Review

Year in review in *Critical Care*, 2003 and 2004: respirology and critical care

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Published online: 1 July 2005
This article is online at http://ccforum.com/content/9/5/517

Critical Care 2005, **9:**517-522 (DOI 10.1186/cc3764)

Abstract

We summarize all original research in the field of respirology and critical care published in 2003 and 2004 in *Critical Care*. Articles were grouped into the following categories to facilitate a rapid overview: pathophysiology, therapeutic approaches, and outcome in acute lung injury and acute respiratory distress syndrome; hypoxic pulmonary arterial hypertension; mechanical ventilation; liberation from mechanical ventilation and tracheostomy; ventilator-associated pneumonia; multidrug-resistant infections; pleural effusion; sedation and analgesia; asthma; and techniques and monitoring.

Introduction

This article summarizes the original research in the field of respirology and critical care that was published in 2003 and 2004 in *Critical Care.* We grouped the articles into sub-categories to help the reader get a rapid overview of the key articles and thus focus on topics of interest.

Pathophysiology, therapeutic approaches, and outcome in acute lung injury and acute respiratory distress syndrome

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) may result from lung ischemia-reperfusion. Putte and coworkers [1] studied the time sequence of pulmonary inflammatory cell infiltration and lung injury in a rat model created by 1 hour of ischemia followed by up to 4 hours of reperfusion. Short term, but not long term, reperfusion resulted in increased lung macrophages and T-cells, while neutrophil counts increased early and remained high after prolonged reperfusion. Lung cell apoptosis, but not necrosis, progressively increased with the duration of reperfusion. This study helps our understanding of the dynamics of inflammatory cell infiltration and lung injury in ischemia-reperfusion, a common form of injury following a number of insults, such as severe resuscitated shock, and following lung transplantation, and may provide us with information that will help us to design future studies.

Much attention has been paid to the interaction between mechanical ventilation and positive end-expiratory pressure (PEEP) and the hemodynamic system. Bruhn and coworkers [2] as well as Akinci and coworkers [3] studied the effects of incremental PEEP levels on cardiac function and gastric mucosal perfusion, assessed by tonometry in ARDS patients. Increasing PEEP in a stepwise fashion from 9 to 20 cmH_2O [2] and from 5 to 13 cmH_2O [3], both studies demonstrated improved arterial oxygen tension (PaO2), while cardiac filling pressures, cardiac index, systemic oxygen delivery, mean arterial pressure, and gastric tonometry measurements remained unchanged. The authors concluded that in ARDS patients adequately resuscitated with fluids and catecholamines, short term titration of PEEP is hemodynamically well tolerated and does not negatively affect gastric mucosal perfusion.

Extracorporeal membrane oxygenation (ECMO) in ARDS using arterio-venous (AV) instead of veno-venous or veno-arterial shunts may theoretically provide advantages, but the degree of carbon dioxide clearance depends on cardiac output. To investigate hemodynamic stability during AV-ECMO using a shunt flow of 15% of cardiac output, Totapally and coworkers [4] studied 17 lambs with lung lavage and

ALI = acute lung injury; ARDS = acute respiratory distress syndrome; ARF = acute respiratory failure; AV = arterio-venous; CoNS = coagulase-negative staphylococci; CPAP = continuous positive airway pressure; ECMO = extracorporeal membrane oxygenation; EELV = end expiratory lung volume; EPAP = expiratory positive airway pressure; ETT = endotracheal tube; EVLW = extravascular lung water; HPV = hypoxic pulmonary vasoconstriction; ICU = intensive care unit; IPAH = idiopathic pulmonary arterial hypertension; IPAP = inspiratory positive airway pressure; MEE = measured energy expenditure; MV = mechanical ventilation; PCP = pulmonary capillary pressure; PEEP = positive end-expiratory pressure; SaO_2 = arterial oxygen saturation; SpO_2 = pulse oximeter oxygen saturation; TER = total energy requirements; V_T = tidal volume.

acid instillation induced ALI. Animals treated with an AV-ECMO had lower arterial oxygen tension, required more hemodynamic support therapy and were more likely to die within the 6 hour study period compared to animals without ECMO. AV-ECMO allowed a maximum reduction in minute ventilation of 30% while the animals remained normocapnic. The authors concluded that substantial cardiovascular support is required to maintain hemodynamic stability during application of AV-ECMO therapy in lambs with severe ALI.

