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Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome

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Abstract. Many animal studies have shown that high peak inspiratory pressures (PIP) during mechanical ventilation can induce acute lung injury with hyaline membranes. Since 1984 we have limited PIP in patients with ARDS by reducing tidal volume, allowing spontaneous breathing with SIMV and disregarding hypercapnia. Since 1987 50 patients with severe ARDS with a "lung injury score" $\geqslant 2.5$ and a mean PaO_2/FiO_2 ratio of 94 were managed in this manner. The mean maximum $PaCO_2$ was 62 mmHg, the highest being 129 mmHg. The hospital mortality was significantly lower than that predicted by Apache II (16% vs. 39.6%, $\chi^2 = 11.64$, $p < 0.001$). Only one death was due to respiratory failure, caused by pneumocystis pneumonia. 10 patients had a "ventilator score" >80, which has previously predicted 100% mortality from respiratory failure. Only 2 died, neither from respiratory failure. There was no significant difference in lung injury score, ventilator score, PaO_2/FiO_2 or maximum $PaCO_2$ between survivors and non-survivors. We suggest that this ventilatory management may substantially reduce mortality in ARDS, particularly from respiratory failure.

Key words: ARDS – Mortality – Mechanical ventilation – Hypercapnia – Fluid Therapy

Extensive evidence has accumulated from animal studies over the last ten years to show that the use of large tidal volumes (Vt) and high peak inspiratory pressures (PIP) during artificial ventilation results in the development of acute lung injury with the production of hyaline membranes and granulocyte infiltration [1–11]. This can occur in surfactant depleted lungs with Vt as low as 12 ml/kg, and with PIP as low as 25 cm H_2O [6, 8]. The lung injury can be progressive and result in death, and it can be prevented by techniques such as high frequency ventilation or apnoeic oxygenation with extracorporeal CO_2 removal, which avoid high PIP [1, 2, 9–11]. It appears that positive end-expiratory pressure (PEEP) may also reduce the extent of such lung injury [7, 8].

Because of this and related evidence [12, 13], since 1984 we have gradually adopted the policy of limiting PIP in patients with severe ARDS. Since using this approach to management we have been aware of only 1 death from progressive respiratory failure in patients with ARDS, and we wondered whether this ventilatory management may have resulted in a reduction in mortality from respiratory failure. This study was conducted to evaluate the total mortality and that due to respiratory failure in patients managed in this manner.

Patient management

During the period of this study, patients with ARDS had the PIP limited to <30 cm H_2O when this was easily achieved, and always to <40 cm H_2O, by reducing Vt as necessary, sometimes to volumes as low as 350 ml (5 ml/kg) in adults with very low lung compliance. This was done in conjunction with spontaneous breathing using synchronised intermittent mandatory ventilation (SIMV), and frequently resulted in a rapid spontaneous respiratory rate and hypercapnia. In patients with less severe lung injury however, spontaneous hyperventilation frequently resulted in a $PaCO_2$ within or even below the normal range even when PIP was limited. We did not increase the Vt or minute ventilation solely because of a moderate degree of hypercapnia ($PaCO_2$ up to 70 mm Hg) even in patients with a PIP <30 cm H_2O. We were careful to exclude causes of high PIP, tachypnoea and hypercapnia other than severe ARDS, such as partial occlusion of the endotracheal tube, pneumothorax or neuromuscular disease. In patients with intracranial hypertension we modified this approach to management. PEEP was used as necessary to allow adequate oxygenation with an FiO_2 of <0.6.

Fluid management consisted of generous fluid replacement using crystalloid fluids, or blood if required, in order to maintain adequate tissue perfusion and urine output, without increasing pulmonary capillary wedge pressure to >20 mmHg when a pulmonary artery catheter was used. All measurements of wedge pressure were made from a calibrated oscilloscope at end expiration without removing PEEP, and with the transducer at mid chest position. Early enteral nutrition was used when possible, and we were sparing in the use of broad spectrum antibiotics which may adversely alter the anaerobic flora of the gastro-intestinal tract. Selective decontamination of the digestive tract was not used.

Methods

The case notes were scrutinized of all patients admitted to our Intensive Care Unit since 1987 who had ARDS, aspiration pneumonia or pneumonia recorded as a diagnosis in our ICU Discharge Book. Patients were included in the study if they fulfilled the following criteria:

1) An underlying disease process known to be associated with ARDS.
2) PaO_2/FiO_2 ratio of <150
3) Diffuse new infiltrates on chest x-ray
4) The condition was thought not to be due to heart failure, atelectasis, or chronic disease processes.

