Review

Year in review 2007: *Critical Care* - respirology

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Published: 14 October 2008
This article is online at http://ccforum.com/content/12/5/231

Critical Care 2008, **12:**231 (doi:10.1186/cc6953)

Abstract

All original research contributions published in *Critical Care* in 2007 in the field of respirology and critical care medicine are summarized in this article. Fifteen papers were grouped in the following categories: acute lung injury and acute respiratory distress syndrome, mechanical ventilation, ventilator-induced lung injury, imaging, and other topics.

Introduction

This article summarizes the research work published in *Critical Care* in 2007 in the field of respiratory critical care. Fifteen original research papers were identified and grouped into different sections by topic of interest.

Acute lung injury and acute respiratory distress syndrome

Definition and epidemiology

The most widely used definitions of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are those proposed by the 1994 American-European Consensus Conference (AECC). ALI/ARDS is diagnosed when there are bilateral infiltrates on the chest x-ray in the absence of left atrial hypertension, with coexisting hypoxemia. The hypoxemia criterion for ALI is a partial pressure of arterial oxygen/fractional concentration of inspired oxygen (PaO_2/FiO_2) ratio of less than or equal to 300 and for ARDS the PaO_2/FiO_2 ratio must be less than or equal to 200. This definition of ALI/ARDS has a number of limitations, including the following: (a) the criteria for bilateral infiltrates are not rigorously defined, (b) PaO_2/FiO_2 can change dramatically with different ventilatory settings, but specific settings are not mandated in the definition, and (c) the definition does not identify a specific disease, but rather patients with a broad spectrum of severity of lung injury caused by different diseases and characterized by variable outcomes.

To examine the oxygenation criterion of the AECC criteria, Karbing and co-workers [1] investigated how the PaO_2/FiO_2 ratio changed as a function of FiO_2. Since the definition does not require the patient to be receiving any specific FiO_2, an implicit assumption of the AECC definition is that the PaO_2/FiO_2 ratio does not change much with FiO_2. Karbing and co-workers examined PaO_2/FiO_2 ratios at four to eight different FiO_2 values in 93 healthy subjects and patients and fit their data to two different mathematical models: a one-parameter 'effective shunt' model and a two-parameter 'shunt and ventilation/perfusion' model. They demonstrated that the 'shunt and ventilation/perfusion' model provided a better fit of the patient data and that the PaO_2/FiO_2 ratio varied with the FiO_2 and oxygen saturation. With the AECC definition, this would have led to a change in disease classification in 30% of their patients. Therefore, the authors suggested a more precise characterization of the hypoxemia by defining the shunt percentage and the ventilation/perfusion mismatch. One approach to address this issue would be to specify the FiO_2 when the blood gases are measured in all patients when defining hypoxemia in the diagnostic criteria for ALI/ARDS. This may partially help, but other critical factors such as level of positive end-expiratory pressure (PEEP), tidal volume (Vt), and lung volume history all can markedly impact PaO_2.

To better define the clinical features of ALI/ARDS, Ferguson and co-workers [2] reported the results of a prospective observational study in patients with ALI/ARDS from three hospitals in Spain, documenting the relationship between predefined clinical risk factors and the development of

AECC = American-European Consensus Conference; Akt = serine/threonine kinase/protein kinase B; ALI = acute lung injury; ARDS = acute respiratory distress syndrome; CT = computed tomography; eNOS = endothelial nitric oxide synthase; ERK = extracellular signal-regulated kinase; FiO_2 = fractional concentration of inspired oxygen; ICU = intensive care unit; JNK = c-jun N-terminal kinase; MIP-2 = macrophage inflammatory protein-2; PaO_2 = partial pressure of arterial oxygen; PC III = procollagen type III; PEEP = positive end-expiratory pressure; VILI = ventilator-induced lung injury; Vt = tidal volume.

ALI/ARDS in patients admitted to the intensive care unit (ICU) as well as in patients followed on the ward [2].

