Thorax 2001;**56**(Suppl II):ii50–ii57

VENTILATOR INDUCED LUNG INJURY AND INFECTION IN THE CRITICALLY ILL

S V Baudouin

Introductory articles

Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome

Acute Respiratory Distress Syndrome (ARDS) Network

*Background: Traditional approaches to mechanical ventilation use tidal volumes of 10–15 ml/kg body weight and may cause stretch-induced lung injury in patients with acute lung injury and the acute respiratory distress syndrome. We therefore conducted a trial to determine whether ventilation with lower tidal volumes would improve the clinical outcomes in these patients. Methods: Patients with acute lung injury and the acute respiratory distress syndrome were enrolled in a multicenter randomized trial. The trial compared traditional ventilation treatment, which involved an initial tidal volume of 12 ml/kg predicted body weight and an airway pressure measured after a 0.5 s pause at the end of inspiration (plateau pressure) of 50 cm H_2O or less, with ventilation with a lower tidal volume, which involved an initial tidal volume of 6 ml/kg predicted body weight and a plateau pressure of 30 cm H_2O or less. The primary outcomes were death before a patient was discharged home and was breathing without assistance and the number of days without ventilator use from day 1 to day 28. Results: The trial was stopped after the enrollment of 861 patients because mortality was lower in the group treated with lower tidal volumes than in the group treated with traditional tidal volumes (31.0% vs 39.8%, P=0.007), and the number of days without ventilator use during the first 28 days after randomization was greater in this group (mean (SD) 12 (11) vs 10 (11); P=0.007). The mean tidal volumes on days 1–3 were 6.2 (0.8) and 11.8 (0.8) ml/kg predicted body weight (P<0.001), respectively, and the mean plateau pressures were 25 (6) and 33 (8) cm H_2O (P<0.001), respectively. Conclusions: In patients with acute lung injury and the acute respiratory distress syndrome, mechanical ventilation with a lower tidal volume than is traditionally used results in decreased mortality and increases the number of days without ventilator use. (**N Engl J Med** 2000;342:1301–8)*

Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial

J Y Fagon, J Chastre, M Wolff, C Gervais, S Parer-Aubas, F Stephan, T Similowski, A Mercat, J L Diehl, J P Sollet, A Tenaillon

Background: Optimal management of patients who are clinically suspected of having ventilator-associated pneumonia remains open to debate. Objective: To evaluate the effect on clinical outcome and antibiotic use of two strategies to diagnose ventilator-associated pneumonia and select initial treatment for this condition. Design: Multicenter, randomized, uncontrolled trial. Setting: 31 intensive care units in France. Patients: 413 patients suspected of having ventilator-associated pneumonia. Intervention: The invasive management strategy was based on direct examination of bronchoscopic protected specimen brush samples or bronchoalveolar lavage samples and their quantitative cultures. The noninvasive ("clinical") management strategy was based on clinical criteria, isolation of microorganisms by non-quantitative analysis of endotracheal aspirates, and clinical practice guidelines. Measurements: Death from any cause, quantification of organ failure, and antibiotic use at 14 and 28 days. Results: Compared with patients who received clinical management, patients who received invasive management had reduced mortality at day 14 (16.2% and 25.8%; difference, –9.6 percentage points [95% CI –17.4 to –1.8 percentage points]; P=0.022), decreased mean sepsis-related organ failure assessment scores at day 3 (6.1 (4.0) and 7.0 (4.3); P=0.033) and day 7 (4.9 (4.0) and 5.8 (4.4); P=0.043), and decreased antibiotic use (mean number of antibiotic-free days, 5.0 (5.1) and 2.2 (3.5); P<0.001). At 28 days, the invasive management group had significantly more antibiotic-free days (11.5 (9.0) compared with 7.5 (7.6); P<0.001), and only multivariate analysis showed a significant difference in mortality (hazard ratio 1.54 [CI 1.10 to 2.16]; P=0.01). Conclusions: Compared with a noninvasive management strategy, an invasive

Department of Anaesthesia and Intensive Care, Royal Victoria Hospital, Newcastle upon Tyne NE1 4LP, UK
S V Baudouin

Correspondence to: Dr S V Baudouin

*management strategy was significantly associated with fewer deaths at 14 days, earlier attenuation of organ dysfunction, and less antibiotic use in patients suspected of having ventilator-associated pneumonia. (**Ann Intern Med** 2000;132:621–30)*

In the last year two important respiratory orientated, randomised controlled trials in critical care have been published. Both studies share a common theme—namely, that mechanical ventilation can produce complications as well as benefits. The first study by the Acute Respiratory Distress Syndrome Network[1] compares the effect of different modes of ventilation on outcome in the acute respiratory distress syndrome (ARDS), and the second by Fagon ***et al***[2] investigates the impact on survival of two different strategies for investigating ventilator associated pneumonia.

