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Ventilator Discontinuation: Why Are We Still Weaning?

In the practice of critical care, discontinuation of mechanical ventilation is an important everyday clinical issue. Clinicians are often too conservative in their practice of liberating patients from mechanical ventilation, potentially submitting them to complications related to unnecessary prolongation of intubation and ventilation. In 2001, evidence-based guidelines were published related to the ventilator discontinuation process, and they remain relevant today (1). These guidelines stress the importance of establishing readiness for a spontaneous breathing trial (SBT), performing an SBT to establish ventilator discontinuation potential, and identifying causes of a failed SBT.

Discontinuing ventilator support is not the same as weaning ventilator support. The former is the termination of ventilation in those patients for whom it is judged no longer necessary; the latter is the process of gradual reductions in the level of ventilator support as tolerated. This distinction is important because weaning in those who no longer need ventilator support will necessarily delay the discontinuation process. Thus, the evidence-based guidelines noted above repeatedly emphasize that, after a commonsense clinical assessment, the best approach to determining readiness for ventilator discontinuation is an SBT (1). Determining SBT tolerance should involve an integrated assessment of gas exchange, respiratory pattern, hemodynamics, and comfort. The use of specific parameters in isolation to guide SBT initiation and tolerance is controversial and probably unwise. For example, one randomized controlled trial reported that the use of a common assessment parameter, the rapid-shallow breathing index, prolonged time on the ventilator (2). In practice, the majority of patients successfully complete their first SBT (3, 4). Those who do not tolerate an SBT are returned to comfortable ventilator settings and the SBT is repeated after the reasons for failure are explored and corrected (1).

An international consensus panel suggested classification of mechanically ventilated patients recovering from respiratory failure into three groups according to the length of the ventilator discontinuation process (5). Unfortunately, this group used the term weaning interchangeably with the discontinuation process. *Simple weaning* refers to patients who proceed from initiation of the discontinuation process to successful extubation on the first attempt, *difficult weaning* refers to patients who fail initial attempts at discontinuation and require up to three SBT or as long as 7 days from the first SBT to achieve successful discontinuation, and *prolonged weaning* refers to patients who fail at least three discontinuation attempts or require more than 7 days of discontinuation attempts after the first attempt.

In this issue of the *Journal*, Peñuelas and coworkers (pp. 430) evaluated the outcomes of ventilated patients according to this classification scheme (6). This is a secondary analysis of patients included in a prospective international observational cohort study (7). Although only 6% of patients in the study by Peñuelas and colleagues were classified as prolonged weaning, not surprisingly this group had significantly longer length of stay and higher mortality. The authors also identified risk factors associated with prolonged weaning, which include severity of illness, days on the ventilator before the first discontinuation attempt, chronic pulmonary disease other than chronic obstructive pulmonary disease, pneumonia as the reason for mechanical ventilation, and the level of positive end-expiratory pressure before initiation of a discontinuation attempt.

Two other studies have also classified patients according this international consensus scheme. Funk and coworkers (8) found that 14% of patients fit the prolonged weaning category, and there was a higher mortality rate in these patients. Tonnelier and colleagues (9) reported that 30% of patients fit the prolonged weaning category. In this study, although prolonged weaning was associated with higher ICU and hospital mortality, it did not affect 1-year mortality.

Peñuelas and coworkers report that the first attempt at ventilator discontinuation was an SBT in 82% of the patients in the simple weaning group, but an SBT was used for the first attempt in less than half of the patients in the difficult weaning and prolonged weaning groups. Instead, gradual support reduction (true weaning) strategies using either synchronized intermittent mandatory ventilation (SIMV) or pressure support ventilation (PSV) was the approach. As noted above, the potential exists that this gradual support reduction approach might have actually prolonged the ventilator discontinuation process in some patients. Indeed, if an SBT identifies ventilator discontinuation readiness, a gradual support reduction approach can only prolong the process.

It is also of interest to note that Peñuelas and colleagues found that a T-piece trial was used in fewer than half of the patients receiving an SBT (6). A significant proportion of patients received an SBT on continuous positive airway pressure (CPAP) or low-level PSV. During an SBT, PSV and PSV plus PEEP/CPAP can markedly modify the breathing pattern, inspiratory muscle effort, and cardiovascular response as compared with a T-piece. The use of low levels of support (PSV $\pm$ PEEP/CPAP) may mislead clinicians about the tolerance of an SBT (10). Thus, it might be important to conduct an SBT with no additional support. However, this does not need to be a T-piece and can be performed by setting both the PSV and PEEP/CPAP on the ventilator to zero.

