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PEEP in the morning, PEEP at night*

Similar to the well-known children's author, Dr. Seuss, positive end-expiratory pressure (PEEP) has received a great deal of press. During mechanical ventilation, PEEP is used on one patient, two patients, red patients, and especially blue patients. Barach et al. (1) first described the use of PEEP in 1938. Ashbaugh and colleagues reported (2) in the classic adult respiratory distress syndrome (ARDS) article that patients had improved oxygenation with lower F_{IO_2} concentrations with the use of PEEP. The benefits of PEEP for patients with ARDS and acute lung injury (ALI) include improvement in lung mechanics, gas exchange, and alveolar recruitment. Alveolar changes from the use of PEEP preserve current distention, prevent closure during expiration, and use collapsed areas of the lung (3). PEEP may limit the amount of injury from mechanical ventilation due to the prevention of alveolar collapse.

It is generally accepted that mechanical ventilation with no PEEP is injurious and, conversely, that using excessive PEEP may also be detrimental, but find-

ing the optimal PEEP may be somewhat elusive. The absolute number for "best" PEEP has been debated in the literature for years without a clear consensus. Multiple studies both in animals and humans have attempted to answer this question. The ARDS Clinical Trial Network reviewed 549 patients with ARDS who received mechanical ventilation comparing high PEEP vs. low PEEP and found no difference in survival, organ failure, or ventilator-free days when controlling for ARDSnet strategy of 6 mL/kg tidal volume of ideal body weight (4, 5). It appears that the best PEEP must be individualized to improve oxygenation, minimize lung injury from mechanical ventilation, and preserve cardiac function.

The ability to easily measure and determine the best PEEP for the individual patient continues to elude practitioners. Many methods have been tested, but ease of use and feasibility continue to be problems. Gattinoni et al. (6) demonstrated by computed tomography (CT) that the disease process in patients with ALI is heterogeneous. A study in 2000 examined 71 patients with ARDS and compared CT scans at 0 and 10 cm H_2O PEEP (7). Patients with diffuse disease by CT showed improved alveolar recruitment without overdistension compared with patients with lobar changes, who demonstrated overdistension and only slight improvement in recruitment. In a recently published study, CT scans were used to assess the relationship between recruitable lung

tissue and the effect of PEEP (8). The authors found wide variation among individual patients in the amount of recruitable lung tissue. Application of PEEP maintained aeration in this segment of lung tissue. Chest CT scans of patients with ARDS/ALI are beneficial in determining "optimal" PEEP for individuals. Unfortunately, this technology is not widely available.

Various respiratory mechanics have been studied in an attempt to find a simple, easily reproducible measure that can be applied routinely at the bedside. Investigators have determined that recruitment with PEEP may occur along the entire volume-pressure curve (9). In a canine model, all of the changes demonstrated in the static pressure volume curve were not seen in the dynamic pressure-volume curve (10). Dynamic respiratory mechanics have been shown to be more beneficial than static pressure-volume curves in a small selection of patients. These conflicting results highlight the differences in the animal and human models. Although laboratory experiments are the first essential step in bringing understanding of disease and treatment to clinicians, all research done on animals may not be applicable to human patients with ARDS/ALI (11).

In this issue of *Critical Care Medicine*, Dr. Bellardine Black and coworkers (12) present comparisons of the effects on oxygenation, static elastance, dynamic respiratory resistance and elastance, and

*See also p. 870.

Key Words: positive end-expiratory pressure; acute lung injury; acute respiratory distress syndrome; lung compliance; respiratory mechanics; computed tomography

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whole-lung image by CT with PEEP ranges from 7.5 to 20 cm H₂O. Lung injury was induced by repetitive whole-lung lavage with 0.15 M NaCl (40 mL/kg) in five sheep. PEEP titrations were performed in increments of 2.5 with a recruitment of lung with 30 cm H₂O PEEP and peak airway pressure of 20 cm H₂O for 30 secs in pressure-control mode. After 10 mins of ventilation, measurements and CT images were obtained. Oxygenation was best at PEEP of 15 cm H₂O. At 15 cm H₂O, PEEP decreases in elastance and resistance occurred. At 17.5 cm H₂O, elastance increased consistent with overdistension and resistance decreased. In this animal model, it appears that dynamic mechanics may be used to guide recruitment without overdistension. These types of measurement can be easily done at the bedside and would greatly aid the clinician in managing patients with ARDS/ALI. Further work must be completed in humans to validate this technique and examine the translation to the bedside in the intensive care unit. Non-invasive guidance of lung management tools in critically ill patients has potential

promise to optimize PEEP in the morning and PEEP at night.

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Understanding another acute respiratory distress syndrome*

Retinoic acid syndrome represents a potentially life-threatening complication that occurs during treatment of acute promyelocytic leukemia (APL) when all-trans retinoic acid is used in addition to other chemotherapy. In a report from 1998 that included 413 patients, 15% experienced retinoic acid syndrome during the course of their induction treatment (1). Primary clinical signs of retinoic acid syndrome in this cohort of 64 patients included pulmonary distress (89%), fever (81%), pulmonary infiltrates (81%), weight

gain (50%), pleural effusion (47%), renal failure (39%), and pericardial effusion (19%).

More recent reviews on this subject indicate that the combination of all-trans retinoic acid with more traditional chemotherapy can significantly improve induction of remission in patients with APL in addition to reducing the incidence of relapse (2). When combined with chemotherapy, all-trans retinoic acid contributes to complete remission in >90% of patients with APL, with an expected cure of approximately 75% with this combination (2). However, retinoic acid syndrome continues to remain a major side effect of this chemotherapeutic approach. Clinicians have discovered that dexamethasone is useful in decreasing the incidence and severity of retinoic acid syndrome, but the underlying pathophysiology for this treatment complication has remained elusive.

In this issue of *Critical Care Medicine*, Dr. Tsai and colleagues from Taipei, Taiwan, report the results of a number of

ingenious experiments designed to provide an *in vitro* model of the retinoic acid syndrome (3). These investigators used a co-culture system with pulmonary 549A cells in the (lower) primary cell culture well and APL cells grown on the (upper) insert membrane. In response to chemotactic signals generated by the A549 cells, APL cells migrate through the porous insert membrane and are subsequently quantified on the undersurface of the membrane insert by microscopy. To investigate specific biochemical pathogenesis, exogenous chemokines were added to the primary cell culture well supra-phase in addition to antibodies to receptors for these cytokines added to the insert well. Additionally, either the A549 or APL cells could be stimulated or modulated by addition of various other exogenous chemical mediators.

Major conclusions from a series of well-controlled experiments include the following: a) all-trans retinoic acid represents the primary determinant governing transmigration of APL cells in this model;

*See also p. 879.

Key Words: acute respiratory distress syndrome; retinoic acid syndrome; neutrophils; interleukin-8; growth-regulated oncogene- α ; promyelocytic leukemia; chemokines

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