Kirov and coworkers [5] assessed extravascular lung water (EVLW) using the transpulmonary single thermodilution method and post-mortem gravimetry in sheep with lipopolysaccharide ($n = 7$) or oleic acid ($n = 7$) induced lung injury or under sham conditions ($n = 4$). There was a close correlation ($r = 0.85$, $P < 0.001$) between the two methods over a wide range of EVLW measurements, but the single thermodilution method was consistently higher compared to post-mortem gravimetry and, therefore, moderately overestimated the true EVLW. The authors concluded that transpulmonary single thermodilution may potentially be useful in quantifying lung oedema.

Although the most obvious clinical abnormalities in ALI and ARDS are referable to the lung, the most common cause of death is dysfunction of remote organs. In a single, medical-surgical intensive care unit (ICU), Flaatten and coworkers [6] identified 529 out of 832 adult patients with acute respiratory failure (ARF) without ($n = 156$) and with ($n = 373$) remote organ failure over 2.5 years. ICU, hospital, and 90-day mortality were 3.2%, 14.7% and 21.8 % in ARF without remote organ dysfunction, 67.6%, 69.6% and 82.1% in ARF with failure of three additional organs, and 30.0%, 40.5% and 46.9% in ARF with any remote organ dysfunction, respectively. The authors concluded that ARF without other organ failure has a comparatively low mortality rate, whereas ARF mortality rates increase with the number of concomitantly failing organs.

The inert gas re-breathing technique does not measure trapped air within the lungs and may, therefore, underestimate total lung gas volume. To assess the volume of poorly or non-ventilated gas, Rylander and coworkers [7] compared end-expiratory lung volume determined by re-breathing sulphur hexafluoride ($EELV_{SF6}$), and total lung gas volume calculated from computed tomography images ($EELV_{CT}$) in anesthetized, paralyzed and mechanically ventilated ARDS patients ($n = 25$, PEEP 5 cmH_2O), as well as spontaneously breathing healthy subjects ($n = 20$). In ARDS patients, $EELV_{SF6}$ and $EELV_{CT}$ were closely correlated ($r^2 = 0.72$; $P < 0.001$) with a mean ± SD difference of 0.71 ± 0.47 l ($EELV_{SF6}$ was 66 ± 14% of $EELV_{CT}$). In healthy subjects, $EELV_{SF6}$ was 99 ± 9% of $EELV_{CT}$ ($r^2 = 0.83$; $P < 0.001$). The authors concluded that about one-third of the total gas volume is poorly or non-ventilated in the lungs of sedated and paralysed ARDS patients when low PEEP levels are used.

Pulmonary capillary pressure (PCP) is the major force determining fluid filtration from pulmonary capillaries into the interstitium; however, assessing PCP is not straightforward. Souza and coworkers [8] estimated PCP based on using best fit monoexponential and biexponential curves of pulmonary artery pressure decay in patients with idiopathic pulmonary arterial hypertension (IPAH; $n = 12$) and ARDS ($n = 11$). The PCP values in the IPAH group were significantly higher than those in the ARDS group, and the different algorithms yielded different PCP within the groups. The time required to reach steady state pulmonary arterial occlusion pressure was longer in the IPAH group (higher time constants). The authors concluded that PCP in IPAH patients is greater than normal, but methodological limitations related to the occlusion technique may limit interpretation. Different disease processes may result in different times for pulmonary arterial emptying.