The authors found that the incidence of ALI/ARDS in the study group was 27.7 cases per 100,000 population per year. The highest likelihood of developing ALI/ARDS was for patients with shock (35.6%). In addition, the incidence of ALI/ARDS was higher (15.2%) for patients with pulmonary diseases than for patients with extrapulmonary risk conditions (4.6%). Once patients were diagnosed with ALI/ARDS, they were rapidly admitted to the ICU, but this process took longer if ALI/ARDS was associated with extrapulmonary conditions. Interestingly, more than half of the patients with ALI were not followed in an ICU, but on a general ward. The mortality rate of this subgroup was not statistically different from patients with ALI who were admitted to the ICU. However, the number of patients involved was too low to draw any definitive conclusions on the indication for ICU admission. Further studies are needed to understand what the best settings for the treatment of these patients are. As pointed out by the authors, the increasing growth of critical care outreach teams or medical emergency response teams may represent an adequate resource to address this important issue.

Since the definition of ALI/ARDS includes patients with a broad spectrum of severity of illness, the prognosis is quite variable. Gajic and co-workers [3] tried to identify potential predictors of outcome in mechanically ventilated patients with ALI. They retrospectively examined patients from three cohorts of recent clinical studies. One of the studies was used to define the derivation cohort model in which the authors identified the prediction parameters. These parameters were then tested using the other two cohorts. This approach of identifying a derivation cohort and then prospectively testing the resulting model developed is a much more rigorous approach than simply defining and using the model without a confirmatory cohort. Interestingly, their analysis demonstrated that the majority of the patients, who are still invasively ventilated 3 days after the initiation of mechanical ventilation, were at relatively high risk of dying or being ventilated for more than 2 weeks. Among these patients, age and cardiopulmonary function were the best predictors of mortality and/or prolonged mechanical ventilation. If confirmed in other studies, these data will be helpful in deciding on the interventions required in the care of these patients and in the design of clinical studies.

Mechanical ventilation in acute lung injury/acute respiratory distress syndrome

Mechanical ventilation represents the most important life-support therapy in acute respiratory failure. In patients with ALI/ARDS, minimizing end-inspiratory stretch by using small Vt values is a well-accepted therapeutic approach. However, uncertainty remains as to the optimal PEEP level to apply to avoid overdistension of the alveoli and de-recruitment, hence minimizing ventilator-induced lung injury (VILI).

Carvalho and co-workers [4] used lung computed tomography (CT) to determine whether setting PEEP based on the minimal elastance of the respiratory system obtained during a descending PEEP titration maneuver was a reasonable approach to minimize VILI. ALI was induced in piglets by intravenous infusion of oleic acid, and mechanical ventilation with low Vt was initiated. A descending PEEP trial was then performed beginning from 26 cm H_2O, with progressive reduction using steps of 2 to 4 cm H_2O until zero PEEP was reached. At each step, the respiratory system elastance and the distribution of the lung aeration based on CT scan images were assessed. In this model, the minimal elastance was found in most of the animals with PEEP values of 16 cm H_2O. The PEEP level resulting in the minimal elastance of the respiratory system corresponded on the CT scan analysis to the best compromise between normally inflated and nonaerated areas in all animals. As pointed out by the authors, if these data receive confirmation in biomolecular investigations, the proposed PEEP strategy may be a promising tool to test at the bedside.

The effect of PEEP in experimental ALI was also investigated by Halter and co-workers [5] by means of a new and very interesting technique of *in vivo* microscopy, allowing direct two-dimensional visualization of the peripheral alveoli. Using a model of surfactant deactivation-induced ALI, the investigators demonstrated that the combination of low Vt (6 cc/kg) and high PEEP (20 cm H_2O) produced the greatest alveolar stability, measured as the difference between the alveolar area at peak inspiration minus the alveolar area at end-expiration. Moreover, they found that the ventilation strategy associated with the most stable alveoli resulted in the least lung injury, measured histologically. In the experimental group ventilated with high Vt (15 cc/kg) and low PEEP (5 cm H_2O), progressive collapse of alveoli was observed as the experiments progressed. This was in contradistinction to the less injurious, low Vt/high PEEP group, in which the number of open alveoli remained constant; however, these alveoli were also less stable than healthy ones. Interestingly, based on the different combination of Vt and PEEP tested in this model, it appears that PEEP level may have a greater impact in stabilizing alveoli than a reduction of Vt.