More than 25% of patients received SIMV in the study by Peñuelas and coworkers (6). Randomized controlled trials have reported the poorest ventilator discontinuation outcomes with this approach (3, 4), and it is not recommended in evidence-based guidelines (1, 5). A recent secondary analysis of the same patients as those in this study was not able to identify benefit for SIMV when compared with continuous mandatory ventilation (11). Perhaps it is time to abandon this mode for which evidence is lacking for benefit (12). New modes are available on the current generation of ventilators with a claim of being able to automatically wean the patient, although evidence supporting benefit is not consistent (13, 14). In some ways, this is reminiscent of the introduction of SIMV almost 40 years ago (12). We have heard it suggested that automatic weaning might be useful in a setting in which adequate staffing is lacking. However,

because ventilators with these automated support reduction modes are more expensive, it is not likely that a hospital can afford these ventilators if they cannot afford adequate staff.

The study design of Peñuelas and colleagues leaves several important unanswered questions. It is not known how often protocols were used to guide sedation management and attempts to withdraw ventilator support. Also unknown is what clinical measures were implemented to resolve the underlying disease process in the patients with prolonged weaning. Accumulating evidence supports the use of noninvasive ventilation to allow earlier extubation and to prevent extubation failure (15). It is not known how often patients were extubated to noninvasive ventilation in this study.

So why are we still weaning patients from the ventilator, despite the fact that the majority of patients successfully complete their very first SBT? The evidence supporting outcome benefits from gradual reduction of respiratory support is nonexistent (1). The ventilator discontinuation process should focus on treatment of the underlying disease process rather than manipulation of the ventilator settings. If the patient is appropriately monitored, SBTs are safe and they are the best way to determine when ventilation can be discontinued. SBTs are often incorporated into multidisciplinary protocols in which the roles of physicians, respiratory therapists, and nurses are identified with the goal of ventilator discontinuation when appropriate.

An important impediment to ventilator discontinuation is excessive use of sedation. Tolerance of a spontaneous awakening trial prior to performing an SBT improves patient outcomes (16). We recommend an approach in which sedation is stopped, a commonsense screen is used to determine readiness for an SBT, extubation is considered if the SBT is successful, comfortable interactive ventilator support is provided to those failing an SBT, and there is an attempt to identify and correct the cause of a failed SBT before it is repeated (Figure 1). There is no need in this schema for gradual support reduction between regular SBT assessments—this likely only serves to unnecessarily stress patients and waste professional resources.

Due to the added morbidity and mortality associated with unnecessary delays in ventilator discontinuation, the underlying disease process should be aggressively treated in any patient who fails an SBT. Most important is to concentrate on correcting the underlying disease process and conducting regular SBTs to identify when mechanical ventilation can be discontinued. It is time to stop weaning from the ventilator and to start weaning old-fashioned ideas.

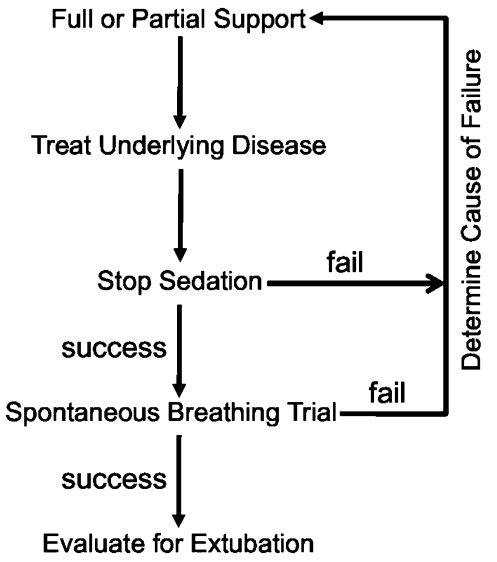

Figure 1. An approach to discontinuation of mechanical ventilation that stresses treatment of the underlying disease process, stopping sedation, and performing spontaneous breathing trials.

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Predicting Mortality in Patients with Acute Lung Injury

Acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) are common disorders estimated to affect nearly 200,000 people per year in the United States alone (1). Despite improvements in supportive care, the overall mortality rate for these patients continues to hover near 40% (2). In King County, Washington, Rubenfeld and coworkers reported that the incidence of ARDS was twice as high in patients over 74 compared with patients between 60 and 64 years of age, and that older patients who developed the syndrome were significantly more likely to die (1). Therefore, the incidence of ALI/ARDS and its associated mortality are likely to rise as the population ages, particularly in the developed world.