Hypoxic pulmonary arterial hypertension

Data concerning the role of angiotensin II in hypoxic pulmonary vasoconstriction (HPV) are conflicting. Hubloue and coworkers [9] studied whether angiotensin-converting enzyme inhibition by enalaprilat and type 1 angiotensin II receptor blockade by candesartan would inhibit HPV in dogs subjected to acute hypoxia. Although plasma renin activity and angiotensin II immunoreactivity increased during hypoxia, angiotensin-converting enzyme inhibition and type 1 angiotensin II receptor blockade did not attenuate HPV. The authors concluded that this suggests that angiotensin II does not play a role in mediating hypoxic pulmonary vascular tone.

Mechanical ventilation studies

In vitro

Al Majed and coworkers [10] used a test lung and a Servo 300 ventilator (Siemens-Elema, Solna, Sweden) to assess the effect of decreased lung compliance and endotracheal tube (ETT) leakage on measurements of exhaled tidal volume (V_T) across a wide range of V_T and lung compliance. In the absence of ETT leakage, calculated effective V_T closely approximated the V_T measured at the ETT, even when lung compliance was markedly decreased, whereas V_T measured at the ventilator became increasingly inaccurate. With ETT leakage, effective V_T overestimated V_T measured at the ETT by at least 0.6 ml/kg. The authors concluded that in the presence of ETT leakage, as frequently encountered in pediatric patients when uncuffed ETTs are used, effective V_T is inaccurate and V_T is most accurately estimated at the airway opening.

Conditioning inspired gases with heat and moisture in invasively ventilated patients helps prevent airway damage and loss of heat and fluid. Chiumello and coworkers [11] compared the efficiency of a new heat and moisture exchanger (Performer, StarMed, Mirandola, Italy) that actively adds water and heat to the inspired gas, to conventional heat and moisture exchangers by measuring airway temperature and absolute

humidity *in vitro* and *in vivo*. The new heat and moisture exchanger outperformed the conventional systems in terms of airway temperature and absolute humidity, and exhibited no loss of efficiency when used over 12 hours *in vivo*.

ETTs often impose higher resistance to spontaneous breathing than the supraglottic airways, resulting in increased work of breathing while intubated. To test the performance of tube compensation algorithms provided by two modern ventilators (Nellcor Puritan-Bennett 840 and Dräger Evita 4) at low and moderate inspiratory flow, Maeda and coworkers [12] used an artificial respiratory system and various tube compensation levels. Although both ventilators provided effective tube compensation, complete compensation for ETT imposed work of breathing did not occur even when 100% tube compensation was used. The overall tube compensation performance of both ventilators was similar.

Partial assist ventilation reduces work of breathing in patients with bronchospasm. Miro and coworkers [13] set out to test which components of the ventilatory cycle contribute to this process using 10 cmH_2O inspiratory (IPAP), expiratory (EPAP), and continuous positive airway pressure (CPAP) in a canine model of methacholine-induced bronchospasm. End expiratory lung volume (EELV) was also assessed. Indices of work of breathing were reduced by IPAP and CPAP, but were increased by EPAP. CPAP and EPAP similarly increased EELV, while the increase in EELV was less pronounced with IPAP. The authors concluded that any reduction in inspiratory effort attributable to positive pressure during acute bronchospasm is generated primarily by the IPAP component of the airway pressure profile, and that for the same reduction in work of breathing by CPAP, end expiratory lung volume increases more.

Intubating the trachea may induce tracheal oedema and may lead to increased post-extubation airway resistance. To evaluate the accuracy of the cuff-leak test in predicting post-extubation airway obstruction, Prinianakis and coworkers [14] studied gas volume loss when the cuff was deflated either throughout the respiratory cycle or only during expiration in mechanically ventilated patients and in a lung model where cross-sectional area around the endotracheal tube and the model mechanics were varied. The inspiratory component of the total leak was more important with decreasing inspiratory flow, decreasing model compliance, and increasing cross-sectional area around the tube. The authors concluded that respiratory system mechanics and inspiratory flow rates are important determinants of gas volume loss during the cuff-leak test in addition to the cross-sectional area around the endotracheal tube. Thus, these factors may confound prediction of post-extubation airway obstruction.

