Review

Year in review 2008: *Critical Care* - respirology

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Abstract

Original research contributions published in *Critical Care* in 2008 in the fields of respirology and critical care medicine are summarized. Eighteen articles were grouped into the following categories: acute lung injury and acute respiratory distress syndrome, mechanical ventilation, mechanisms of ventilator-induced lung injury, and tracheotomy decannulation and non-invasive ventilation.

Introduction

Original research in the field of critical care respirology published in 2008 yielded a broad spectrum of interesting results ranging from epidemiological analyses, identification of biomarkers and ventilator management, to pharmacological intervention for acute lung injury (ALI). To provide context and for comparison with the papers described here, we also cite studies on the same subjects published in journals other than *Critical Care*.

Acute lung injury and acute respiratory distress syndrome

ALI and acute respiratory distress syndrome (ARDS) are major causes of morbidity and mortality, and account for a large proportion of intensive care unit (ICU) bed use. Many pharmacological interventions for these entities have been evaluated, but none has clearly been shown to decrease mortality [1]. To help develop novel treatment strategies for patients with ALI/ARDS, the Irish Critical Care Trials Group conducted a study in a cohort of patients with ALI/ARDS in the Irish adult ICU population [2]. The investigators described the epidemiology and management of ALI/ARDS in order to identify factors associated with outcome, and to identify whether standardized care is being delivered across participating centres in a research network. There were 1,029 admissions during a 10-week study period in 14 participating centres. A total of 196 (19%) patients had ALI/ARDS; of these 141 (72%) had ALI/ARDS on admission. The most common predisposing risk factors were pneumonia (50%) and extrapulmonary sepsis (26%). Although protective lung ventilation (mean tidal volume 7.0 ± 1.7 ml/kg) was used commonly throughout participating centres, the overall ICU mortality for ALI/ARDS was 32.3%. Lower arterial oxygen tension (Pa_{O_2})/fractional inspired oxygen (Fi_{O_2}) ratios and higher Sequential Organ Failure Assessment scores at admission were associated with increased mortality. These data are helpful in planning future multicentre clinical trials in patients with ALI/ARDS.

ALI/ARDS is characterized by an excessive inflammatory response involving a variety of inflammatory mediators; this allows for the identification of reliable biomarkers for diagnostic and therapeutic purposes in this often fatal disease. Direct collection of lung fluids such as lung lavage and sputum is not always feasible at the bedside for a number of reasons. Collection of exhaled breath condensate (EBC) is an alternative approach to obtaining lower respiratory tract samples in patients breathing spontaneously as well as in those undergoing mechanical ventilation [3]. Roca and coworkers [4] studied patients with ALI who were ventilated using the ARDS Network low tidal volume protocol [5]. EBC was collected before and 30 minutes after administration of inhaled salbutamol, a short-acting β_2-adrenergic receptor agonist. A significant increase in EBC pH and a trend toward decreased inflammatory markers, including nitrosative species

ALI = acute lung injury; ARDS = acute respiratory distress syndrome; CT = computed tomography; EBC = exhaled breath condensate; EELV = end-expiratory lung volume; Fi_{O_2} = fractional inspired oxygen; ICU = intensive care unit; NPPV = noninvasive positive-pressure mechanical ventilation; Pa_{O_2} = arterial oxygen tension; PAPC = 1-palmitoly-2-arachidonoyl-sn-glycero-3-phosphorylcholine; PARP = poly (ADP-ribose) polymerase; PEEP = positive end-expiratory pressure; VILI = ventilator-induced lung injury.

and 8-isoprostane concentration, were observed after salbutamol administration. Although the study was conducted in a small cohort of patients, the results suggested that EBC analysis may be useful for evaluating the effectiveness of therapy in ventilated patients.

Further down the cascade of inflammatory responses observed in patients with ALI/ARDS, the deposition of fibrin in the alveolar space can result in hyaline membrane formation, and deposition in microcirculation leads to thrombosis. It is thus reasonable to speculate that the properties of heparin, which exhibits both anticoagulant and fibrinolytic actions, may help to limit fibrin deposition in the alveolar space and microcirculation. In an open label phase I trial, Dixon and coworkers [6] examined the effects of four escalating doses of nebulized heparin from 50,000 to 400,000 U/day in 16 ventilated patients with ALI. They found no serious side effect for any dose used. The time course of Pa_{O_2}/Fi_{O_2} ratio, lung compliance and the alveolar dead space fraction levels were similar across all doses used. There were trends toward an increase in the activated partial thromboplastin time and thrombin clotting time, and toward a reduction in prothrombin fragment levels at higher doses. Of note, phase I studies are used to assess initial safety issues, pharmacokinetics, pharmacodynamics, feasibility and dose ranging, and are not powered and are not expected to provide positive outcome signals. Further trials are required to define the safety and efficacy of nebulized heparin in patients with ALI/ARDS.