A predicted mortality was obtained for each patient using the Apache II Scoring System using physiologic values within 24 hours of admission to the ICU [14]. For this purpose our estimate of the unsedated Glascow Coma Score was used in patients who had received sedative drugs.

A "lung injury score" (LIS) as described by Murray [16] was also obtained for each patient. This allocates a score of 0–4 according to the severity of the chest X-ray infiltrates, the derangement of PaO_2/FiO_2 ratio, the level of PEEP used, and the lung compliance if available. The score from each component is then averaged giving a lung injury score of 0–4. The score was calculated for each patient on the day of the lowest PaO_2/FiO_2 ratio. Murray suggests that a score of >2.5 reflects severe lung injury which could be called "ARDS".

The 50 patients with a lung injury score $\geqslant 2.5$ were classified as "severe ARDS" and further data relating to severity of illness and management were recorded for these patients as detailed below, along with hospital survival or the cause of death.

In 24 of these 50 patients records of PIP were available, whereas in the remaining 26 patients the ventilator record chart containing these recordings had not been filed by the Medical Records Department. This appeared to have occurred on a random basis depending on which member of the Medical Records Staff had filed the case notes. In the 24 patients with records of PIP, a "ventilator score" was calculated as described by Smith and Gordon [17]. This score is calculated as

$$0.5\times\text{age}+0.6\times AaDO_2+1.2\times PaW$$

where $AaDO_2$ is the alveolar to arterial oxygen tension gradient expressed in kPa and PaW is the mean PIP over 24 h minus a "control" PIP derived from patients with normal lungs undergoing ventilation at the same Vt and rate. This control value is obtained from a table provided by the authors. The value of this score was recorded on the day of highest PaW.

In order to estimate the effect of any respiratory acidosis on the Apache II predicted mortality in patients who had such respiratory acidosis in the first 24 h following admission, the pH was corrected towards, but not above, normal for the effect of the hypercapnia using the equation $\Delta LOG\ PaCO_2/\Delta pH = 1.451$ [15], and the predicted mortality was calculated again using this corrected pH. Organ failures were scored as described by Goris et al. [18].

Results

All patients (n = 70)

70 patients had ARDS, pneumonia or aspiration pneumonia recorded as a diagnosis during the study period and all met the inclusion criteria. The hospital mortality for these patients (13 of 70, or 18.6%) was significantly lower than the mean Apache II predicted mortality of 37.8% ($\chi^2 = 11.01$, $p<0.001$).

Severe ARDS (Lung injury score $\geqslant 2.5$, n = 50)

50 patients had a lung injury score $\geqslant 2.5$ (mean score 3.18, SD 0.5) and all of the subsequent data relate to these patients. The hospital mortality (8 of 50 or 16%) was significantly lower than the mean of 39.6% predicted by Apache II ($\chi^2 = 11.64$, $p<0.001$). The actual mortality was thus 40% of that predicted. The mean predicted mortality was 34.6% for survivors and 64.1% for non survivors. The mean Apache II points score was 20.8 (SD 8.2), 19.5 (SD 7.8) for survivors and 27.9 (SD 5.5) for non survivors. Using non cardiogenic pulmonary oedema as the diagnosis rather than the patient's primary diagnosis, the mean Apache II predicted mortality was 38.5%.

Sixteen patients had some degree of respiratory acidosis in the first 24 h of admission, although in most patients this was mild. When the pH was corrected to its estimated value with a $PaCO_2$ of 40 mmHg (but not to above the normal range), the "corrected" mean predicted mortality was 38.3%, which is still significantly greater than the actual mortality ($\chi^2 = 10.52$, $p<0.005$). Thus the lower than predicted mortality was not simply due to an artifactual increase in predicted mortality resulting from the respiratory acidosis.

The primary diagnoses and causes of death are shown in Tables 1 and 2. Only 1 death was due to progressive hypoxic respiratory failure, this being in a neutropenic girl with unresponsive pneumocystis pneumonia following chemotherapy for acute lymphocytic leukaemia. The majority of deaths were clearly due to sepsis or to the underlying illness, and occurred whilst adequate oxygenation was being maintained with only moderate levels of FiO_2 and PEEP, and in 3 patients after almost complete recovery of lung function.

