Review

Year in review 2006: *Critical Care* - respirology

Daniela Vasquez, Jeffrey M Singh and Niall D Ferguson

Interdepartmental Division of Critical Care Medicine, University of Toronto, and University Health Network, Toronto, Ontario, Canada

Corresponding author: Niall D Ferguson, n.ferguson@utoronto.ca

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Abstract

The present article summarises and places in context original research articles from the respirology section published in *Critical Care* in 2006. Twenty papers were identified and were grouped by topic into those addressing acute lung injury and ventilator-induced lung injury, those examining high-frequency oscillation, those studying pulmonary physiology and mechanics, those assessing tracheostomy, and those exploring other topics.

Introduction

In the field of respiratory critical care, 2006 was another productive year. Several pulmonary critical care articles made appearances in high-impact general medical journals, addressing the use of nitric oxide in neonates [1,2], exploring therapy and monitoring in acute lung injury/acute respiratory distress syndrome (ALI/ARDS) [3-6], assessing hospital volume and mechanical ventilation outcomes [7], and summarising evidence for noninvasive ventilation in acute cardiogenic pulmonary oedema [8]. Similarly, 2006 was another prolific year for respiratory research published in *Critical Care*. In the present article, we highlight and summarise these findings from the journal, grouped by topic into those examining ARDS and ventilator-induced lung injury (VILI) [9-16], those addressing high-frequency oscillation (HFO) [17-21], those studying pulmonary physiology and mechanics [22-24], those assessing tracheostomy [25,26], and those addressing other topics [27,28].

ALI/ARDS and ventilator-induced lung injury

Diagnosis and therapy

ALI/ARDS remains of primary interest to intensivists not least because it is relatively common and the condition is still associated with a high morbidity and mortality [29,30]. Current clinical criteria assemble a heterogeneous group of conditions under this diagnostic umbrella [31,32]; methods to improve diagnostic specificity might be helpful in refining treatments or in defining a subpopulation of interest [33].

Kao and coworkers conducted a retrospective study in order to assess the clinical impact and safety of open lung biopsy in patients with ARDS of suspected noninfectious origin within 1 week of intubation [13]. Of the 41 patients studied who underwent this procedure, nearly 75% of patients had changes made in their therapeutic management due to open lung biopsy findings – most commonly the addition of corticosteroids (25 patients). The treatment alteration rate was higher in patients with nonspecific pathological diagnoses (for example, diffuse alveolar damage) than in patients with specific diagnoses ($P = 0.0024$). Postoperative complications occurred in 20% of the patients. The authors conclude that open lung biopsy was a useful and acceptably safe diagnostic procedure in selected patients with early-stage ARDS.

When interpreting these findings readers must be cognisant of the selection bias introduced by a clinician's decision to pursue open lung biopsy in a given patient. The study sample represented only 5% of all ARDS cases at the study centre during the study period. This limits the generalisability of the study findings to other patients, but is a common limitation of studies examining lung biopsy. It is also not clear whether changes in therapy such as adding corticosteroids were positively linked to specific pathological findings, or rather represented nonspecific 'rescue' therapy once infection had been ruled out. Nevertheless, open lung biopsy may be an important diagnostic tool early in ARDS if the underlying aetiology is unknown, although patient selection and timing needs to be defined more precisely prior to widespread implementation.

Injurious versus lung-protective ventilation

Mechanical ventilation can worsen pre-existing lung damage, producing VILI, which in turn can induce or worsen damage to other end organs [34]. Prone positioning of patients with ARDS has been shown to have beneficial effects on

ALI = acute lung injury; ARDS = acute respiratory distress syndrome; HFO = high-frequency oscillation; ICU = intensive care unit; IL = interleukin; PEEP = positive end-expiratory pressure; RAP = right atrial pressure; VILI = ventilator-induced lung injury; VP = volume–pressure.

oxygenation, although no definite benefit in mortality has been noted in clinical trials to date [35,36].

