

## Mid-Frequency Ventilation in Acute Respiratory Distress Syndrome: The New Wave...length?

Patients with acute respiratory distress syndrome (ARDS) clearly benefit from a ventilator strategy that limits transpulmonary pressure (ie, aims for a tidal volume [ $V_T$ ] of 6 mL/kg and a plateau pressure < 32 cm H<sub>2</sub>O).<sup>1</sup> Indeed, some have suggested that all patients on mechanical ventilation could benefit from such an approach.<sup>2</sup> Because  $V_T$  in the range used in the ARDS Network study can occasionally result in patient-ventilator asynchrony (and therefore the need for greater sedation) and elevated  $P_{aCO_2}$ , some have suggested that  $V_T$  above 6 mL/kg is defensible as long as the plateau pressure is less than 32 cm H<sub>2</sub>O.<sup>3,4</sup> However, others have argued that there is no safe plateau pressure threshold below which patients can be safely ventilated.<sup>5,6</sup> Importantly, despite the apparently linear relationship between plateau pressure and mortality, lowering the  $V_T$  to less than 6 mL/kg is rarely suggested, for fear that adverse consequences of hypercapnia could offset the benefit of lower  $V_T$ . Potential adverse consequences of hypercapnia include increased intracranial pressure, cardiac arrhythmia, pulmonary vasoconstriction, and decreased renal perfusion.<sup>7</sup> On the other hand, hypercapnia has shown protective effects in lung injury models,<sup>8</sup> and some have suggested that the high respiratory cycling frequency necessary with a low  $V_T$  may be injurious independent of  $V_T$ .<sup>9,10</sup> Thus, despite the fact that clinicians want to use a “protective” ventilator strategy in ARDS, the factors that are most important in achieving this goal are still elusive.

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In theory, if the goal is to maintain minute volume ( $\dot{V}_E$ ), respiratory rate can be increased to maintain  $\dot{V}_E$  despite decreasing  $V_T$ , but this strategy is limited by the development of intrinsic positive end-expiratory pressure (auto-PEEP). In this issue of *RESPIRATORY CARE*, Mireles-Cabodevila and Chatburn present a novel approach that uses pressure-control ventilation to maintain adequate  $\dot{V}_E$  with low  $V_T$ .<sup>11</sup> Their approach capitalizes on the physiologic differences between pressure-control and volume-control ventilation modes. In volume control an increase in frequency (at a fixed inspiratory-expiratory ratio) results in a linear increase in  $\dot{V}_E$ , but also decreases expiratory time and therefore causes auto-PEEP. By contrast, in a pres-

sure-control mode the delivered  $V_T$  is determined by the mechanical properties of the respiratory system (resistance and compliance), the airway pressure change, and the frequency. As frequency increases, the  $V_T$  drops, but the  $\dot{V}_E$  may be maintained or actually go up (as in high-frequency oscillatory ventilation). However, if the dead space remains constant, alveolar ventilation could actually decrease with increasing frequency, because of the decreased  $V_T$  and therefore increased ratio of dead space to  $V_T$ . Mireles-Cabodevila and Chatburn used a simple mathematical model that enables the calculation of the optimum frequency at which these trends are balanced and alveolar ventilation is maximized. This turns out to be at frequencies in the range of 50–60 breaths/min, which they have termed “mid-frequency ventilation.” A key point is that as the frequency rises, the expiratory time decreases (thus favoring the development of auto-PEEP), but the decrease in inspiratory time also reduces the inspired  $V_T$ , thus limiting the development of auto-PEEP. Detailed calculations<sup>12</sup> indicate a non-linear relationship between lung mechanical properties, ventilator settings, and auto-PEEP, but with values in the range explored by Mireles-Cabodevila and Chatburn, and with the linear single-compartment model they employed, they found that auto-PEEP does not develop, despite the elevated frequency.

The calculations Mireles-Cabodevila and Chatburn outline clearly could be performed at any values of resistance, compliance, set PEEP, and peak pressure. Mireles-Cabodevila and Chatburn chose mechanical properties and pressure settings representative of those in the ARDS Network study. Interestingly (and relevant to the need to keep plateau pressure below 32 cm H<sub>2</sub>O), those settings, at the optimum frequency, produced an alveolar ventilation greater than the predicted requirement, which allows reducing the peak inspiratory pressure. In the end, their model predicts that alveolar ventilation can be maintained at a peak inspiratory pressure of approximately 22 cm H<sub>2</sub>O above set PEEP, and with resultant  $V_T$  < 6 mL/kg. Indeed, depending on compliance,  $V_T$  could be as low as 4.3 mL/kg.

An important potential barrier to implementing Mireles-Cabodevila and Chatburn’s model strategy is ventilator performance at the suggested frequencies. High-frequency ventilation requires specialized equipment and expertise. Mireles-Cabodevila and Chatburn’s mathematical model

assumes a perfect square pressure wave (ie, instantaneous rise to peak pressure, no fluctuations about that pressure, and equally instantaneous drop to PEEP). Because deviations from such a square wave will result in a different airway-pressure change than they used in their model calculation, the predicted benefits may not be realizable in practice. To address this concern they tested several commercially available ventilators with a lung simulator and found that almost all the ventilators were able to achieve results similar to those of the mathematical model; the optimum frequencies were approximately 50 breaths/min.

Mireles-Cabodevila and Chatburn's work raises the interesting possibility of using mid-frequency pressure-control ventilation with patients with ARDS and other severely ill patients, at even lower  $V_T$  than that in the ARDS Network study, with peak inspiratory pressure in the ARDS Network range, and with commonly used ventilators. One must ask, however, if the goal of mechanical ventilation in ARDS (and the goal of Mireles-Cabodevila and Chatburn's modeling) is to maximize alveolar ventilation. Perhaps the protective benefits of elevated  $P_{aCO_2}$  and detrimental effects of higher respiratory frequency per se would mitigate any gains made by improvements in alveolar ventilation. An important caveat to Mireles-Cabodevila and Chatburn's study is that it used only a mechanical model and a lung simulator, which both assume a single lung compartment, and constant compliance, resistance, and dead space. None of those assumptions are perfectly accurate with a real patient. Indeed, dead space is known to increase with increasing lung volumes, and previous studies have described a complex relationship between pressure-control settings, PEEP, alveolar ventilation, and frequency.<sup>13</sup> An important and often overlooked issue in lung mechanics is its intrinsic heterogeneity, which can lead to complex and unexpected behaviors in asthma,<sup>14</sup> chronic obstructive pulmonary disease,<sup>15</sup> and probably ARDS. Because relevant outcome variables such as auto-PEEP and alveolar ventilation can be a sensitive function of respiratory-system resistance and compliance, the effect of mid-frequency ventilation in diseased lungs needs further study. For example, auto-PEEP is likely to develop preferentially in lung units with high resistance and high compliance (slow time constants)—a situation that may not be well represented by a one-lung-unit model. It remains to be seen whether

mid-frequency ventilation will prove to be a useful strategy and the new "wave" for lung protection in ARDS.

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