Novel therapies identified through bench and clinical research and translated to clinical practice have led to substantial improvements in ICU care in the past decade. Advances in imaging and laboratory diagnostics have dramatically improved our ability to identify and treat primary causes of critical illness, reducing diagnostic procedure–related morbidity and mortality. New antimicrobials and vasoactive agents, more effective therapies to prevent stress ulcer and venous thromboembolism, and a variety of new agents to treat other complications of critical illness effectively reduce the risk of ICU-related complications. In addition, we have learned to better use the resources available to us in the ICU. Positive pressure ventilation strategies designed to prevent ventilator-induced lung injury, interruptions in sedation, improved fluid management, limitation of empiric antibiotic usage, strategies to prevent ventilator-associated pneumonia, and the use of protocols and checklists to ensure consistent patient care delivery have all improved the supportive care of patients with ALI/ARDS (3–8).

Given these and other research-driven improvements in supportive care, it is surprising that the crude mortality in most studies conducted in patients with ARDS remains relatively constant (2). One possible explanation is that the lack of change represents a true success as our ICUs fill with older patients with more co-morbidities. Even if this is true, it is clear that for a significant proportion of patients with ALI/ARDS, even the best supportive therapy is not enough. For these patients, novel therapies designed to interrupt ongoing lung injury or promote healing lung that investigators have identified as effective in preclinical or phase II trials may improve outcomes (9). Therefore, when testing potentially toxic new therapies investigators need biomarkers to identify subsets patients with ARDS at a higher risk of death, as the risk-to-benefit profile in these patients is more likely to be favorable. Investigators have frequently examined bronchoalveolar lavage fluid to identify predictive biomarkers, as the procedure can be done safely, is often performed as part of routine clinical care, and can reveal valuable insight into the severity of damage to the alveolar membrane (5, 10).

The low-density lipoprotein receptor–related protein (LRP-1) is a large endocytic receptor that is expressed in many tissues, including the lung (11). LRP-1 recognizes more than 30 different ligands with varying affinity, facilitating their cellular uptake via endocytosis (11). In the low pH of the endosome, a conformational change in the structure in LRP-1 causes it to release the ligand, which can be recycled or degraded in the lysosome (12). In this issue of the *Journal*, Wygrecka and colleagues (pp. 438) found that the levels of soluble LRP-1 (sLRP-1) were increased in patients with ARDS compared with a control group of spontaneously breathing subjects or mechanically ventilated patients with cardiogenic pulmonary edema (13). The BAL levels of sLRP-1 were positively correlated with APACHE II scores and were significantly higher in patients who died from ARDS compared with those who survived. BAL fluid from patients with ARDS induced sLRP release from lung fibroblasts (but not epithelial cells or macrophages) through a mechanism that required TNF-α and membrane type-1 matrix metalloproteinase. The investigators went on to show that sLRP-1 inhibited the uptake of matrix metalloproteinases-2 and -9, which might enhance tissue injury. In support of this hypothesis they found that BAL fluid levels of MMP-2 and -9, and the basement membrane protein laminin, were positively correlated with the levels of sLRP-1 in the patients with ARDS.

Wygrecka and coworkers have identified one important mechanism by which LRP-1 might contribute to the pathophysiology of ARDS. In addition, LRP-1 has been shown to regulate the activity of platelet-derived growth factor and transforming growth factor-β1, promote the clearance of Factor VIII, modulate the activity of the fibrinolytic system by binding with the urokinase-type plasminogen activator, contribute to the tPA-mediated increase in blood–brain barrier permeability after stroke, promote focal adhesion disassembly, and enhance cell migration, all of which may be important in the development and resolution of ALI (11). In addition, LRP-1 plays an important role in the phagocytosis of apoptotic cells and foreign particles. For example, Gardai and colleagues reported that in the lung LRP-1 interacts with surfactant proteins-A and -D to promote phagocytosis and induce inflammation in response to foreign particles or damaged cells (14). Further study will be required to determine the predominant mechanism(s) by which LRP-1 might contribute to the pathogenesis of ALI/ARDS.

Before it can be used to direct treatment, a biomarker must be shown to have a high sensitivity, specificity, and positive and negative predictive value for the predicted outcome; be reproducible outside of the institution or laboratory in which it was developed; demonstrate biological plausibility; and be validated in a cohort of patients independent from the original cohort (15). Substantial further investigation is required before bronchoalveolar lavage fluid levels of sLRP-1 can be used as a biomarker to identify patients at risk of death from ARDS. However, the findings of Wygreka and coworkers add to those conducted by other investigators who collectively have identified an array of physiologic and laboratory parameters to improve our ability to identify patients at high risk of death earlier in their clinical course (16). Rigorous prospective examination of their utility as clinical prediction tools may open the door for the use of active pharmacologic or biological interventions to prevent ALI/ARDS-associated mortality.