The Effect Of External Positive End-Expiratory Pressure On Extubation Rate In Patients With Intrinsic Positive End-Expirtory Pressure

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A. Study Purpose and Rationale

Intubation and mechanical ventilation are associated with several major complications despite their lifesaving potential. It is thus important to discontinue mechanical ventilation and remove the endotracheal tube from the patient when spontaneous ventilation is sustained. The process of discontinuing mechanical ventilation may constitute a major clinical challenge and become the principal cause of prolonged patient stay in an intensive care unit. Thus, for both clinical and economic reasons, every effort should be made to determine as soon as possible which patients can be rapidly extubated, and to keep the weaning period to a minimum.

In the intensive care unit (ICU) setting, chronic obstructive pulmonary disease COPD is perhaps the most common cause of acute ventilatory failure characterized by the inability of a failing respiratory pump to provide a level of alveolar ventilation sufficient to meet the required metabolic demands. Weaning patients with chronic obstructive pulmonary disease (COPD) is a particularly difficult issue. The reasons explaining these difficulties are mainly related to respiratory muscle weakness, abnormalities in arterial blood gases, malnutrition, derangement in respiratory system mechanics, and eventually other co-morbidities. It has been shown that COPD is one of the main factors explaining weaning duration: these patients are more difficult to be weaned than those who had an acute respiratory failure without COPD or those who needed mechanical ventilation for a neurological disease,

Positive end- expiratory pressure (PEEP) has been considered unhelpful and contraindicated because (1) the level of hypoxemia in patients with COPD generally is mild and responds readily to low levels of supplemental oxygen and (2) severe COPD is characterized by augmentation of lung, volume; a further increase in lung volume eventually induced by application of PEEP would impair respiratory muscle efficiency and enhance risk of barotrauma and hemodynamic depression.

The presence of intrinsic (or auto-) PEEP implies that the inspiratory muscles have to produce an initial effort to overcome the opposing recoil pressure before inspiratory flow can begin. In that respect, intrinsic PEEP acts as an inspiratory threshold load and represents an additional impedance the respiratory muscles have to face. Application of external PEEP may reduce the gradient between alveolar and airway opening pressure, thereby counterbalancing the inspiratory threshold load caused by intrinsic PEEP. Recent work has suggested that, in COPD patients with expiratory flow limitation, the application of external PEEP during assisted mechanical ventilation can counterbalance and reduce the inspiratory threshold load imposed by auto-peep without causing further hyperinflation. Furthermore, in patients with COPD during acute ventilatory failure, the addition of PEEP decreased the inspiratory work of breathing by reducing the inspiratory mechanical load caused by intrinsic PEEP. Several studies have shown that further hyperinflation is observed only when the applied PEEP was higher than 85- 100% of the measured intrinsic PEEP. Although there is evidence that external PEEP is effective in decreasing the work of breathing and can be applied safely without increasing the hyperinflation and the risk of barotrauma, there has been no direct evidence that external PEEP decreases time to extubation.

Intrinsic PEEP can be measured as the end-expiratory airway plateau obtained by occluding the airway until peak airway opening pressure remains unchanging. Alternatively, several newer ventilator models are equipped to give accurate measurements of intrinsic PEEP. Part of the positive end-expiratory alveolar pressure observed in patients with COPD, in stable condition or during acute exacerbation, can be explained by expiratory muscle contraction during expiration. The presence of abdominal muscle activity during the occlusion may overestimate the measured auto-PEEP. This error can be corrected if

one knows (by measuring gastric pressure) the changes in abdominal pressure during the end-expiratory occlusion. An alternative is to suppress all respiratory muscle activity prior to hyperventilating for a short period (then briefly restoring, the normal ventilatory pattern) or giving small doses of short duration sedative. It has been shown that respiratory mechanics measurements do not change in mechanically ventilated patients if they are obtained during sedation alone or with sedation associated with muscle paralysis.

B. Study Design and Statistical Analysis

Patients will be enrolled in a prospective, randomized blinded study to determine whether use of extrinsic PEEP in COPD patients with intrinsic PEEP will shorten the duration of weaning and/or lead to a higher success rate of extubation. It will be conducted in the intensive care unit of the Columbia Presbyterian Medial Center Milstein Hospital and Allen Pavilion. Intubated patients with COPD are identified by their primary physician to be ready for weaning trials. Those patients with permanent neurologic or muscular abnormalities indicating they would need indefinite ventilator support will be excluded. Those with concurrent pneumothorax, prior history of spontaneous pneumothorax or latrogenic pneumothorax within six months will be excluded. The patients are candidates for an extubation protocol when they were in medically stable condition, afebrile, the cause for instituting mechanical ventilation is resolved or is significantly improved, generate tidal volumes above 5 ml per kilogram of body weight, have a respiratory frequency of less than 35 breaths per minute, and mean oxyhemoglobin saturation (Sa02) greater than 90% with inspired oxygen fraction (Fi02) of 0.40 to 0.50. The diagnosis of COPD will be confirmed by history and physical examination and previous pulmonary function tests, if available.