VENTILATION STRATEGIES IN ARDS

Over 20 years of intensive research by both clinical and basic scientists has established that ARDS is an inflammatory condition of the lung.[3] Histopathological studies, later complemented by investigations using bronchoalveolar lavage (BAL) techniques, showed the presence of a large number of acute inflammatory cells (neutrophils and monocytes/macrophages), pro-inflammatory cytokines, and cytotoxic neutrophil release products within the alveolar spaces. These observations, coupled with the findings of marked damage to the endothelial/epithelial interface of the lung, suggested that acute inflammatory damage to the alveoli was the central mechanism of acute lung injury.

Biotechnology companies rapidly developed a range of anti-cytokine/anti-inflammatory agents, mostly based on the new monoclonal technology, which formed the basis for a number of randomised controlled trials in ARDS (often secondary to severe sepsis).[4 5] At best, the trials showed no treatment benefit and a few suggested that the intervention was positively harmful.[5] It is understandable that a feeling of gloom began to settle over the critical care community. However, this has changed in the last 18 months following the publication of a North American multicentre study comparing two modes of ventilation in ARDS.[1] It seems that the Holy Grail of clinical ARDS research has finally been reached—a randomised controlled trial where the intervention was beneficial!

The results of the trial should be set in the context of an interesting paradox in clinical lung injury research that emerged during the 1990s. Despite the clear negative randomised controlled trials being reported, a number of groups in both the UK and North America were claiming improved survival rates for patients with ARDS treated at their institutions.[6] Comparison of survival rates in ARDS is difficult because of the problems of case mix. The initial severity of lung injury (as judged by gas exchange criteria) is only poorly related to survival. Of much greater importance is the cause of the lung injury and the co-morbidity of the patient. In the European Collaborative ARDS Study, for example,[7] 65% of patients with trauma related lung injury survived compared with only 20% with pneumonia.

Despite potential confounding factors, groups from the UK and North America produced persuasive evidence for a real fall in mortality.[8 9] The UK group[8] reported a fall in mortality from 66% in the early 1990s to 34% in the later period. The US group[9] reported a 60% mortality in the late 1980s with a fall to 36% in the early 1990s. It is interesting to note that these reduced mortality rates are similar to those reported in the ***intervention*** limbs of the recent randomised controlled trials of ventilation modes in ARDS.

An attractive explanation for the reported fall in ARDS mortality rates was the adoption by these groups of beneficial ventilatory strategies before the demonstration of their efficiency in recent randomised controlled trials. This can be best understood by examining the experimental literature that began to emerge in the late 1980s and early 1990s on ventilator induced lung injury.

Ventilator induced lung injury

Neonatal intensivists were perhaps the first group to recognise the possible role of prolonged mechanical ventilation in inducing lung injury. Although the features of bronchopulmonary dysplasia were originally only thought to occur in the immature lung, similar changes have been reported in necroscopic studies of adults with ARDS.[10]

In 1974 Webb and Tierney[11] published one of the first reports on experimental ventilator induced lung injury. Rats mechanically ventilated with peak airway pressures of 45 cm H_2O rapidly developed severe, usually fatal, pulmonary oedema. These results were reproduced and extended by other groups in several animal species. Even relatively low airway pressures of the order of 25–30 cm H_2O can cause significant lung injury and increased microvascular permeability.

Table 1 Summary of four randomised controlled trials of lung protection ventilation strategies in ARDS. Information on total patient entry to the studies, treatment modes and outcomes are shown

Study	No of centres	Total patient entry	Conventional limb	Protection limb	Control mortality	Intervention mortality	p value
Brochard (1998)[16]	25 (worldwide)	116 with ARDS	TV ⩾10 ml/kg, normal $Paco_2$	TV <10 ml/kg, plateau pressure <25 cm H_2O	37.9%	46.6%	0.38
Stewart (1998)[17]	8 (Canada)	120 high risk ventilated patients	TV 10–15 ml/kg, peak inspiratory pressure ⩽50 cm H_2O	TV <8 ml/kg, peak inspiratory pressure ⩽30 cm H_2O	47%	50%	0.72
Amato (1998)[18]	1 (Brazil)	53 with ARDS	TV 12 ml/kg, $Paco_2$ 4.7–5.1 kPa, least PEEP to maintain Pao_2	TV <6 ml/kg, PEEP >LIP on P/V curve peak pressure <20 cm H_2O above PEEP	71%	38%	<0.001
ARDS Network (2000)[1]	10 (North America)	861 with ARDS	12 ml/kg predicted body weight, plateau airway pressure ⩽50 cm H_2O	6 ml/kg predicted body weight, plateau airway pressure ⩽30 cm H_2O	39.8%	31.0%	0.007

Previously injured lungs may be more sensitive to the effects of mechanical ventilation. In one experimental study neither mild oleic acid lung injury or mechanical ventilation caused pulmonary oedema in rabbits, but the combination produced severe lung injury.[12] In another study of hydrochloric acid induced lung injury in the dog, low tidal volume ventilation (15 ml/kg) produced less pulmonary oedema than "high" tidal volumes (30 ml/kg).[13]