In vivo

To compare the energy requirement and the nutrition support in hemodynamically stable patients ventilated for at least 7 days, Kan and coworkers [15] used indirect calorimetry to measure energy expenditure (MEE), and defined the calculated total energy requirements (TER = 1.2 × MEE) as the nutrition goal. On a daily basis, they recorded the caloric input ordered by the attending physician and assessed nutritional status on admission and after the 7 day study period. They found that 15, 20 and 19 patients were underfed (<90% TER), adequately fed (TER ± 10%), and overfed (>110% TER), respectively. Improvement of nutritional status related indices was highest in adequately fed patients. The authors concluded that providing at least 120% of resting MEE seems adequate to meet the caloric energy needs of hemodynamically stable, mechanically ventilated patients.

Liberation from mechanical ventilation and tracheostomy

To determine how nurse-driven, protocol-based weaning compared with usual physician-directed weaning for discontinuation of mechanical ventilation (MV) in patients ventilated for more than 48 hours, Tonnelier and colleagues [16] compared a prospectively studied protocol group with an historical, case matched control group ($n = 104$ each). The duration of MV (16.6 ± 13 days versus 22.5 ± 21 days; $P = 0.02$) and ICU length of stay (21.6 ± 14.3 days versus 27.6 ± 21.7 days; $P = 0.02$) were both lower in the group with nurse driven, protocol-directed weaning, whereas ventilation and extubation associated complications were similar. The authors concluded that the nurse-driven, protocol-based weaning procedure helped reduce duration of MV and ICU stay.

Koksal and coworkers [17] compared plasma insulin, cortisol, glucose and urinary vanilmandelic acid in patients ventilated for more than 48 hours before, during and after liberation from mechanical ventilation using pressure support, CPAP, and T-piece ($n = 20$ each). During weaning, plasma insulin and glucose as well as urinary vanilmandelic acid increased with pressure support and T-piece but not with CPAP, and plasma cortisol increased only with T-piece. All measurements were higher in the T-piece group compared to the other modes 48 hours after extubation. The authors concluded that weaning via T-piece resulted in the most pronounced response of biochemical stress markers.

Dosemeci and coworkers [18] used pediatric airway exchange catheters after extubation in 36 patients with maxillofacial or major neck surgery at risk for difficult re-intubation. Emergency re-intubation of four patients in the postoperative course using the pediatric airway exchange catheter was uneventful and fast. The authors concluded that routine use of a pediatric airway exchange catheter in patients with anticipated difficult re-intubation may be potentially life-saving.

A failed tracheal extubation entails a worse prognosis. Using a retrospective methodology in a single, non-teaching

hospital, Seymour and coworkers [19] studied the impact of failed (defined as reinstitution of mechanical ventilation within 72 hours; $n = 60$) versus successful (randomly selected cohort, $n = 93$) extubation in mechanically ventilated patients with acute respiratory failure. In patients requiring re-intubation within 72 hours, post-extubation ICU and hospital length of stay as well as ICU mortality were significantly increased. Estimated total hospital costs increased by an average of nearly US$34,000 per re-intubated patient. The authors concluded that re-intubation increases mortality, prolonged inpatient care, and costs.