Nakos and coworkers compared the effect of a prone position versus a supine position on the development of VILI and end-organ injury (as measured by epithelial cell apoptosis) after mechanical ventilation with injurious ventilator settings [9]. The authors ventilated 10 sheep with a tidal volume of 15 ml/kg for 90 minutes, one-half of the animals randomly assigned to the prone position and the other half to a supine position. The prone position appeared to decrease the severity and the extent of VILI and was associated with decreased apoptosis in the lung and other organs, including the liver and the diaphragm. The clinical importance of these findings is not clear, and further study is needed to see whether these findings are replicated when more lung-protective ventilation is applied.

In a complementary study, O'Mahony and colleagues demonstrated in a murine model that the combination of mechanical ventilation and low-dose endotoxaemia synergistically acts to induce distal organ injury [15]. Neither mechanical ventilation with tidal volumes of 10 ml/kg or systemic lipopolysaccharide treatment individually was associated with lung damage or end-organ damage. The combination of lipopolysaccharide and this ventilation strategy, however, resulted in extrapulmonary end-organ injury, even in the absence of demonstrable acute lung injury.

These two studies reinforce previous findings that VILI can lead to nonpulmonary organ dysfunction.

There are few data in the medical literature informing clinicians how best to manage spontaneously breathing patients with ALI. Cepkova and coworkers sought to determine whether initiation of lung-protective positive-pressure ventilation exacerbates pre-existing lung injury in nonintubated, spontaneously breathing patients [16]. The authors compared levels of inflammatory biomarkers before and after intubation in a cohort of adults with ALI. Inflammatory cytokines and biological markers of endothelial and epithelial injury (IL-6, IL-8, intracellular adhesion molecule-1, von Willebrand factor) were elevated prior to intubation. Nevertheless, the institution of a lung-protective strategy (tidal volume 7–8 ml/kg predicted body weight) did not further increase the levels of these biomarkers in the first 24 hours after intubation. The authors suggest that a lung-protective ventilation strategy did not worsen pre-existing lung injury in most patients with ALI. This does not necessarily mean that VILI was not induced by the initiation of ventilation; it may have occurred at a later time point, or VILI may have been mediated through pathways not assessed in this study.

Prone position and extracorporeal membrane oxygenation

As stated above, the prone position improves oxygenation in most patients with ALI/ARDS but may or may not improve outcomes [35,36]. The use of supports under the ribcage and the pelvis of patients in the prone position (thoraco-pelvic supports) has been proposed as a method to improve the effectiveness of prone positioning by increasing abdominal wall compliance, and consequently total chest wall compliance – but the effectiveness of this approach is debated. Chiumello and coworkers studied the effect of these supports on gas exchange, haemodynamics and respiratory mechanics in 11 patients with ALI/ARDS managed in the prone position [11]. The addition of thoraco-pelvic supports in the prone position did not affect oxygenation or the lung volume, but did decrease chest wall compliance, increase pleural pressure, and slightly worsen haemodynamics. Given these results, the authors recommend against the use of these supports when caring for patients in the prone position.

Another adjunctive therapy for the management of severe ARDS is extracorporeal respiratory support. Pumpless arterio-venous extracorporeal membranes have a well-documented effect in enhancing CO_2 removal, but the effect on oxygenation is less clear. Zick and colleagues showed that the use of this technique improved oxygenation in a porcine model of severe ALI, although this effect was small (less than 10 mmHg on average) [10]. These results suggest that pumpless arterio-venous extracorporeal oxygenators may not be effective in significantly improving oxygenation, a limitation probably related to the low blood flow rates through the pumpless circuit. A more compelling potential application of these devices that could be explored in future studies lies in enhancing CO_2 removal and thereby facilitating more lung-protective ventilation in patients with severe ARDS.

Volume–pressure curves

The volume–pressure (VP) curve has been used in research and in some clinical settings to assess the elastic properties of the respiratory system. In the research setting, however, the construction of a static VP curve itself could affect oxygenation and thus interfere with early evaluation of a therapeutic intervention delivered just after a VP curve measurement. Roch and coworkers therefore investigated the effect of VP curve measurement on gas exchange and haemodynamics over time in 17 patients with ARDS [14]. They assessed both the super syringe method and the constant flow method, setting the positive end-expiratory pressure (PEEP) back to the baseline level (10 cmH_2O) immediately after each VP manoeuvre. VP curve measurements did not significantly and durably affect the oxygenation or haemodynamics parameters in the group as a whole, although two out of 17 patients did have a sustained improvement in oxygenation with the constant flow method. The authors conclude that evaluations of a strategy aimed at improving oxygenation might be reliably recorded after VP curve measurement. The observation that oxygenation may improve in a few patients with the constant flow technique may be a threat to validity if this method is employed in studies with very few patients.