Permissive hypercapnia and controlled hypoventilation

Hickling and collaborators[14 15] were one of the first groups to attempt to translate these experimental findings into clinical practice. In ARDS the lungs are stiff and non-compliant. In order to achieve a normal arterial carbon dioxide tension ($Paco_2$) it is often necessary to use high tidal volume/airway pressures during ventilation. Most intensive care units in the 1970s and 1980s ventilated their patients to a target of normocapnia, accepting that high tidal volumes would be necessary. In 1990 Hickling and co-authors produced a retrospective case series of 50 patients with ARDS who they had deliberately underventilated in order to reduce airway pressures and ventilator induced lung injury.[15] Hypercapnia was frequent as a consequence of this strategy (mean $Paco_2$ 8.3 kPa). They reported significantly lower hospital mortality compared with that predicted using the APACHE scoring system. This was later followed by a prospective descriptive study of 53 patients with severe ARDS managed by a similar low tidal volume protocol.[14] Once again, observed mortality was significantly lower than that predicted using the APACHE II system.

Randomised controlled trials of lung protective ventilation in ARDS

In the last three years four randomised controlled trials of lung protective mechanical ventilation in patients with either established ARDS or at high risk of ARDS have been published.[1 16–18] In total, over 1000 patients have been recruited into these studies (table 1). On initial analysis the results of the trials differ. Two studies (the largest and the smallest) were strongly in favour of protective ventilation, while the other two showed no difference in outcome. Each of these trials will be reviewed in detail and possible explanations for these differences discussed.

Brochard and co-workers enrolled 116 patients with ARDS (but no other organ failure) from 25 centres, mostly in France.[16] Case mix stratification was used to adjust for known survival differences between multi-trauma, immunosuppressed, and other cases of ARDS. The level of positive end expiratory pressure (PEEP) was set before the study based on a titrated trial to maximise oxygenation. The standard treatment group received volume targeted ventilation with a tidal volume (TV) of 10–15 ml/kg to achieve normocapnia. However, peak airway pressure was not allowed to exceed 60 cm H_2O. In the pressure limitation group, TV was adjusted to keep end inspiratory plateau pressure at or below 25 cm H_2O. TV was therefore maintained in the 6–10 ml/kg range. Respiratory acidosis (as a consequence of relative hypoventilation) was tolerated, but sodium bicarbonate was given if pH fell below 7.05. Target Fio_2 was at or above 92%. As expected, the pressure limitation group achieved lower TV and plateau pressures, but higher $Paco_2$. Mean PEEP levels were similar (10.7 cm H_2O). The study was powered to detect a reduction in mortality from 50% to 30% but was stopped prematurely after an interim analysis of the first 100 patients showed that no significant difference in outcome would be detected. Mortality at day 60 was 46.6% in the pressure limited group and 37.9% in the standard group. There was also no difference in secondary end points of duration of ventilation, incidence of pneumothorax, or the occurrence of secondary organ failure.

In the second study Stewart and co-workers randomised a total of 120 patients at high risk of developing ARDS into a standard and pressure/volume limited ventilation.[17] Patients were selected on the basis of being intubated with significant gas exchange abnormalities (defined by a combination of Pao_2/Fio_2/PEEP received) and the presence of one or more risk factors for ARDS (sepsis, aspiration, lung contusion, multiple transfusions, multiple fractures, pneumonia, burn/inhalation injury, acute pancreatitis, drug overdose, shock). In the standard ventilation group TV was maintained at 10–15 ml/kg with peak inspiratory pressures up to 50 cm H_2O. In the limited ventilation group TV was kept at 8 ml/kg or less and peak inspiratory pressures at no more than 30 cm H_2O. PEEP was adjusted in both groups to 5–20 cm H_2O to maintain Fio_2 at 0.5 or less with Sao_2 of 89–93%. Severe respiratory acidosis (pH <7.0) was treated with sodium bicarbonate. Both mean TV and peak inspiratory pressures were lower in the limited group and mean $Paco_2$ was higher. There was no significant difference in the primary study end point of mortality with 47% in the standard group and 50% in the limited ventilation group. Secondary end points of barotrauma and incidence of multiple organ failure were also similar.

The first positive randomised controlled trial of protective ventilation in ARDS was published by Amato and colleagues in 1998.[18] They randomised 53 patients with ARDS into conventional and protective ventilation groups. The trial was performed in a single centre and over a five year time period from 1990 to 1995. The conventional treatment group was

