in which Conti et al[3] evaluated nine weaning parameters prospectively. Likelihood ratios for all weaning parameters ranged from 0.61 to 1.87, indicating only small, clinically unimportant changes in the posttest probability of success or failure. The authors applied Bayes' theorem and concluded that all indexes were of little use in discriminating those who could be successfully weaned and those who would fail extubation. Consistent with our guideline, they concluded "…the systematic use of these weaning predictors is thus of little use clinically."

The second critique relates to how to initiate the weaning process and expresses a concern that beginning with a spontaneous breathing trial (SBT) will prolong weaning unnecessarily. Our recommendation specifically addresses how to conduct an SBT once patients meet readiness criteria. The purpose of using readiness criteria, which some refer to as a safety screen, is to identify patients ready to be assessed with an SBT. We agree that readiness criteria are not meant to predict success during an SBT. Thus, readiness criteria, which we chose not to define, should not be overly restrictive. Indeed, a randomized controlled trial found that screening subjects receiving ventilation with *f*/Vt as part

might tolerate an SBT sooner than he/she otherwise thinks and move that SBT to an earlier time. By waiting until caregivers have decided to undertake a 30- to 120-min confirmatory test, as opposed to a 1- to 2-min screening test, the committee is axiomatically prolonging the duration of ventilation.

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Response

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of the weaning algorithm delayed weaning by 1 day, a difference that was statistically significant.[4] Moreover, use of *f*/Vt did not reduce the incidence of extubation failure, leading the authors to conclude that it should not be used routinely in weaning decision-making.

The third point relates to the sensitivity and specificity of SBTs, but Dr Tobin misstates our recommendation. We at no point make "explicit recommendations for weaning/extubation based on sensitivity/specificity of SBTs." Our recommendation to use pressure augmentation was not based on sensitivity/specificity data but, rather, on clinical outcomes; that is, we made recommendations about how to conduct SBTs based on the outcomes observed in randomized trials. Dr Tobin is correct that determining sensitivity and specificity of SBT would require extubating subjects who fail the SBT. Perhaps not all intensivists would be comfortable with the ethics of conducting such a study, but this approach has been used in a pediatric population, with the following results: sensitivity, 95%; specificity, 37%; positive predictive value, 92%; and negative predictive value 50%.[5]

We agree that pressure augmentation during the SBT reduces the work of breathing compared with work of breathing after extubation, during T-piece breathing, or during continuous positive airway pressure of 0 cm H_2O.[6] Regardless, it does not necessarily follow that conducting the SBT with pressure augmentation leads to premature extubation. Models limited to mathematical and physiologic data are not sufficient, as highlighted by data showing that pressure augmentation not only increases the likelihood of a successful SBT but also of successful extubation.[7] Although complications associated with failed extubation are relevant, Dr Tobin fails to acknowledge the risks associated with prolonging mechanical ventilation.

We appreciate the opportunity to clarify our recommendations. Although we would welcome a stronger evidence base, we believe these guidelines reflect best practice based on current information.

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Instability of Willingness to Accept Life-Sustaining Treatments

Does Race Play a Role?

To the Editor:

I read with extreme interest the recent article by Houben et al[1] entitled, "Instability of Willingness to Accept Life-Sustaining Treatments of Patients With Advanced Chronic Organ Failure During 1 Year" published in this issue of *CHEST* (May 2017). The authors' findings certainly echo the complexity of end-of-life (EOL)