Twenty patients (52%) had a pulmonary artery catheter inserted, the mean PCWP at insertion being 14 (SD 3.9) mmHg.

The mean organ failure score was 5.56 (5.07 in survivors and 8.12 in non-survivors) and the mean number of organ failures was 3.5 (3.26 in survivors and 4.88 in non-survivors). The number of patients with specified numbers of organ failures is shown in Table 3. Cardiovascular failure occurred in 36 patients, renal failure in 16, liver failure in 33, haematologic failure in 12, gastro-intestinal failure in 14 and CNS failure in 23. Using the criteria for

Table 1. Primary diagnoses for 50 patients with LIS $\geqslant 2.5$

Bacterial pneumonia	11
Aspiration secondary to head injury, C.V.A., drug O.D., epilepsy	9
Ruptured aortic aneurysm	7
Sepsis	8
Trauma	6
Aspiration secondary to surgery/anaesthesia	6
Acute pancreatitis	2
Massive G.I. haemorrhage	1
Total	50

Table 2. Causes of death for patients with LIS $\geqslant 2.5$

Sepsis, hypotension, renal failure	4
Bowel infarction	1
CVA	1
Acute pancreatitis, sepsis	1
Respiratory failure, pneumocystis carinii pneumonia	1
Total	8

Table 3. Numbers of the 50 patients with LIS ≥ 2.5 who had 2 or more organ failures as defined by Goris et al. [18]. The bottom 2 rows show numbers using the criteria for severe organ failure. The 2 rows above show numbers using the criteria for mild organ failure, which therefore include the severe organ failures

Number of organ failures	2	3	4	5	6	7
Mild or severe failure						
Number of patients	8	12	8	4	4	6
Number of deaths	1	1	1	2	1	2
Severe failure						
Number of patients	12	9	2	3	2	0
Number of deaths	2	2	1	1	1	0

severe organ failure, cardiovascular failure occurred in 17 patients, renal failure in 7, liver failure in 17, haematologic failure in 5, gastro-intestinal failure in 4 and CNS failure in 10.

The ventilator scores for the 24 patients in whom records of PIP were available are shown in Fig. 1, along with those of the 30 patients described in Smith and Gordon's paper for comparison. Whereas in Smith and Gordon's series a ventilator score > 80 was universally associated with death from respiratory failure, 10 patients in this study had scores > 80 with only 2 deaths, neither being from respiratory failure. There were no significant differences between the mean values for lowest PaO_2/FiO_2 ratio, maximum $PaCO_2$, lung injury score and mortality for patients who did and for those who did not

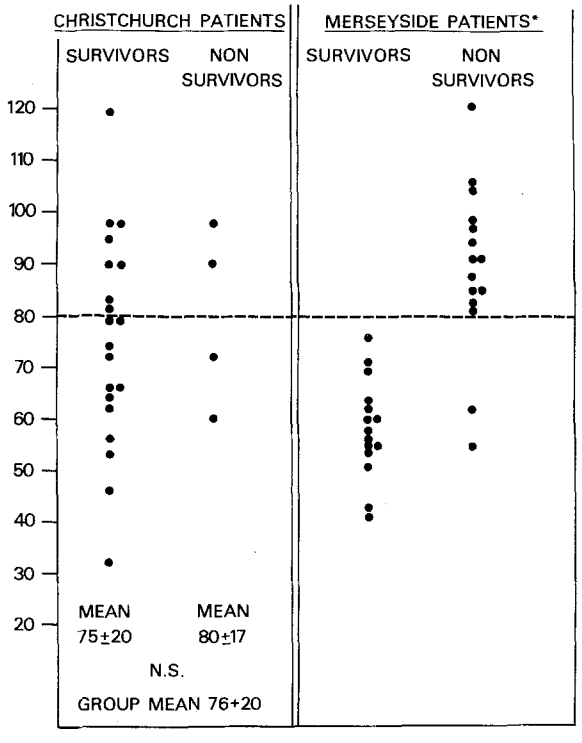

Fig. 1. Ventilator scores of survivors and non-survivors for patients in this study with LIS ≥ 2.5, and for the Merseyside patients of Smith and Gordon[a] [17]. The difference in mean ventilator score between survivors and non-survivors for the patients in this study is not significant. [a]Reproduced with kind permission of the authors and the publishers