ventilated at 12 ml/kg TV to achieve a $Paco_2$ of 4.7–5.1 kPa. PEEP was adjusted by an algorithm involving the Fio_2 and Pao_2. The protective group received TV of less than 6 ml/kg and sodium bicarbonate was used to keep the pH above 7.2. Unlike previous randomised controlled trials, PEEP in the protective ventilation group was adjusted following measurements of lung mechanics. This approach was based on the observations that, in early ARDS, lung injury and alveolar collapse is not a uniform process. Functionally, three compartments exist: (1) a number of normal gas exchanging units, (2) a substantial number of completely collapsed units which are no longer available to gas exchange, and (3) a number of partially collapsed lung units which can be recruited/derecruited depending on the ventilatory mode used. The differing and dynamic properties of the compartments lead to a characteristic relationship of the pressure volume (P/V) curve of the injured lung. The P/V curve has a sigmoid relationship. The lower inflexion point (LIP) corresponds to the pressure required to recruit collapsed lung units while the upper inflection point (UIP) is thought to represent the point at which alveolar overdistension occurs.[19] In the functionally reduced ARDS lung even modest tidal volumes of 10–12 ml/kg can cause overdistension. Amato and colleagues measured P/V relationships in 60 potential patients and a classic sigmoid distribution found in 49 who subsequently entered the study. In the protective lung group PEEP was preset at 2 cm H_2O above the pressure of the LIP. If an LIP could not be determined, then 16 cm H_2O of PEEP was applied. Peak airway pressures were kept below 40 cm H_2O; 28 day mortality in the conventional group was 71% while mortality in the protective group was 38%. The high mortality in the control group has attracted considerable comment, but the large differences in outcome between the groups cannot be ignored.

The largest and most recent study was conducted in 10 North American tertiary referral centres from 1996 to 1999.[1] Patients were recruited within 36 hours of developing ARDS and randomised into either a conventional or low TV limb of the study. The conventional ventilation group received an initial TV of 12 ml/kg predicted body weight which was reduced, if needed, to maintain a plateau airway pressure of 45–50 cm H_2O. The low TV group received an initial TV of 6 ml/kg, subsequently reduced to maintain a plateau pressure of 25–30 cm H_2O. Changes in the inspiratory:expiratory ratio from 1:3 to 1:1 were allowed in both groups. One interesting aspect of the study was the use of a simple algorithm to adjust PEEP. This gave allowable combinations of Fio_2 and PEEP—for example, Fio_2 0.8 and PEEP 14 cm H_2O—to maintain a target of Sao_2 of 88–95%. The trial was stopped after the fourth interim analysis because of a clear difference in favour of the low TV strategy. A total of 861 patients with well matched baseline characteristics has been recruited by this point. In approximately one third of subjects the ARDS was caused by pneumonia while in approximately another third the condition was caused by sepsis. Trauma and aspiration accounted for most of the remaining cases. The low TV group received significantly lower TV and had lower airway pressures. Mean $Paco_2$ was higher in the low volume group. The main end point of death before discharge occurred in 31.0% in the low TV group and 39.8% in the conventional group. Other significantly different end points were breathing without assistance at day 28; number of ventilator-free days from days 1 to 28, and number of days without failure of non-pulmonary organs. Interestingly, barotrauma (as judged by pneumothoraces) was not significantly different.

Lung protection or lung injury?

All four trials had the same aim in min—to demonstrate that low volume/low pressure ventilation improves survival in ARDS. However, only two of the four demonstrated this result. Is the case proven or not? Table 2 summarises the important differences in ventilator settings used in the studies. It should be noted that: (1) Plateau airway pressures in the control groups were highest in the two positive studies. The study by Amato *et al*[18] had both the highest control mortality and used the highest control airway pressures. (2) Mean $Paco_2$ was lowest in the conventional ventilation limbs of the two positive studies. In one it was at the lower end of normal (4.7 kPa) and in the other it was below normal (4.4 kPa). This suggests that hyperventilation was occurring in these control groups. (3) The mean PEEP used in the most positive study in the protection limb was considerably higher than in the other studies.

Two conclusions can be drawn from these very important trials. Firstly, "conventional ventilation", which produces plateau airway pressures above 30 mm Hg and reduces $Paco_2$ to a low normal range, damages the lung and reduces survival in ARDS. Low pressure/volume ventilation strategies should become standard in the treatment of acute lung injury. Secondly, it is possible that levels of PEEP above those normally used in ARDS may protect the lung against further injury. This conclusion is less firm and current trials are being carried out to test this hypothesis.

Mechanisms responsible for ventilator induced lung injury

The role of pro-inflammatory cells and cytokines in the pathogenesis of sepsis and trauma-related ARDS is well established.[20] Experimental studies suggest that similar mechanisms are relevant in ventilator induced lung injury. For example, hyperventilation of the isolated perfused rat lung increased mRNA expression of tumour necrosis factor (TNF)α and interleukin (IL)-6 and increased the release of these cytokines into the lung perfusate.[21] At a cellular level, mechanical forces have been shown to activate a wide range of inflammatory and pulmonary cells,[22] although the precise intercellular pathways which transduce mechanical forces have not been completely identified.