The patients with intrinsic PEEP (greater than 2 em H20) are easily ascertained by manipulation of the ventilator in those models equipped with this function. Alternatively, intrinsic PEEP can be determined by occluding the expiratory port of the mechanical ventilator for two seconds at the end of expiration and reading the positive needle defection on the pressure manometer. The average of five trials is taken as the intrinsic PEEP. All measurements will be taken while patient is fully sedated with fentanyl or propofol. Those patients with significant intrinsic PEEP (greater than 2 cm H20) will be enrolled in the study. Patients or their surrogates will provide informed consent.

Patients enrolled in the study will be stratified into 3 groups based on their risk to require prolonged mechanical ventilation. Two points each will be given to the following variables: age greater than 65, time on ventilator greater than or equal to 10 days, alveolar- arterial oxygen gradient (A-02 gradient) greater than 30 and spontaneous tidal volume (VT) less than 325 ml, and prior history of difficult extubation. A history of difficult extubation is defined as having one of the following: prior intubation requiring tracheostomy, prolonged intubation in a non-ICU setting (e.g. regional weaning center, medical or surgical bed in a hospital) or history of failed extubation. One point will be given to the following variables: age greater than 50 but less than 65, time on ventilator greater than 5 days but fewer than 10 days, A-a02 gradient 30-40. Patients will then be divided into three groups based on their scores: high risk (6-8 points), moderate risk (3-5 points) and low risk (0-2 points).

Assuming a standard deviation of three and expecting a difference of two days, 45 patients will be enrolled in each group (total 90 patients). Patients in each stratum will be randomized into two groups using, a random number table. One group will receive no external PEEP and the other group will receive external PEEP at a value equal to 75% of their intrinsic PEEP. The physicians, nurses and respiratory therapists will be blinded to patient assignment by covering the PEEP indicator on the mechanical ventilators. Patients will be followed from the start of their weaning, trials to their successful extubation. Weaning will proceed by the method and duration decided by the primary physician. The primary physician will terminate the trial if a patient has any of the following signs of distress: a respiratory frequency more than 40 breaths per minute, arterial oxygen saturation below 90%, heart rate above 140 beats per minute or a sustained increase or decrease in the heart rate of more than 20 percent, systolic pressure above 180 mm Hg or below 90 min Hg, agitation, diaphoresis, or anxiety. Patients who have

none of these features and adequate blood gas analysis as determined by the primary physician will be extubated. Extubation can be postponed for a maximum of 24 hours if the primary physician thought that a patient might not be able to clear secretions or protect the airway against aspiration. A successful extubation will be defined as removal from mechanical ventilation for at least 3 days. Those requiring resumption of mechanical ventilation will resume in the trial in the same group until successfully extubated.

The mean and standard deviation of length of time (in days) from the initiation of weaning to successful extubation will be compared between the two groups. T-test will be used to compare the results. All patients are expected to be extubated within 2 weeks. Kaplan-Meier plots will be made of the probability of successful weaning in each group.

C. Study Procedures

a. Study Drugs

None.

b. Medical Devices

Patients will receive mechanical ventilation from the Puritan/Bennett 7200 Series ventilator.

c. Study Questionnaires

None

d. Study Subjects

Study subjects will be patients with COPD receiving mechanical ventilation for more than 24 hours.

e. Recruitment of Subjects

The surrogate or, when appropriate, meeting the inclusion criteria will be approached by the primary physician and asked for consent.

f. Confidentiality of Study Data

Except for the identity of those subjects receiving extrinsic PEEP, data will be available only to those physicians, nurses, and respiratory therapists caring directly for the subjects and the principal investigator.

g. Potential Conflict of Interest

None

h. Location of the Study

Data will be collected from the 16-bed intensive care unit of the Columbia Presbyterian Medical Center Milstein hospital and the 12 bed ICU of the Allen Pavilion.

i. Potential Risks

The potential risks faced by patients enrolled in the study are the same as those of mechanical ventilation, including barotrauma, infection and pneumothorax.

j. Potential Benefits

Earlier removal from mechanical ventilation as compared to those not receiving the intervention would reduce the likelihood of complications of mechanical ventilation.

k. Alternative Therapies

External PEEP is not routinely given to patients with COPD and intrinsic PEEP despite research suggesting its benefits. Therefore, a standard-of-care therapy will not be withheld from those patients not receiving external PEEP.

l. Compensation to Subjects

None.

m. Costs to Subjects

None.

n. Minors as Research Subjects

No patients younger than 18 years of age will be enrolled in the study.

o. Radiation or Radioactive Substances

None.