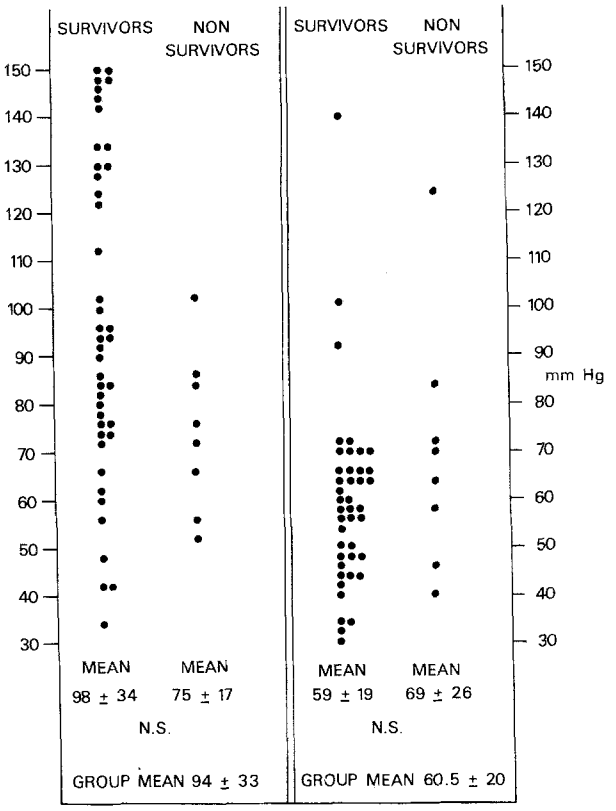

Fig. 2. Values of lowest PaO_2/FiO_2 ratio (*left*) and maximum $PaCO_2$ (*right*) for the 50 patients with LIS ≥ 2.5. The difference between the mean value for survivors and non-survivors is not significant for either variable

have a ventilator score calculated, suggesting that those with ventilator scores were representative of the whole group. The mortality was 4 of 24 (16.6%) for those with ventilator scores and 4 of 26 (15.4%) for those without.

Figures 2 and 3 show values for the lowest PaO_2/FiO_2 ratio, maximum $PaCO_2$, lung injury score, and maximum PIP for survivors and non-survivors, and the ventilator scores for survivors and non-survivors are shown in Fig. 1. There is no significant difference between survivors and non-survivors for any of these values, supporting our view that the majority of deaths were not due to respiratory failure. The non-surviving patient with a PIP of 55 cm H_2O had developed a rapidly rising PIP over several hours and died before the Vt was reduced.

The lowest Vt used was significantly lower in patients with a ventilator score > 80 than in those with a score < 80 (535 ± 74 ml vs 710 ± 88 ml, $p < 0.001$) demonstrating that it had indeed been reduced in the patients with more severe ARDS. The mean of the maximum level of PEEP used in each patient was 9 cm H_2O (SD 6.1), with a range of 0–25 cm H_2O. The mean value of the pH at the time of the maximum $PaCO_2$ in each patient was 7.29 (SD 0.11) with a mean base excess of +1 (SD 6.1) mmol/L. In the 24 patients who had a maximum $PaCO_2 > 60$ mm Hg, the mean pH at the time of the maximum $PaCO_2$ was 7.23 (SD 0.1) with a range of 7.02–7.38, and the mean base excess was +7.3 (SD 1.8) mmol/L with a range of −13 to +14. The mean values