It is likely that these mechanisms are relevant to ventilator induced lung injury in man. Ranieri and co-workers[23] randomised 44 patients with ARDS to either conventional

Table 2 Comparison of mean positive end expiratory pressure (PEEP), tidal volume (TV), plateau airway pressures, and arterial carbon dioxide tension ($Paco_2$) in the protection (P) and conventional (C) limbs of the four randomised controlled trials of lung protection ventilation in patients with ARDS

Study	PEEP (cm H_2O)		TV (ml/kg)		Plateau pressure (cm H_2O)		$Paco_2$ (kPa)	
	P	C	P	C	P	C	P	C
Brochard[16]	10.7	10.7	7.1	10.3	25.7	31.7	7.9	5.5
Stewart[17]	8.6	7.2	7.0	10.7	22.3	26.8	7.3	6.1
Amato[18]	16.4	8.7	348 ml	768 ml	30.1	36.8	7.3	4.4
ARDS network[1]	9.4	8.6	6.2	11.8	25.0	33.0	5.3	4.7

ventilation or a lung protection strategy with tidal volumes and PEEP based on pressure-volume curve measurements. Pulmonary and systemic concentrations of inflammatory mediators were measured at entry and again at approximately 36 hours after randomisation. Tidal volumes and plateau pressures were significantly lower in the protection group and PEEP higher. In the conventional ventilation group BAL fluid and plasma levels of IL-1β, IL-6, and IL-1 receptor agonists increased over time while in the lung protection group these fell. The numbers of neutrophils in the BAL fluid also fell over time in the protection group but were unchanged in the conventional limb. In addition, both plasma and BAL fluid levels of TNFα, IL-6, and IL-8 fell over time in the protected group but were unchanged in the conventional limb. Overall concentrations of all pro-inflammatory mediators were lower in the protected group than in the control group at 36 hours.

The increase in systemic, as well as lung, levels of pro-inflammatory cytokines may explain the survival advantage of lung protective strategies in ARDS. It has long been recognised that patients with ARDS tend to die of multi-organ failure rather than pure respiratory failure. The multicentre North American study[1] found that progression to multi-organ failure was reduced in the lung protection group. They also found lower systemic levels of IL-6 in the protection group than in the conventional limb. Taken together, these results generate an attractive hypothesis. Conventional mechanical ventilation locally upregulates inflammatory mechanisms in the lung which "spill over" into the systemic circulation. The systemic mediators in turn damage multi-organs and ultimately induce multi-organ failure. A vicious circle of organ damage is then perpetuated. Systemic inflammation produces lung injury which requires mechanical ventilatory support. This increases lung damage and releases systemic inflammatory mediators that induce further organ damage. In this situation, the failure of single anti-inflammatory agents to alter the outcome is clear. The lung has, in effect, been acting as a continuing source of sepsis.

Future directions in research in ventilator induced lung injury

There can no longer be any doubt that mechanical ventilation can result in lung injury and increased mortality in ARDS. However, many units had already abandoned the ventilation strategies used in the control limbs of the positive trials. This may, in part, explain the falling mortality previously reported by a number of groups. Could mortality be further reduced by additional changes in ventilatory practice? A number of issues remain. The role of PEEP and the correct level of PEEP to use in acute lung injury need further investigation. It is possible that high PEEP and high airway pressures have been incorrectly associated and that higher levels of PEEP should be used routinely in the treatment of ARDS. The role of bedside measurements of lung mechanics is also under investigation. The reproducibility and accuracy of these curves has been challenged,[24] but the concept of adjusting ventilation based on lung mechanics rather than gas exchange remains attractive. Finally, the pro-inflammatory nature of conventional mechanical ventilation makes the re-examination of "unconventional" ventilation and respiratory support (jets, oscillators, ECMO) inevitable. Many of these devices were rejected on the basis of small poorly designed studies.[4] They may yet have a role in the management of ARDS.

Ventilator induced pneumonia

Ventilator associated pneumonia remains a controversial topic in the critical care literature. By definition, it is a nosocomial infection acquired within hospital. Most studies take a minimal time period of 48 hours between intubation and diagnosis to exclude cases of community acquired pneumonia. Estimates of incidence vary widely with 7–40% of all critically ill patients reportedly having at least one episode of ventilator associated pneumonia.[25] Other data suggest that over 50% of all infection in ventilated patients is due to ventilator associated pneumonia,[26] while a recent Canadian multicentre study[27] reported that 177 of 1014 patients (17.5%) invasively ventilated for more than 48 hours developed ventilator associated pneumonia.

The variable incidence rates reported point to two related problems in research into ventilator associated pneumonia. Firstly, there is no gold standard for the diagnosis and, secondly, there is no standard definition of ventilator associated pneumonia. Traditional clinical approaches to diagnosis have used a combination of pyrexia, raised white blood cell count, new infiltrates on the plain chest radiograph, and a positive endobronchial sputum culture as indicating the presence of ventilator associated pneumonia. There is considerable evidence that this approach will produce a significant rate of overdiagnosis. Each of the above clinical features occurs commonly in critically ill patients and have multiple explanations. Pulmonary infiltrates may be due to oedema, atalectesis, haemorrhage, or pulmonary emboli while the differential diagnosis of pyrexia and leucocytosis is large. Purulent endobronchial secretions are also common in the intubated population and often indicate the presence of tracheobronchitis alone. Finally, the culture of organisms from these secretions does not necessarily indicate the presence of an invasive pathogen. Prior use of antibiotics (common in intensive care units) encourages the emergence of resistant microbial colonisation of the airways and it is often these organisms which are cultured.