In the same way, the VP curve may be a diagnostic and monitoring tool that can be employed at the bedside. Lu and colleagues compared alveolar derecruitment after removal of the PEEP, measured by the VP curve and computerised tomography in 19 patients with ALI or ARDS [12]. Although there was a statistically tight correlation between these methods ($R = 0.82$, $P < 0.0001$), more sophisticated analysis with a Bland–Altman plot revealed significant deviation between the two measurement instruments, with limits of agreement (two standard deviations) from −158 ml to +130 ml. The authors conclude that these large limits of agreement indicate that the VP curve method and computerised tomography measurement are not interchangeable for assessing derecruitment. The relative accuracy of these techniques in measuring alveolar recruitment (as opposed to derecruitment) is also uncertain.

High-frequency oscillation

HFO is a mode of ventilation that is receiving more attention in the adult intensive care unit (ICU) as we learn more about the importance of VILI in patients with ALI/ARDS [37]. This interest is evidenced by the fact that one-quarter of the 2006 respirology publications in *Critical Care* dealt with HFO.

Determinants of mortality

The clinical literature in adult HFO remains relatively small (fewer than 1,000 patients), and, although differences between survivors and nonsurvivors have been reported, the strength and independence of these associations had not been well studied. To address this issue, Bollen and colleagues conducted a systematic review and abstracted data from adult case series and randomised trials that compared HFO survivors with HFO nonsurvivors [17]. They found that higher age, higher Acute Physiology and Chronic Health Evaluation II score, higher oxygenation index, higher number of days of conventional ventilation prior to HFO, and lower pH were all associated with mortality. When the authors considered the effects of these variables together, the oxygenation index continued to predict mortality whereas the effect of the duration of prior conventional ventilation disappeared after accounting for differences in pH. These results suggest that the baseline oxygenation index will be an important variable to be balanced between groups in future HFO trials.

Work of breathing on high-frequency oscillation

Unlike neonates, adults on HFO must have their respiratory efforts suppressed with sedation, and sometimes paralysis, because their high inspiratory flow demands can outstrip the set constant bias flow in the oscillator circuit [38]. In the first of two related studies, van Heerde and coworkers demonstrate why this is so, using a test lung and calculating the imposed work of breathing [18]. They documented that, even with high bias flow settings (60 l/min), adults and large children would have an imposed work of breathing in excess of 1.1 J/l (normal physiological work of breathing in an adult 0.3–0.6 J/l); while at lower bias flow rates, the work of breathing approached 2 J/l. The authors conclude that these high levels for work of breathing imply the need for a demand-flow system if spontaneous breathing is to be allowed on HFO in adults.

In a follow-up paper the same group of investigators studied the addition of an external demand-flow system to the standard HFO circuit, in terms of effects on the work of breathing in a test-lung environment [20]. When employed with a relatively slow respiratory rate (12/min), the demand flow system significantly reduced the inspiratory work of breathing, bringing it into the normal range at around 0.5 J/l; at faster rates (24/min), the work of breathing was lower than without the system, but was still elevated at 1.5 J/l. These results suggest that such a system may be able to reduce work of breathing for adults on HFO, but its efficacy *in vivo* needs to be assessed. In addition, we must carefully consider whether and when we would want adults with ARDS breathing spontaneously on HFO. This would clearly be useful, and probably beneficial, when patients were improving and were in the process of weaning from HFO. In the more acute phase, however, such a demand-flow system may not be desirable. The system might help maintain a constant mean airway pressure in the circuit, but the transpulmonary pressure would surely be increased, potentially leading to increased volutrauma and barotrauma. The key to the lung-protective potential of HFO is its extremely small delivered tidal volumes. While a demand-flow system might reduce the work of breathing, we need to be careful not to circumvent the primary mechanism through which this mode may exert benefit.