Optimized timing of tracheostomy may impact outcome. To compare early (prior to active weaning attempts; ET group, $n = 21$) with more selective (after weaning attempts; ST group, $n = 25$) tracheostomy, Boynton and colleagues [20] retrospectively analysed data from surgical patients requiring 72 hours or more of MV. Duration of weaning was shorter in the ET group than in the ST group, but duration of MV was not. Hsu and coworkers [21] reported retrospectively collected data from 163 tracheotomized patients. Patients tracheotomized early (within 21 days after intubation, $n = 110$) were more likely to be successfully liberated from mechanical ventilation (defined as >72 hours without support), had lower ICU mortality and ICU stay, but similar length of hospital stay and similar incidence of nosocomial pneumonia during weaning compared to patients tracheotimised beyond day 21 after intubation ($n = 53$). These observational studies found that early tracheostomy hastens liberation from MV and delayed tracheostomy is associated with worse outcome. Both studies acknowledge that prospective trials are needed to better define optimal timing of tracheostomy.

To compare short-term and long-term perioperative and postoperative complications arising from guide wire dilating forceps and Ciaglia Blue Rhino tracheotomy techniques, Fikkers and colleagues [22] retrospectively analyzed data from two sequential cohorts ($n = 171$ each). Major peri-operative complications (major bleeding, false route, oesophageal perforation, failure to insert cannula, pneumothorax) were evenly distributed between the groups (guide wire dilating forceps, 13/171; Ciaglia Blue Rhino, 9/171) and minor complications were somewhat more frequent with Ciaglia Blue Rhino tracheotomy. Late complications were rare. Overall, the authors observed closely comparable performance of both techniques in their sequential cohorts.

Owing to geometrical (shorter length) and material (more rigid) characteristics, tracheostomy tubes impose lower resistance to breathing compared to ETTs. Amygdalou and coworkers [23] set out to compare respiratory system mechanics before (with ETT) and immediately after (with tracheostomy tube) surgical tracheostomy. Respiratory system elastance increased and respiratory system resistance decreased, while respiratory system impedance, end expiratory pressure and blood gases remained unchanged after tracheostomy. The authors speculated that anaesthesia, high FiO2 and limited aspiration during the procedure might help explain the increased respiratory system elastance immediately after tracheotomy.

Dongelmans and colleagues [24] reported the case of a patient who developed an intratracheal blood clot acting as a one-way ball valve several days after tracheostomy. The clot was successfully removed using the intratracheal tube as an extension of the suction system.

Ventilator associated pneumonia

Camargo and colleagues [25] set out to test if quantification of bacterial colonies in tracheal aspirates, as compared to qualitative cultures, would better correlate with clinically diagnosed ventilator associated pneumonia. On the basis of clinical criteria, 38 of 219 assessments in 33 of 106 patients were classified as ventilator associated pneumonia. Qualitative cultures of tracheal aspirates revealed a sensitivity of 81% (specificity 23%), quantitative cultures with a threshold of $\geq 10^5$ cfu/ml yielded a sensitivity of 65.8% (specificity 48%), and with a threshold of $\geq 10^6$ cfu/ml a sensitivity 26.3% (specificity 78%). The authors concluded that quantitative cultures are not suitable to confirm or exclude clinically diagnosed ventilator associated pneumonia.

Multi-drug resistant infections

To investigate airway and stomach colonization with coagulase-negative staphylococci (CoNS) and the rate of CoNS cross-transmission between patients, Agvald-Öhman and coworkers [26] genotyped CoNS in samples collected from the oropharynx, the stomach, the subglottic space and the trachea in 20 consecutive patients mechanically ventilated for at least 3 days. In their study, 17/20 patients were colonized with CoNS on at least one occasion, in 16/20 patients the lower airways were colonized by CoNS, and 14/20 patients were involved in at least one and up to eight probable transmission events. The authors concluded that CoNS was frequently transmitted between ICU patients.

Michalopoulos and coworkers [27] reviewed eight patients treated with aerosolized colistin as an adjunct to intravenous antimicrobial therapy (including intravenous colistin in 6/8 patients) for Gram-negative nosocomial pneumonia (seven *Acinetobacter baumannii*, one *Pseudomonas aeruginosa*). Isolated microorganisms were all susceptible to cholistin, and 4/8 were resistant to at least five antipseudomonal classes of antimicrobial agents. Pneumonia improved in 7/8 patients, and one patient died. The authors concluded that inhaled colistin may be beneficial in the treatment of nosocomial pneumonia due to multi-drug resistant, Gram-negative bacteria.