The same research group used the *in vivo* microscopy technique to study ALI induced by mechanical ventilation in healthy lungs [6]. In rats ventilated with high peak pressure (45 cm H_2O) and either high (10 cm H_2O) or low (3 cm H_2O) PEEP, the stability of the alveoli was measured in the dependent and nondependent regions of the lung. The results showed that high PEEP, despite the high peak pressure, prevented alveolar instability, reproducing the findings of Webb and Tierney [7]. When using a high-pressure/low PEEP ventilation strategy, alveolar instability, and therefore VILI, surprisingly occurred earlier in the non-dependent rather than dependent lung regions. These results may be explained by the lower compliance in this experi-

mental model of the dependent lung leading to uneven distribution of Vt. The study highlights the inhomogeneous distribution of injury in the lung and suggests that body position may play a role in the progression of lung injury.

Uttman and co-workers [8] tested a physiologically based computer simulation as a tool for guiding ventilator settings in experimental ARDS. By applying a goal-oriented ventilation strategy based on the computer simulation, it was possible to significantly reduce Vt as the respiratory rate increased, especially when the aspiration of dead space technique was also used. This strategy led to a reduction of airway pressure, while normal gas exchange was maintained.

Wolthuis and co-workers [9] studied the influence of low Vt mechanical ventilation on sedation and analgesia requirements in patients with or without ARDS. The authors performed a secondary analysis of data from a previous study investigating the effectiveness of an educational program in reducing the Vt used for invasive mechanical ventilation. They found that the amount of sedatives or analgesics prescribed was not dependent on the applied Vt. Therefore, mechanical ventilation with lower Vt did not require deeper sedation or analgesia, nor was there a difference in terms of sedative or opioid prescription between patients with or without ARDS.

Molecular mechanisms of ventilator-induced lung injury

Mechanical ventilation *per se* can trigger or sustain a local and systemic inflammatory response, which may lead to greater lung damage and to dysfunction of other organs. A large body of scientific work has been performed to better define the molecular mechanisms of injury caused by mechanical ventilation.

Along this line, Li and co-workers investigated the interaction between high Vt mechanical ventilation and hyperoxia in the development of VILI. The authors performed two studies analyzing the role of the mitogen-activated protein kinase pathways [10] and the role of serine/threonine kinase/protein kinase B (Akt) and endothelial nitric oxide synthase (eNOS) [11] in the modulation of high Vt and hyperoxia-induced lung injury. In the first study [10], wildtype or c-jun N-terminal kinase (JNK)-deficient knockout mice ($JNK1^{-/-}$) were ventilated with high Vt (30 mL/kg) with two different fractions of inspired oxygen: 21% O_2 (room air) or greater than 95% O_2 (hyperoxia). JNK is one of the intracellular proteins of the mitogen-activated protein kinase pathway. The effect of a specific inhibitor of extracellular signal-regulated kinase (ERK), a second intracellular mediator of the mitogen-activated protein kinase pathway, was also tested in this study. The authors found that hyperoxia increased high Vt-induced neutrophil infiltration, macrophage inflammatory protein-2 (MIP-2) production, microvascular permeability, and apoptosis in lung epithelial cells as compared with controls. All of these effects were significantly reduced in $JNK1^{-/-}$ mice and those with pharmacological inhibition of ERK. However, mice pretreated with an ERK inhibitor were protected from the injury caused by hyperoxia, but not from the injury caused by high Vt ventilation, suggesting a direct effect of oxygen on the ERK intracellular pathway.