Techniques for opening the lung with high-frequency oscillation

It has long been appreciated that a key aspect of HFO is the integration of this technique with a strategy to open the lung and maintain adequate end-expiratory lung volume. We review two papers from the group in Mainz, reporting studies in a porcine saline-lavage lung injury model that examined techniques for recruiting lung volume with HFO.

In the first article, David and colleagues document that stepwise increases in the transpulmonary pressure from 15 to 23 cmH_2O led to improvements in oxygenation, but also led to concomitant small increases in left heart filling pressures and to reductions in the mean arterial pressure and cardiac output [19]. Of note, blood flow to other organs (brain, kidneys, heart, and jejunum) was not affected. Perhaps not unexpectedly, their results were consistent when the same recruiting pressures were applied using the pressure control mode on a conventional ventilator.

In contrast with this incremental airway pressure titration, this author group also studied the effects of a decremental airway pressure titration strategy [21]. After the induction of lung injury, the authors set a continuous distending pressure of

45 cmH_2O for 2.5 minutes, and then decreased this pressure by 5 cmH_2O every 5 minutes to 20 cmH_2O. This strategy resulted in a rapid and effective reduction in the amount of intrapulmonary shunt and an increase in oxygenation. A reduction in cardiac output was seen at higher airway pressures; however, the magnitude of this reduction is of questionable clinical relevance, and animals were clinically stable throughout the procedure. The study is consistent with a previous human study showing the safety and efficacy of recruitment manoeuvres and a decremental airway pressure titration [39], and is consistent with the physiological goal of ventilating on the deflation limb of the VP curve [40].

Pulmonary physiology and mechanics

Predictors of fluid responsiveness in spontaneously breathing patients

Administration of intravenous fluids to improve physiologic parameters (fluid challenge) is common in ICUs, although the response to such a challenge is variable. Although previous studies have identified several potential predictors of fluid responsiveness, none of these studies have evaluated spontaneously breathing patients.

Heenen and colleagues evaluated several static and dynamic measurements of preload as predictors of fluid responsiveness [22]. The pulmonary artery occlusion pressure, the right atrial pressure (RAP), the inspiratory variation in RAP and the pulse pressure variation were measured before and after fluid administration in 21 spontaneously breathing patients on a face mask ($n = 12$) or on pressure support ventilation ($n = 9$). These patients were classified as responders and nonresponders according to an increase in the cardiac index by 15%. The authors found no significant differences in any of these indices between responders and nonresponders. Although the pulmonary artery occlusion pressure and the RAP were slightly better predictors of fluid response (area under the receiver-operating curve = 0.73 ± 0.13 and 0.69 ± 0.12 for pulmonary artery occlusion pressure and RAP, respectively) compared with dynamic indices of preload (area under the receiver-operating curve = 0.40 ± 0.13 and 0.53 ± 0.13 for pulse pressure variation and inspiratory changes in RAP, respectively), they did not observe a useful cut-off value for pressure measurements to allow accurate prediction of fluid responsiveness. In summary, the pulse pressure variation and the inspiratory variation in RAP were not found to be clinically useful predictors of the response to fluid challenge in patients with spontaneous respiratory efforts.

Optimal positive end-expiratory pressure for anaesthesia

Atelectasis during general anaesthesia and neuromuscular blockade is common and can result in significant intrapulmonary shunt as well as in an increased risk of postoperative complications. PEEP is commonly applied to counteract this phenomenon, although the optimum level of PEEP is not easy to determine clinically and high levels of PEEP may have detrimental effects on haemodynamics – and extreme levels of PEEP may lead to lung injury through overdistention of aerated lung units.

Carvalho and colleagues attempted to use respiratory system elastance to determine the optimum level of PEEP to safely prevent atelectasis in an animal model [23]. Using computed tomography region of interest analysis, they measured lung aeration and respiratory system elastance in six anaesthetised and paralysed healthy piglets at descending PEEP levels. Levels of PEEP higher than 8 cmH_2O resulted in a significant hyperinflation. The amount of hyperinflated lung decreased with a reduction in PEEP, although poorly aerated areas of lung increased with PEEP below 6 cmH_2O. The minimum respiratory system elastance corresponded to the greatest amount of normally aerated lung with minimal tidal recruitment and hyperinflation.