From the physiological perspective, patients with ALI/ARDS may have right-to-left pulmonary shunts that can lead to alveolar dead space. To analyze the influence of pulmonary shunt on dead space in ARDS conditions, Niklason and coworkers [7] analyzed the effects of varying systemic blood flow, anaemia, high metabolic rate and acid-base instability by computer modelling. They reported that the alveolar dead space increased with right-to-left shunt fraction. Several factors can contribute to the alveolar dead space, including reduced cardiac output, decreased haemoglobin levels and metabolic acidosis due to hyperventilation. This study enhances our understanding of how physiological alternations may lead to pulmonary shunt in ARDS.

Mechanical ventilation

Mechanical ventilation is often a life-saving intervention, but it may cause or exacerbate lung damage in patients with ALI/ARDS. Arterial oxygenation is frequently used as an intervention target for mechanical ventilation. Although hypoxia is a major concern to the clinician, hyperoxia is also highly toxic but may be overlooked at bedside. de Jonge and coworkers [8] investigated the relationship between Fi_{O_2} administered, Pa_{O_2} levels achieved and hospital mortality in 36,307 consecutive patients admitted to 50 Dutch ICUs treated with mechanical ventilation. The authors demonstrated that the achieved Pa_{O_2} values in the ICU patients were higher than those recommended in the literature. The mortality rate was linearly related to Fi_{O_2}. Both low Pa_{O_2} and high Pa_{O_2} during the first 24 hours after ICU admission were associated with hospital mortality, forming a U-shaped curve. This study suggests that hyperoxia might have been overlooked in the ICU, and optimizing oxygenation targets may help to improve outcomes.

In patients with pulmonary shunts, increases in Fi_{O_2} have a minimal effect on arterial oxygenation. One approach to increase Pa_{O_2} is to perform recruitment manoeuvres. Constantin and coworkers [9] compared two recruitment manoeuvres in 19 patients with ARDS using a randomized crossover design. The recruitment manoeuvres were applied based on pulmonary mechanics in each patient, beginning with either continuous positive airway pressure or extended sigh. Both recruitment manoeuvres increased oxygenation, but the increase in Pa_{O_2}/Fi_{O_2} was significantly greater with extended sigh than with continuous positive airway pressure. The investigators also used lung computed tomography (CT) scans and pressure-volume curves to examine the impact of the recruitment manoeuvres.

Several studies examined the utility of monitoring end-expiratory lung volume (EELV) to help to optimize ventilatory settings or predict the effects of lung recruitment manoeuvres in ALI/ARDS. The application of positive end-expiratory pressure (PEEP) can lead to increased EELV as a result of recruitment or further distension of already ventilated alveoli. Koefoed-Nielsen and coworkers [10] examined whether the measurement of EELV combined with the use of pressure-volume curves would be helpful in predicting changes in lung mechanics in response to recruitment manoeuvres. They speculated that EELV measurement could determine whether lung volume is reduced in clinical situations with low respiratory system compliance and low Pa_{O_2}/Fi_{O_2} ratios, whereas an analysis of pressure-volume curves could predict whether recruitment manoeuvres and increased PEEP would be effective. In a pig model of ALI induced by lung lavage and high airway pressure ventilation, the difference in lung volume was measured from pressure-volume curves and the changes in EELV were assessed after each recruitment manoeuvre. The authors showed that the maximal volume hysteresis obtained from pressure-volume curves predicted changes in lung mechanics better than changes in gas exchange in response to recruitment manoeuvres. Similar observations were obtained in a pig model of ARDS induced by oleic acid injection, in which Lambermont and coworkers [11] measured functional residual capacity, statistic pulmonary compliance and Pa_{O_2} during a sequential reduction in PEEP from high to low levels. The investigators reported that combined EELV and lung compliance measurements may help to optimize the PEEP level.

These interesting observations in animal models were also reported in the clinical setting. Bikker and coworkers [12] measured EELV at PEEP levels that were reduced sequen-

tially from 15 to 5 cmH_2O in 45 mechanically ventilated patients with and without lung injury. In all patients, EELV decreased significantly corresponding to the sequential reduction in PEEP, whereas the PaO_2/FiO_2 ratio remained unchanged. Interestingly, a correlation between the change in EELV and the change in respiratory system compliance was found in patients with extrapulmonary injury. These clinical results suggest that, in combination with the assessment of pulmonary compliance, measurement of EELV may provide useful information to help optimize the ventilatory settings in ALI/ARDS conditions.