One "gold standard" for the diagnosis of pneumonia would be the classic histopathological features of abscess formation or areas of neutrophil accumulation with a positive quantitative culture of lung parenchyma ($>10^4$ micro-organisms/g lung tissue). In the majority of proposed cases of ventilator associated pneumonia this standard cannot be realistically reached. Occasional necroscopic studies suggest a poor correlation between the clinical diagnosis of ventilator associated pneumonia and histological appearances. Agreement among four histopathologists in a recent study of ventilator associated pneumonia was poor, with the diagnosis of ventilator associated pneumonia ranging from 18% to 38%.[28] The difficulty in diagnosing ventilator associated pneumonia in the presence of ARDS is even greater with a quoted sensitivity using conventional clinical criteria of less than 50%.[29] Markedly conflicting estimates of the incidence of ventilator associated pneumonia in ARDS have been published, varying from more than 70% to less than 16%.[30]

A number of factors are associated with an increased risk of developing ventilator associated pneumonia. Length of mechanical ventilation raises the risk. In the Canadian study[27] the chance of developing ventilator associated pneumonia increased over time, although the hazard rate actually decreased. Rates of ventilator associated pneumonia were 3% per day in the first week of ventilation, 2% per day in the second week, and 1% per day in the third week and after. Similar findings have been reported in other studies.[31] Severity of illness is also related to the development of

ventilator associated pneumonia. In a multicentre European study of infection in the intensive care unit, a logistic regression analysis identified high APACHE II scores (>16) as an independent risk factor for the development of ventilator associated pneumonia.[32] Certain specific conditions also appear to be associated with a higher incidence. These include head injury, severe burns, and patients with acute and chronic respiratory conditions.[31]

The mortality rate of patients with ventilator associated pneumonia is significantly higher than in those who do not develop pneumonia. Crude mortality rates vary between 24% and 76%.[25] A number of studies have compared the mortality of patients with ventilator associated pneumonia with those without and have reported that ventilator associated pneumonia increases the risk of mortality by 1.7–4.[25] These studies demonstrate a higher mortality in patients with a diagnostic label of ventilator associated pneumonia but do not prove that it is the cause of the excess mortality. Such an association is difficult to establish given the strong link between severity of illness and ventilator associated pneumonia. Lack of agreed diagnostic criteria has also hampered attempts to establish a causal relationship.

Both multivariate and case control studies have been performed in an attempt to establish a causal relationship between ventilator associated pneumonia and mortality. Unfortunately, these studies have not reached a uniform conclusion. Studies using multivariate analysis have not found an independent association between ventilator associated pneumonia and outcome,[33] while the EPIC study found that ventilator associated pneumonia increased the risk of death with an odds ratio of 1:9 and Fagon and colleagues[34] also found it to be an independent predictor of mortality.

Case control studies have also given variable results. Castree[25] identified five such studies, four of which suggested an independent association between ventilator associated pneumonia and mortality. However, the negative study[35] was the most recent and also used invasive diagnostic methods (lavage and protected brush specimens) to establish the diagnosis. It also focused on a relatively homogeneous group of ventilated trauma patients.

This last study highlights recent trends to investigate potential cases of ventilator associated pneumonia by using invasive techniques. Two methods have been used—protected brush specimens and bronchoalveolar lavage (BAL). In the first technique a special catheter with a distal tip protected by a plug to reduce microbial contamination from the upper airway is placed by bronchoscopy in the lung segment of interest. The plug is expelled, the distal brush pushed into the segment, a specimen obtained, and the brush retracted. Finally, a quantitative culture technique is used to improve discrimination with a positive cut off threshold of 10^3 cfu/ml. With the BAL technique a volume of sterile fluid is injected into the peripheral lung segments by the bronchoscope, retrieved, and set for staining and quantitative culture. Many studies have taken 10^4 cfu/ml as a cut off for the diagnosis of pneumonia.