Unfortunately the practical application of this measure appears to be limited because most cases did not exhibit a defined minimum value, with the minimum respiratory system elastance occurring within a range of PEEP values between 4 and 8 cmH_2O.

Respiratory system mechanics on pressure-support ventilation

Pressure-support ventilation is a popular mode of assisted mechanical ventilation commonly used in the ICU to provide assisted ventilation to spontaneously breathing patients without the use of heavy sedation and neuromuscular blockade. Aliverti and colleagues demonstrated that the degree to which pressure-support ventilation leads to synchronised (that is, natural) chest and abdominal mechanics during respiration depends on the level of pressure support used [24]. They reported the results of a study evaluating patient–ventilator interactions in a group of patients with moderate to severe ALI/ARDS, excluding those patients with known chronic obstructive lung disease. The authors measured respiratory parameters, thoraco-abdominal muscle synchrony and respiratory muscle action at three levels of pressure support (3 cmH_2O, 15 cmH_2O and 25 cmH_2O). The breathing pattern was significantly modified by changes in the level of pressure support, with large variations in the frequency/tidal volume ratio while the minute ventilation remained constant. Specifically, when the pressure support level was less than 10 cmH_2O there was recruitment of both the inspiratory and expiratory muscles during early expiration, leading to asynchrony in thoraco-abdominal expansion and an alteration in the distribution of the tidal volume. The authors conclude that during pressure-support ventilation the ventilatory pattern is very different depending on the level of pressure support; furthermore, in patients with acute lung injury pressure, support greater than 10 cmH_2O permits homogeneous recruitment of respiratory muscles, with resulting synchronous thoraco-abdominal expansion.

This study would suggest that when pressure-support ventilation is used in patients with ALI/ARDS, the use of support levels higher than 10 cmH_2O may reduce the work of breathing and may potentially improve the distribution of the delivered breath. Clinicians should be vigilant to evaluate such patients for thoraco-abdominal asynchrony and other indicators of increased respiratory workload.

Tracheostomy

Tracheostomy is one of the more commonly performed procedures in critically ill patients, yet the optimal method, optimal timing and benefits of performing tracheostomies in this population remain to be established [41-44].

Optimal technique for tracheostomy in the critically ill

Delaney and colleagues performed a systematic review and meta-analysis of randomised clinical trials comparing elective percutaneous dilatational tracheostomy and surgical tracheostomy in adult critically ill patients, with regards to major short-term and long-term outcomes [26]. They included 17 randomised controlled trials comparing percutaneous dilatational tracheostomy and surgical tracheostomy involving a total of 1,212 subjects. In critically ill patients who require an elective tracheostomy, percutaneous dilatational tracheostomy is associated with a significantly reduced odds of wound infection compared with surgical tracheostomy (odds ratio = 0.28, 95% confidence interval = 0.16–0.49). There was no evidence that percutaneous dilatational tracheostomy was associated with an overall increase in the rate of bleeding, with other major complications or with long-term complications. Furthermore, in subgroup analysis the authors found that, when compared with surgical tracheostomy performed in the operating room, percutaneous dilatational tracheostomy is associated with a reduced incidence of bleeding and mortality. The authors conclude that percutaneous dilatational tracheostomy performed in the ICU should be considered the technique of choice for critically ill patients who require a tracheostomy.

Despite the contribution of this study, there are several questions that remain regarding tracheostomy in the ICU: the timing of tracheostomy, identifying patients who would benefit from early tracheostomy, and identifying which of the available methods for percutaneous dilatational tracheostomy is best.

Effect of tracheostomy on sedation requirement in the intensive care unit

Patients in the ICU often need sedation and analgesia to treat pain and anxiety associated with endotracheal intubation and mechanical ventilation. It has been suggested that tracheostomy is associated with a decrease in sedation requirements and may in part explain the finding of improved outcomes with early tracheostomy in some studies [42].