In their second article, to investigate the role of Akt and eNOS in the interaction between mechanical stress and hyperoxia, Li and co-workers [11] ventilated wildtype mice with or without pretreatment with specific inhibitors for Akt and eNOS. Akt-deficient mice were also used in confirmatory experimental groups. High Vt (30 mL/kg) with or without hyperoxia was used as the ventilation strategy. The authors demonstrated that hyperoxia enhanced large Vt-induced epithelial cell injury by stimulation of MIP-2 release with the consequent increase in pulmonary neutrophil sequestration. These effects were dependent, at least in part, on the Akt and eNOS pathways, as demonstrated by the protective effect of pretreatment with the specific Akt and eNOS inhibitors.

The pathophysiological alterations associated with VILI are characterized by a change in the composition of the extracellular matrix. In this regard, de Carvalho and co-workers [12] studied the effect of alveolar overdistension induced by mechanical ventilation on procollagen type III (PC III) expression in an experimental model of ALI. The amount of PC III mRNA was measured in the lungs of rats mechanically ventilated with different strategies. The expression of PC III was higher in the rats with ALI induced by oleic acid/high Vt/low PEEP in the supine position and ALI from oleic acid/low Vt/high PEEP in the supine position compared with control rats treated with oleic acid, but not mechanically ventilated. Interestingly, a lower expression of PC III was observed in rats with ALI induced by oleic acid/high Vt/low PEEP ventilated in the prone position. In general, PC III mRNA was higher in the nondependent lung regions compared with the dependent regions. Overall, these data demonstrated that the alteration of the extracellular matrix may be triggered by alveolar overdistension. PC III was more expressed during mechanical ventilation with high Vt or high PEEP and in the nondependent area of the lungs, where the alveolar overdistension is more likely to occur.

Imaging

Dellinger and co-workers [13] used a new technology to assess functional and structural images of the lungs based on the vibration energy generated by the lungs during the respiratory cycle. The authors found that pressure-targeted modes (pressure support more than pressure control) are characterized by a larger area of distribution of the vibrations, involving the lower regions of the lungs, as compared with volume control when Vt was held constant.

Le Guen and co-workers [14] highlighted the potential utility of three-dimensional reconstruction of the airways by a specific multidetector CT scanner in clinical practice. The

authors reported a clinical case of post-traumatic disruption of a major airway, for which the use of the three-dimensional extraction of the tracheobronchial tree was superior to the traditional helical CT and to bronchoscopy in establishing the diagnosis.

Other topics

Lung biopsy

Open-lung biopsy is the gold standard for the diagnosis of parenchymal lung disease. However, there are concerns about its utility and safety in critically ill and mechanically ventilated patients. Lim and co-workers [15] studied a retrospective case series of 36 mechanically ventilated patients who had undergone an open-lung biopsy for respiratory failure of unknown origin. No life-threatening complications were associated with the procedure, which allowed a specific diagnosis in 86% of the patients and more interestingly led to a therapeutic change in 64% of the cases. In these patients, mortality was predicted by the number of comorbidities, the Simplified Organ Failure Assessment score, and the PaO_2/FiO_2 ratio on the day of the biopsy. This study suggests a more aggressive diagnostic approach for patients with respiratory failure. However, further prospective controlled clinical trials are needed if we are to change the indications for lung biopsy in clinical practice.

Endotracheal cuff pressure

Nseir and co-workers [16] tested a new pneumatic device for the continuous monitoring of endotracheal cuff pressure in piglets intubated and mechanically ventilated for 48 hours. The use of the pneumatic device resulted in a significantly lower cuff pressure compared with animals managed manually according to current guidelines. However, both groups showed evidence of hyperemia, hemorrhages, deep mucous ulceration, and metaplasia at the cuff contact area. There were no differences between groups. Further studies will be required to determine whether there is any potential benefit of this new device in subjects ventilated for long periods of time.

Competing interests

ASS is a consultant for Maquet (Rastatt, Germany), Linde Gas Therapeutics (Lidingo,Sweden), Novalung (Talheim, Germany), BOC, LEO Pharma and Eli Lilly.

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