Doubts about the diagnosis, investigation, prognosis, and outcome of ventilator associated pneumonia prompted the French based group to conduct a multicentre study.[2] They compared the effect on clinical outcome of two different diagnostic approaches to suspected ventilator associated pneumonia. A total of 413 patients from 31 intensive care units in France were recruited into the study. Patients were enrolled once clinical suspicion of ventilator associated pneumonia had been raised (as defined by a new and persistent radiological shadow and at least one of the following: purulent tracheal secretions, pyrexia of at least 38.3°C, leucocytosis). In the clinical management group treatment was based on clinical evaluation and a Gram stain of endotracheal secretions. The American Thoracic Society recommendations for the treatment of ventilator associated pneumonia were used.[36]

In the invasive strategy group either BAL fluid or a protected brush specimen was obtained. The choice of method was left to each unit. Specimens were immediately stained and a decision to start antibiotic treatment made on

Learning points

- Experimental studies have shown that mechanical ventilation, at even moderate pressures and volumes, can both cause and worsen acute lung injury.
- The pathophysiology of ventilator induced lung injury appears similar to “classic” ARDS.
- Four randomised controlled trials of lung protection ventilation strategies in ARDS have been performed. Two of these trials demonstrated benefit, both of which employed the highest ventilator pressures/volumes in the control limb.
- Low volume/pressure ventilatory strategies should become standard treatment in ARDS.
- Ventilator associated pneumonia is common in patients receiving ventilation. A recent study comparing outcome following empirical versus targeted antibiotic therapy (following BAL or protected brush sampling) showed a possible advantage in the targeted group which may be explained by the difference in the reduction in antibiotic usage in the two groups.
- Prolonged mechanical ventilation causes significant complications. There is good evidence that these may be reduced by specific ventilation strategies and protocols for the management of ventilator associated pneumonia.

these results. Subsequent culture results were then used to modify or stop treatment.

The primary end point chosen by the trial groups was 14 day mortality. The authors stated that 14 day mortality was chosen "because this period corresponds to that during which ventilator associated pneumonia has its maximal impact on survival". Mortality was significantly different at day 14 with a 16.2% mortality in the invasive group compared with a 25.8% mortality in the clinical management group. By 28 days, mortality in the invasive group still tended to be lower (30.9% *v* 38.8%) but was no longer significantly different. At day 14 organ failure was also less in the invasive group, as was the use of antibiotics.

The authors interpret their findings as evidence for the efficacy of invasive approaches to the diagnosis of ventilator associated pneumonia. They propose that the improved outcome in the invasive group was due to (1) the reduction in the use of inappropriate antibiotics, and (2) the search for other sites of infection when the chest was shown not to be the source. However, the fact that the difference in 28 day mortality was much smaller and no longer significant must raise some doubts about the authors' conclusions. Long term survival still remains the "gold standard" outcome in clinical trials in intensive care units, despite debate on surrogate measures. Interventions that improve 14 day mortality but have no impact on longer survival may just prolong dying and may not be beneficial. The authors did perform a Cox multivariate proportional hazards analysis for 28 day mortality and found a significant difference in mortality between the two groups, once adjustment for covariables was made. The possibility that the difference in mortality reported at day 14 might disappear if subjected to the same complex analysis was not raised in the paper.

The trial raises the important issue of the possible impact of antibiotic usage on mortality in the intensive care unit. The study successfully reduced antibiotic usage in the invasive diagnostic group (91% received antibiotics in the control group, 52% in the invasive group). If reduced antibiotic use improves outcome, would an even greater reduction further improve mortality? Much antibiotic usage on intensive care units is empirical and strategies to further reduce usage need to be explored.

Conclusions

The studies in both the introductory articles have shown that mechanical ventilation is associated with a range of complications. Could there be a link between the findings in these trials? Perhaps ventilator induced lung injury and ventilator associated pneumonia are part of the same process? Mechanical ventilation can damage the lung, cause inflammation, and release cytokines into the systemic circulation. This process will cause fever, leucocytosis, and new pulmonary infiltrates. If ventilator associated pneumonia is really ventilator induced lung injury, then antibiotics will have little effect. Only a change in ventilatory strategy will improve outcome.

References

1 **Acute Respiratory Distress Syndrome (ARDS) Network**. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;**342**:1301–8.

2 **Fagon JY**, Chastre J, Wolff M, *et al*. Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial. *Ann Intern Med* 2000;**132**:621–30.

3 **Reid PT**, Donnelly SC, Haslett C. Inflammatory predictors for the development of the adult respiratory distress syndrome. *Thorax* 1995;**50**:1023–6.

4 **Baudouin SV**. Surfactant medication for acute respiratory distress syndrome. *Thorax* 1997;**52**:S9–15.

5 **Zeni F**, Freeman B, Natanson C. Anti-inflammatory therapies to treat sepsis and septic shock: a reassessment. *Crit Care Med* 1997;**25**:1095–100.

6 **Baudouin S**. Improved survival in ARDS: Chance, technology or experience? *Thorax* 1998;**53**:237–8.

7 **Squara P**, Dhainaut JF, Artigas A, *et al*. Hemodynamic profile in severe ARDS: results of the European Collaborative ARDS Study. *Intensive Care Med* 1998;**24**:1018–28.

8 **Abel SJ**, Finney SJ, Brett SJ, *et al*. Reduced mortality in association with the acute respiratory distress syndrome (ARDS). *Thorax* 1998;**53**:292–4.

9 **Milberg JA**, Davis DR, Steinberg KP, *et al*. Improved survival of patients with acute respiratory distress syndrome (ARDS): 1983–1993. *JAMA* 1995;**273**:306–9.