Veelo and colleagues conducted a retrospective single-centre observational study to evaluate this hypothesis [25]. They measured the daily dose of morphine, midazolam and propofol in 117 patients before and after tracheostomy, using each patient as their own control by adjusting the daily dose to the mean daily dose for the study period. The daily dose of all three drugs sharply declined in the days prior to tracheostomy, and then remained stable without a further decrease after tracheostomy. This finding was consistent across early-tracheostomy and late-tracheostomy and across a range of patient types (elective surgical, nonelective surgical and nonsurgical). Tracheostomy had no effect on sedation requirements.

The interpretation of these findings may be made difficult by the fact that the sedation protocol did not explicate a systematic withdrawal of sedation, an important limitation in a study measuring sedation dose. Also, the median time to tracheostomy was 9 days (interquartile range 5–14 days). As in previous studies, the timing of tracheostomy is possibly critically important and early tracheotomy (for example, within 72 hours) may perhaps be necessary to observe a significant benefit of tracheotomy on sedation. Despite these limitations, the practices used in the study of Veelo and coworkers are similar to clinical practice throughout much of the world, and their study contributes to the debate by refuting the popular belief that tracheotomy decreases sedation requirements.

Other topics

Acute respiratory failure in the elderly

The aging population in most industrialised countries will probably be manifest as an increasing incidence of consultation for acute respiratory failure in the elderly. Ray and colleagues set out to evaluate the epidemiology and initial treatment of acute respiratory failure – defined as dyspnoea and at least one of respiratory rate >25/min, hypoxaemia (PaO_2 <70 mmHg or SpO_2 <92% on room air), and respiratory acidosis ($PaCO_2$ >45 mmHg with pH <7.35) – in elderly patients in the emergency department [28]. The authors conducted a prospective observational study of 514 patients aged 65 years or older. Cardiogenic pulmonary oedema was the cause of respiratory failure in 43% of cases, although one-half of patients had more than two contributing diagnoses. The mortality rate for elderly patients with acute respiratory failure was high (16%), and inappropriate initial treatment in the emergency department was associated with a twofold increase in mortality. In multivariate regression modelling, $PaCO_2$ >45 mmHg, renal insufficiency (creatinine clearance <50 ml/min) and clinical signs of acute ventilatory failure were independently associated with inhospital mortality. It should be noted that the definition of acute respiratory failure in this study was significantly less severe than is often seen in the critical care literature, which often requires the need for mechanical ventilation [45]. In addition, the population in this study may not be typical of that served by many hospitals; the average age was 80 years and the population was generally highly functioning with high activity of daily living scores; fewer than 10% were living in an institution.

Kinetic bed therapy to prevent nosocomial pneumonia

Ventilator-associated pneumonia is associated with poor outcomes and high healthcare costs. Furthermore, ventilator-associated pneumonia has been identified as one of the most preventable causes of morbidity in ICUs. Kinetic bed therapy has been proposed as a tool to avoid the prolonged patient immobilisation that is thought to be a risk factor for nosocomial pneumonia in ventilated patients.

Delaney and colleagues conducted a systematic review and meta-analysis to evaluate whether kinetic bed therapy was associated with less nosocomial pneumonia in mechanically ventilated, critically ill patients compared with manual turning and repositioning [27]. From a thorough search of the literature, the authors included 15 prospective trials in their final analysis, although none of the studies met their stringent methodological and validity criteria. There was also significant heterogeneity among studies. Kinetic bed therapy was associated with a significant reduction in the incidence of nosocomial pneumonia (pooled odds ratio = 0.38, 95% confidence interval = 0.28–0.53), but with no reduction in mortality, duration of mechanical ventilation or length of stay in the ICU. Because of the poor methodological quality and heterogeneity of the studies analysed, the authors concluded that definitive recommendations regarding the use of kinetic bed therapy could not be made at that time.

Competing interests

NDF is a consultant for Roche, has received honoraria for speaking at scientific meetings from Viasys Healthcare, Pfizer, and Summit Technologies, and is the co-PI of a pilot randomised trial funded by the Canadian Institutes of Health Research comparing HFO with conventional ventilation in adults with ARDS.

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