Commentary

Is it time to increase the frequency of use of high-frequency oscillatory ventilation?

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Abstract

In this issue of *Critical Care*, Bollen and colleagues present the results of a multicentre randomised controlled trial, comparing high-frequency oscillatory ventilation with conventional ventilation as the primary ventilation mode for adults with acute respiratory distress syndrome. The study was stopped early after recruiting only 61 patients because of declining enrolment, and although no differences were detected in any primary or secondary endpoint, this trial only had sufficient power to detect extreme differences in outcomes between groups. This editorial attempts to put these results in context with previous work and highlights challenges to be addressed in future studies.

Recognition of the impact of ventilator-induced lung injury on morbidity and mortality in patients with acute respiratory distress syndrome (ARDS) has led to an ongoing search for ventilation strategies that limit further damage to the already injured lung. In this issue of *Critical Care*, Bollen and colleagues [1] present the results of a multicentre randomised controlled trial, comparing high-frequency oscillatory ventilation (HFOV) with conventional ventilation as the primary ventilation mode for adults with ARDS.

HFOV applies a continuous distending pressure to the lung around which pressure oscillations are generated. These pressure swings are attenuated by the time they reach the alveolar level, resulting in very small delivered tidal volumes. HFOV is theoretically ideal for lung protection, as this minimal tidal variation in alveolar volume may allow clinicians to recruit the lung, minimising atelectrauma and oxygen toxicity, while still avoiding volutrauma from tidal overdistension. However, potential drawbacks to HFOV also exist, most notably the fact that the majority of adults must have their spontaneous respiratory efforts suppressed since their inspiratory flow demands are often greater than the constant flow of gas in the circuit. This need for heavy sedation (and frequently neuromuscular blockade) means that HFOV may not be an appropriate therapy for patients with mild forms of acute lung injury.

An extensively studied and accepted therapy in neonates [2], HFOV is still an emerging ventilator mode in adults. Previous work in this area has shown that HFOV is safe and effective in improving oxygenation in ARDS patients who are failing conventional ventilation [3-5]. However, when HFOV is considered as a primary ventilatory mode to prevent ventilator-induced lung injury, only one clinical trial has been previously published [6]. Mortality was not the primary outcome of this study and the control group arguably did not receive what would today be considered optimal conventional ventilation; nevertheless, a tantalising trend towards improved mortality was seen in the HFOV group of this study [6]. Consequently, HFOV in adults with ARDS remains a therapy with significant potential, but one requiring considerably more data before it can be endorsed for routine use.

In the study under consideration, Bollen and coworkers set out to determine the effect of HFOV on the rate of survival without mechanical ventilation or oxygen dependence at 30 days, compared with conventional ventilation [1]. Unfortunately the trial was stopped early, after recruiting only 61 patients because of declining enrolment, and a further 11% of subjects had incomplete follow-up for the primary endpoint. Although no differences were detected in any primary or secondary endpoint, this study only had sufficient power to detect extreme differences in outcome between groups. This low power was further eroded by the fact that

ARDS = acute respiratory distress syndrome; HFOV = high-frequency oscillatory ventilation.

18% of patients crossed over to the alternative therapy, making detection of a difference between groups highly improbable.

Interpretation of these results is further complicated by the fact that the two treatment groups differed significantly in numbers as well as in baseline hypoxia (oxygenation index of 25 in the HFOV group, versus 18 in the control group). Furthermore, comparison and integration of these results with the existing body of knowledge regarding HFOV in ARDS are made more difficult by the lack of very explicit ventilation protocols. Because it is very clearly how a ventilator mode is used, not just which mode is chosen, clear descriptions of the ventilator protocols and the adherence to them are essential for interpreting the results of comparative trials of ventilation strategies and modes.

Despite these limitations, the study does generate some new hypotheses. In a *post hoc* analysis, the authors found that the subgroup of patients with the most severe hypoxaemia (highest oxygenation indices) tended to benefit from HFOV compared with those undergoing conventional ventilation. As discussed by the authors, this finding may relate to the fact that the 'safe' window for lung protective mechanical ventilation, in which both overdistension and cyclical tidal recruitment and derecruitment are avoided, is so narrow in severe lung injury that conventional ventilation is no longer able to accomplish the goals of lung protection. The implications of this finding are for future investigators to consider stratifying the randomisation of patients by oxygenation index, or indeed to limiting enrolment to those patients with the most severe forms of ARDS [7]. The potential benefits of this latter decision in terms of potential increased effect size would need to be weighed carefully with an inevitable decrease in the number of potential study patients, which might threaten both the feasibility and generalisability of the study [8]. Indeed, another important lesson from this study is that future randomised trials must be collaborative multicentre efforts, because even in centres with a special interest in ARDS a realistic estimate of the recruitment rate into such trials is somewhere in the range of one patient every other month [1,6].

Ultimately, many of the questions regarding the use of HFOV in patients with ARDS remain unanswered: in which patients, at what time and using what settings should HFOV be applied? Several studies have documented worse outcomes when patients received longer periods of conventional ventilation before initiation of HFOV, suggesting that an early transition to HFOV might be needed [3-6]. Lung volume recruitment is vital in HFOV and is affected by both the HFOV settings and the use of lung volume recruitment manoeuvres. A strategy targeting lung volume was instrumental in the successful application of HFOV in newborn infants [9], and a comparable protocol has been found to be safe and effective in adults [10]. The decision and method of weaning HFOV back to conventional mechanical ventilation are even more indistinct, with no clear direction with respect to the priority of airway pressure, frequency and pressure amplitude (ΔP) in weaning. These issues only underline the importance of explicit ventilation protocols so as to standardise across treatments and allow comparison between them.

Although the utility of HFOV as rescue therapy is clearer, its precise role as primary therapy in patients with ARDS remains unclear. The trial by Bollen and colleagues serves to demonstrate the challenges and complexities in studying mechanical ventilation protocols in a heterogeneous population of sick patients, and the necessity for explicit protocols to guide treatment and experimental methods.

Competing interests

The author(s) declare that they have no competing interests.

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