10 **Churg A**, Golden J, Fligiel S, *et al*. Bronchopulmonary dysplasia in the adult. *Am Rev Respir Dis* 1983;**127**:117–20.

11 **Webb HH**, Tierney DF. Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end-expiratory pressure. *Am Rev Respir Dis* 1974;**110**:556–65.

12 **Hernandez LA**, Coker PJ, May S, *et al*. Mechanical ventilation increases microvascular permeability in oleic acid-injured lungs. *J Appl Physiol* 1990;**69**:2057–61.

13 **Corbridge TC**, Wood LD, Crawford GP, *et al*. Adverse effects of large tidal volume and low PEEP in canine acid aspiration. *Am Rev Respir Dis* 1990;**142**:311–5.

14 **Hickling KG**, Walsh J, Henderson S, *et al*. Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. *Crit Care Med* 1994;**22**:1568–78.

15 **Hickling KG**, Henderson SJ, Jackson R. Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. *Intensive Care Med* 1990;**16**:372–7.

16 **Brochard L**, Roudot-Thoraval F, Roupie E, *et al*. Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trail Group on Tidal Volume reduction in ARDS. *Am.J.Respir.Crit Care Med*. 1998;**158**:1831–8.

17 **Stewart TE**, Meade MO, Cook DJ, *et al*. Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. *N Engl J Med* 1998;**338**:355–61.

18 **Amato MB**, Barbas CS, Medeiros DM, *et al*. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998;**338**:347–54.

19 **Maggiore SM**, Brochard L. Pressure-volume curve in the crtically ill. *Curr Opin Crit Care* 2000;**6**:1–10.

20 **Pittet JF**, Mackersie RC, Martin TR, *et al*. Biological markers of acute lung injury: prognostic and pathogenetic significance. *Am J Respir Crit Care Med* 1997;**155**:1187–205.

21 **von Bethmann AN**, Brasch F, Nusing R, *et al*. Hyperventilation induces release of cytokines from perfused mouse lung. *Am J Respir Crit Care Med* 1998;**157**:263–72.

22 **Dos Santos CC**, Slutsky AS. Invited review: mechanisms of ventilator-induced lung injury: a perspective. *J Appl Physiol* 2000;**89**:1645–55.

23 **Ranieri VM**, Suter PM, Tortorella C, *et al*. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 1999;**282**:54–61.

24 **Hickling KG**. The pressure-volume curve is greatly modified by recruitment. A mathematical model of ARDS lungs. *Am J Respir Crit Care Med* 1998;**158**:194–202.

25 **Castree J**, Fagon JY. Ventilator-associated pneumonia. In: Hall JB, Schmidt GA, Wood LDH, eds. *Principles of critical care*. New York: McGraw-Hill, 1998:617–52.

26 **Valles J**, Leon C, Alvarez-Lerma F. Nosocomial bacteremia in critically ill patients: a multicenter study evaluating epidemiology and prognosis. Spanish Collaborative Group for Infections in Intensive Care Units of Sociedad Espanola de Medicina Intensiva y Unidades Coronarias (SEMIUC). *Clin Infect Dis* 1997;**24**:387–95.

27 **Cook DJ**, Walter SD, Cook RJ, *et al*. Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients. *Ann Intern Med* 1998;**129**:433–40.

28 **Corley DE**, Kirtland SH, Winterbauer RH, *et al*. Reproducibility of the histologic diagnosis of pneumonia among a panel of four pathologists: analysis of a gold standard. *Chest* 1997;**112**:458–65.

29 **Gallego M**, Rello J. Diagnostic testing for ventilator-associated pneumonia. *ClinChest Med* 1999;**20**:671–9.
30 **Sutherland KR**, Steinberg KP, Maunder RJ, *et al.* Pulmonary infection during the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1995;**152**:550–6.
31 **Cook DJ**. Ventilator-associated pneumonia. *Curr Opin Crit Care* 1999;**5**:350–6.
32 **Moine P**, Vercken JB, Chevret S, *et al.* Severe community-acquired pneumonia. Etiology, epidemiology, and prognosis factors. French Study Group for Community-Acquired Pneumonia in the Intensive Care Unit. *Chest* 1994;**105**:1487–95.
33 **Kollef MH**. Ventilator-associated pneumonia. A multivariate analysis. *JAMA* 1993;**270**:1965–70.
34 **Fagon JY**, Chastre J, Vuagnat A, *et al.* Nosocomial pneumonia and mortality among patients in intensive care units. *JAMA* 1996;**275**:866–9.
35 **Baker AM**, Meredith JW, Haponik EF. Pneumonia in intubated trauma patients. Microbiology and outcomes. *Am J Respir Crit Care Med* 1996;**153**:343–9.
36 **American Thoracic Society**. Hospital-acquired pneumonia in adults: diagnosis, assessment of severity, initial antimicrobial therapy, and preventive strategies. A consensus statement, American Thoracic Society, November 1995. *Am J Respir Crit Care Med* 1996;**153**:1711–25.