Given these findings, an important issue at the bedside is what is the best way clinically to perform an EELV measurement. The helium dilution technique has been used for a decade but the procedure is both time consuming and labour intensive. Chiumello and coworkers [13] compared EELV measured by the conventional helium dilution technique with that obtained by a modified nitrogen wash-out/wash-in system in 30 patients with ALI/ARDS. EELV was also compared with CT scans, which were considered to be the 'gold standard'. The authors reported that the EELV measured with either the helium dilution technique or the modified nitrogen wash-out/wash-in system exhibited good correlation with the CT scan data. In particular, the helium dilution technique appeared to be more precise at low lung volumes, and the modified nitrogen wash-out/wash-in system worked well at all lung volumes. This study provides an alternative approach to measurement of EELV at the bedside.

As discussed above, several studies have examined the importance of shunt fraction, dead space and EELV within the context of ALI/ARDS. Varelmann and coworkers [14] conducted an elegant study to address the question of whether spontaneous breathing during pressure-controlled ventilation improves oxygenation, ventilation/perfusion matching, dead space and EELV. ALI was induced either by hydrochloric acid aspiration as a direct lung injury model or by increasing intra-abdominal pressure combined with intravenous oleic acid injection as an indirect lung injury model in pigs. The authors demonstrated that spontaneous breathing during pressure-controlled ventilation improved PaO_2/FiO_2 ratio by reducing pulmonary shunt fraction and increasing EELV, as compared with the animals without spontaneous breathing. Systemic oxygen delivery was higher due to greater cardiac output during spontaneous breathing.

Mechanisms of ventilator-induced lung injury

Ventilator-induced lung injury (VILI) is characterized by biotrauma and vascular barrier disruption leading to pulmonary oedema. In addition to proposed low tidal volume ventilatory strategies, our understanding of the underlying inflammatory responses in VILI has greatly advanced. Three excellent studies examined the effects of pharmacological interventions in rat models of VILI-associated ALI/ARDS.

One of the therapeutic interventions aimed at reducing vascular leakage. Clearance of alveolar oedema depends on a number of factors, including active transport of sodium across endothelium and epithelial barriers and the stability of cell membranes. β-Adrenergic agonists such as dopamine and salbutamol exert anti-inflammatory effects as well as augmenting pulmonary oedema clearance [15,16]. Chamorro-Martin and coworkers [17] examined the effects of intratracheal administration of dopamine on pulmonary oedema and survival in a rat model of surfactant deficiency and VILI-induced surfactant removal by lung lavage with a saline solution, which was followed by ventilation with high tidal volumes (25 ml/kg) for 60 minutes. A lower wet/dry lung weight ratio, reflecting decreased lung permeability, and a greater survival rate was obtained in rats treated with dopamine compared with the control group. This study suggests that the administration of dopamine may enhance clearance of alveolar oedema within the context of VILI.

It is noteworthy that β-adrenergic agonists are bronchodilators, and delivery of bronchodilators with metered-dose inhalers has been used in mechanically ventilated patients. Malliotakis and coworkers [18] administered the long-acting β_2-adrenergic agonist salmeterol by metered-dose inhaler and a spacer in 10 mechanically ventilated patients who had acute exacerbations of chronic obstructive pulmonary disease. The bronchodilator effect was evident at 30 minutes after salmeterol delivery and was well maintained over 8 hours.

As described above, increased lung permeability is a hallmark of VILI. It is known that plasma membranes are barriers for hydrophilic molecules and ions because of the hydrophobic core of the phospholipid bilayer. The main structural components of plasma membranes are phospholipids such as 1-palmitoly-2-arachidonoyl-sn-glycero-3-phosphorylcholine (PAPC). Oxidized PAPC has been shown to exhibit anti-inflammatory effects in ALI [19]. Nonas and coworkers [20] examined the effects of oxidized PAPC on lung inflammation and barrier disruption in a rat model of VILI caused by using high tidal volume ventilation. Pretreatment of rats with a single intravenous injection of oxidized PAPC markedly attenuated lung permeability, reflected by decreased protein concentrations and decreased neutrophil infiltration in the lung, compared with an untreated control group. The mechanisms by which oxidized PAPC exerts protective effects may be through suppression of Rho signalling, leading to decreased endothelial paracellular gap formation. Although the therapy in this study was given before induction of injury, the authors generated a proof-of-concept for this approach, and hence the study is very encouraging. Further studies are required to examine the effects of oxidized PAPC in established ALI/ARDS.