Pleural effusion

Singh and colleagues [28] successfully used 16 G indwelling central venous catheters to drain large, non-loculated pleural effusions in 10 patients (8 mechanically ventilated). No

pneumo- or hemothorax, catheter displacement or disconnection were encountered and the authors suggested that this technique might safely be used in selected patients.

Sedation and analgesia

Sensory stimuli evoked potentials may better reflect the brain's responsiveness during sedation than the electroencephalogram alone. Yppärilä and colleagues [29] evaluated electroencephalogram and auditory event-related potentials during reduction and after discontinuation of propofol sedation in 19 intensive care patients. Electroencephalogram (root mean squared power) as well as auditory event-related potentials (N100 amplitude) increased in response to interruption of sedation, but only the N100 component differed between sedation levels. The authors concluded that auditory event-related potentials may potentially complement neurophysiological methods to monitor sedation levels.

Muellejans and coworkers [30] compared efficacy and safety of remifentanil and fentanyl for analgesia and sedation in 152 mechanically ventilated patients. Both remifentanil and fentanyl were effective and safe in providing targeted sedation and a similar proportion of patients required additional propofol sedation. Patients experiencing pain in the peri-extubation period did so for a longer time in the remifentanil group. The authors concluded that using a dosing algorithm that includes frequent reassessment, analgesia based sedation with remifentanil and fentanyl is similar; however, rapid offset of analgesia with remifentanil accounts for more patient discomfort if pain is not treated proactively.

Memis and colleagues [31] assessed whether adding magnesium sulphate (2 g/hour) would affect sufentanil infusion rates over 6 hours in 30 mechanically ventilated patients when a bispectral index range of 61–88 was targeted. Sufentanil infusion rates were significantly lower when magnesium sulphate was administered in parallel. The authors concluded that combining magnesium sulphate has sufentanil-sparing effects during short term application.

Asthma

Gupta and coworkers [32] used a large database to examine characteristics of 2152 (1.7% of 129,647) patients admitted to England, Wales and Northern Ireland ICUs with asthma. Median ICU stay was 1.5 days; 1223 (57%) required early mechanical ventilation, 147 (7.1%) died in the ICU, and 199 (9.8%) died before hospital discharge. Older age, female sex, pre-admission cardiopulmonary resuscitation, acute neurological insult, higher heart rate, and hypercapnia were associated with risk of in-hospital death. The authors concluded that asthma accounts for only few ICU admissions but remains associated with appreciable in-hospital mortality.

Techniques and monitoring

To investigate the relation between changes in pulse oximeter oxygen saturation (SpO_2) and changes in arterial oxygen saturation (SaO_2) as well as to evaluate the effects of acidosis and anaemia on this relationship, Perkins and coworkers [33] compared 1085 paired readings from 41 critically ill patients. The pulse oximeter tended to overestimate changes in SaO_2 as by blood gases, and changes in SpO_2 and changes in SaO_2 were only moderately correlated ($r = 0.606$; $P < 0.01$). Anaemia increased the degree of positive bias whereas acidosis reduced it; however, the magnitude of these changes was small. The authors concluded that changes in SpO_2 do not reliably predict equivalent changes in SaO_2 in the critically ill and neither anaemia nor acidosis alters the relation between SpO_2 and SaO_2 to any clinically important extent.

Competing interests

ASS is a consultant for Maquet, Hamilton Medical, KCl, and chaired a DSMB for Leo Pharma in relation to surfactant therapy for ARDS.

Acknowledgements

LB is the recipient of grant 1130 of the Swiss Foundation for Fellowships in Medicine and Biology provided by Novartis AG.

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