Mid-Frequency Ventilation: A Viable Option for Lung Protection?

Prevention of lung injury caused by mechanical ventilation has rightfully assumed high priority in the support of patients with acute lung injury. The pathophysiology of ventilator-induced lung injury is complex, with both mechanical stresses and diverse non-mechanical background factors (such as position, vascular flows, F_{IO_2} , and body temperature) determining the magnitude of its expression.¹ Under predisposing background conditions, repeated overstretching of fully aerated alveoli and force amplification at the interface of closed and open tissues may result in release of inflammatory mediators, intolerable shearing stresses, vascular disruption, and small airway damage from incessant opening and closing of unstable lung units. The alveolar pressures that determine whether ventilator-induced lung injury will be caused or avoided include the maximum and minimum values encountered at the extremes of the tidal cycle (plateau pressure and total PEEP) and the difference between them, often designated as the driving pressure. Since the landmark ARDS Network study, which confirmed that lower tidal volumes (V_T 6 mL/kg of ideal body weight) are associated with better outcomes than high ones (12 mL/kg of ideal body weight),² there has been an understandable preoccupation with limiting the tidal excursions of pressure and volume so as to reduce the lungs' exposure to damaging tidal cycles. Some authors have pointed out the difficulty of identifying safe lower threshold limits for V_T and plateau pressure in the setting of acute lung injury,³ which for any given patient might co-depend on the integrity of right ventricular function.⁴

In this issue of *RESPIRATORY CARE*, Mireles-Cabodevila and colleagues present experimental work demonstrating the feasibility of significantly reducing V_T and excursions of tidal pressures by using ventilator frequencies higher than those customarily targeted.⁵ This method, previously described in conceptual fashion by these authors as mid-frequency ventilation (MFV),⁶ uses algorithm-adjusted pressure controlled ventilation over a frequency range of ~50–70 breaths/min. Because alveolar pressure during

pressure controlled ventilation rises and falls quasi-exponentially toward the airway pressure extremes of the tidal cycle,⁷ V_T declines as progressively increasing frequency allows less time for alveolar pressures to build and fall to their fixed airway pressure targets. Lower V_T means lower plateaus, higher total PEEP, and reduced driving pressure. What could be better than that?

Caution is advisable. As exemplified by the HIFI trial in neonates 25 years ago⁸ and by the more recently failed OSCILLATE trial of high-frequency oscillation in adults,⁹ limiting V_T cannot alone assure better outcome. One of the more appealing explanations for the disappointing results of those clinical trials relates to the higher mean alveolar pressures and their hemodynamic consequences that higher frequencies entail. The afterload to the right ventricle, often dysfunctional in ARDS and pumping against high pulmonary vascular resistance,¹⁰ tends to increase with mean

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alveolar pressure. Furthermore, the efficiency of ventilation, expressed as the ratio of total minute ventilation to P_{aCO_2} , also suffers as the dead-space fraction inevitably rises with the small V_T associated with high-frequency oscillatory ventilation due to a disproportionate concomitant rise in the series (anatomic) dead-space component. Whatever the mode, using higher cycling frequencies augments the intensity of exposure to any damaging tidal force (in the language of physics, the mechanical work delivered per unit time, or power increases). Finally, as frequency rises, intracycle repair time following overstretch is also abbreviated.¹¹ In a nutshell, minute volume should not be ignored when the object is to reduce the risk of iatrogenic injury.

Similar issues regarding altered ventilatory efficiency and hemodynamics may well apply at the rates associated with MFV, which are closer to conventional range. The data of Mireles-Cabodevila and colleagues,⁵ collected in animals with mild lung injuries, raise some concerns. In comparison to conventional pressure controlled ventilation, the algorithm-optimized MFV V_T was lower by ~20%, whereas the MFV-optimized minute volume needed to maintain a similar P_{aCO_2} was greater than the control by a much higher percentage. Heart rate also increased rather impressively during MFV, even though cardiac output and mean vascular pressures changed very little. The cause for this tachycardia is not

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evident; however, alveolar pressure during MFV was modestly higher due to the auto-PEEP generated at rapid frequencies. This pilot study of MFV, conducted in an anesthetized animal model of acute lung injury, is a convincing demonstration that such an approach is feasible for those specific experimental conditions and for the limited duration of observation. Its performance in other models, over longer periods of observation, and in more severely injured lungs cannot be assumed. As the authors point out, translation directly to clinical practice cannot be advised on the strength of sound theory and these data alone.

Should reducing tidal pressures and V_T below current recommendations prove beneficial (and currently, that issue is still widely open), exploration of a higher frequency range with an approach like MFV would be one of several ways to implement the desired V_T reduction. Acceptance of the hypercapnia attendant to reducing V_T at conventional frequency would be another, and use of extracorporeal gas exchange a third.¹² The nature and severity of the clinical problem would dictate the approach to be tried first, and as always, the patient's integrated cardiorespiratory response would decide its value.

Whether MFV is eventually deployed and proves its worth at the bedside, the work presented here by Mireles-Cabodevila and colleagues⁵ provides interesting preclinical data motivated by a strongly mechanistic rationale. It is precisely this type modeling and testing of a clinical problem, once so prevalent in the science of respiratory care, that tests our assumptions, helps develop a solid base for designing clinical studies, and provides insights for improving care delivery. Unfortunately, although such experiments in applied physiology are still much needed, they are rapidly vanishing from our nation's funded research agenda.

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