An increasing body of evidence suggests that VILI is associated with muscle atrophy that alters diaphragm contractile properties [21]. Controlled mechanical ventilation

induces muscle proteolysis through several mechanisms, including the lysosomal (i.e. cathepsins), the calcium-dependent proteinases (calpains) and the activation of ubiquitin-proteasome system. Futier and coworkers [22] hypothesized that mechanical ventilation in pressure support ventilation would attenuate diaphragmatic proteolysis, thus preserving muscle activity compared with controlled mechanical ventilation. The authors demonstrated that diaphragmatic protein catabolism was significantly increased and protein synthesis decreased after 18 hours of controlled mechanical ventilation compared with control rats. The high protein catabolism and low synthesis were associated with an increased activity of both 20S proteasome and tripeptidylpeptidase II. The animals treated with pressure support ventilation exhibited reduction in the mechanical ventilation-induced proteolysis and inhibition of protein synthesis. This study suggests that pressure support ventilation may be superior to controlled ventilation with respect to limiting ventilator-induced diaphragmatic dysfunction.

VILI is often accompanied with distal organ injury associated with overwhelming inflammatory responses involving many inflammatory mediators. For example, excessive activation of poly (ADP-ribose) polymerase (PARP) enzyme after massive DNA damage may aggravate inflammatory responses. PARP-1 is the most abundant PARP family member to 'sense' DNA damage, repair DNA and maintain genomic stability. However, when severe DNA injury occurs in response to oxidative stress, excessive upregulation of PARP may be harmful by depleting cellular ATP stores, resulting in cell dysfunction and death. The potent PARP inhibitor PJ-34 has been shown to decrease PARP-1 activity and nuclear factor-κB activation in animal models of endotoxic and haemorrhagic shock. Kim and coworkers [23] hypothesized that pharmacological inhibition of PARP by PJ-34 would attenuate VILI. Mice were ventilated with either low or high airway pressure in the presence or absence of PJ-34 treatment given before mechanical ventilation. The investigators demonstrated that the PJ-34-treated animals had improved lung histology and attenuated inflammatory responses associated with a decreased nuclear factor-κB activation, as compared with the untreated groups. This study was consistent with a recent publication showing that the administration of PJ-34 attenuated VILI in a rat model in which two-hit injury was induced by intratracheal lipopolysaccharide instillation followed by mechanical ventilation [24]. Taken together, these studies suggest that pharmacological interventions targeting specific inflammatory molecules may eventually have a role to play in the treatment of VILI.

Tracheotomy decannulation and noninvasive ventilation

Tracheotomy is performed in approximately one-tenth of mechanically ventilated patients to facilitate prolonged airway management. The relatively new technique for percutaneous dilatational tracheotomy may result in tracheotomy becoming an even more common surgical procedure in the ICU. The majority of tracheotomized patients who survive their illness can eventually be effectively decannulated. However, there is a lack of consensus as to when a tracheotomy tube should be removed. Stelfox and coworkers [25] conducted a cross-sectional survey of 225 responding clinicians involved in routine tracheotomy management at 118 medical centres. The patients' levels of consciousness, ability to tolerate tracheotomy tube capping, cough effectiveness and secretions were rated as the most important factors in the decision to remove a tracheotomy tube from a patient. The survey indicated that patients were most likely to be recommended for decannulation if they were alert and interactive, had a strong cough, had scant thin secretions and required minimal supplemental oxygen. Decannulation failure was defined as the need to re-establish an artificial airway within 48 to 96 hours of planned tracheotomy removal, which ranged between 2% and 5%.

A number of complications may occur during invasive mechanical ventilation, such as complications of intubation, ventilator-associated pneumonia, VILI (barotrauma, volutrauma and biotrauma), cardiovascular effects and so on. Noninvasive positive-pressure mechanical ventilation (NPPV) has been investigated as an alternative in the management of patients with ALI. Trevisan and coworkers [26] addressed the question of whether NPPV would be beneficial in weaning patients from invasive mechanical ventilation. Of 65 patients who failed a spontaneous breathing T-piece trial during weaning, 28 were randomly assigned to NPPV and 37 were assigned to invasive mechanical ventilation. The incidence of complications (pneumonia and tracheotomy) was lower in the NPPV group than in the invasive mechanical ventilation group. Although there was a tendency toward decreased ICU and hospital stays, the differences did not achieve statistical significance. The authors concluded that the combination of early extubation and NPPV is a useful and safe alternative for ventilation of patients who fail initial weaning attempts.

Conclusions

A number of excellent studies published in *Critical Care* in 2008 have addressed the mechanisms, examined monitoring techniques and explored potential therapeutic approaches in the context of ARDS and VILI both in the ICU population and in animal models. The great quality and quantity of the respiratory research in such a dynamic and opportune time will impact patient care.

Competing interests

The authors declare that they have no competing interests.

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