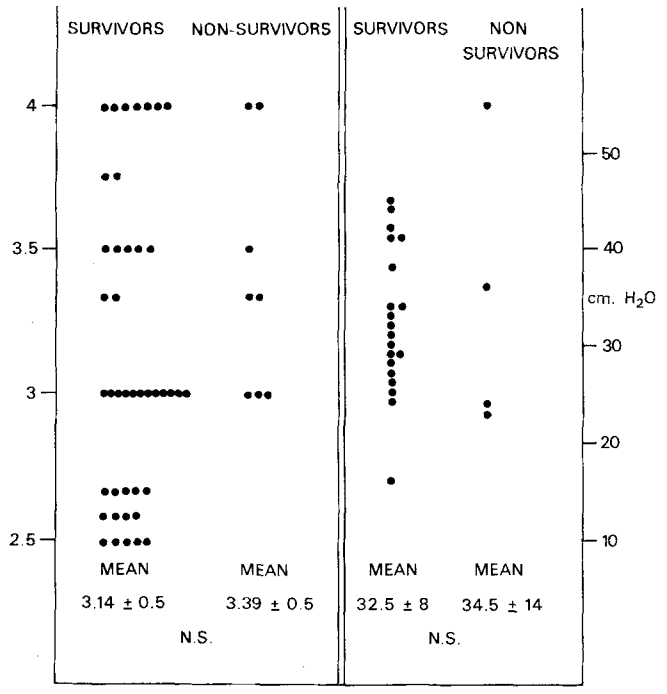

Fig. 3. Lung injury scores (LIS) (*left*) and peak inspiratory pressures (PIP) (*right*) for the 50 patients with LIS $\geqslant$ 2.5. The PIP shown for each patient is the highest value of the mean over each 24-h period. The difference between the mean value for survivors and non-survivors is not significant for either variable

for the ventilator rate and spontaneous respiratory rate at the time of the maximum $PaCO_2$ in each patient were 6.6 (SD 5.6) and 20 (SD 11) breaths per minute respectively. No sodium bicarbonate or other alkali therapy was used in any patient. The mean time from commencement of ventilation to the maximum $PaCO_2$ was 5.2 days (range $<1-22$ days). The mean duration of ventilation was 8.1 (SD 8.6) days for survivors and 9.0 (SD 9.6) days for non-survivors.

Discussion

It has now been demonstrated clearly in many animal studies that the use of high PIP can induce acute lung injury very similar to ARDS [1–11], and that this can result in progressive respiratory failure and death. Gattinoni's technique of extracorporeal CO_2 removal in patients with severe ARDS [12] was conceived primarily to allow lung "rest" by using a low ventilator rate with limitation of PIP, CO_2 being removed by the extracorporeal circuit. Gattinoni has recently suggested that it may be possible to reduce mortality by using a form of partial extracorporeal CO_2 removal at an earlier stage in the disease process, allowing a reduction in minute ventilation, and hopefully preventing progression of the lung injury associated with the ventilatory management. This would still be invasive and expensive however. It seemed to us that an alternative approach would be to simply limit the PIP by reducing Vt, and to allow the $PaCO_2$ to rise. The $PaCO_2$ would then stabilise at a new higher level and CO_2 elimination would be maintained at a lower level of alveolar ventilation, as occurs in patients with hypercapnia due to chronic obstructive airways disease (COAD). Patients with COAD appear to tolerate hypercapnia well, and in this situation hypercapnia has been viewed as an adaptive mechanism allowing the maintenance of CO_2 clearance with reduced respiratory work [19]. We suggest that it should be viewed in the same way in severe ARDS, allowing a reduction of PIP, and we have been aware of no serious complications attributable to hypercapnia when it has developed gradually. Many of the hypercapnic patients spontaneously developed a metabolic compensation with a large base excess, and did not become markedly acidotic. No specific treatment was used to raise the pH in patients with respiratory acidosis even with a pH as low as 7.02 however.

The use of SIMV with a low ventilator rate in these severely ill patients could raise the theoretical concern that the increased oxygen consumption of the respiratory muscles may reduce oxygen availability to other organs. A respiratory acidosis may facilitate tissue oxygen uptake because of its effect on the haemoglobin dissociation curve, partially offsetting this effect. In any event most patients appeared to tolerate the technique well and it is possible that limitation of PIP from the commencement of ventilation may prevent the respiratory failure from progressing to such a severe stage.

The 16% mortality in this group of patients with severe ARDS as defined by a lung injury score $\geqslant$ 2.5 is low compared to that in other published studies [20–22]. It has been widely recognised however that most patients with ARDS in published studies have tended to be very ill patients with multiple organ failure, having been selected by the requirement to have a pulmonary artery catheter in place in order to meet the inclusion criteria [20, 21], and indeed it was for this very reason that Murray devised the lung injury score. 34 patients in this study had 3 or more organ failures (16 patients using the criteria for severe organ failure – see Table 3), but it is possible that hypercapnia may have resulted in a greater number of patients meeting the criteria for CNS failure. Thus some patients in this study are probably not comparable to those in other studies with mortality rates approximating 60%.

In spite of this, however, the substantially lower mortality than that predicted by Apache II, the survival of 9 patients with 5 or more organ failures, and the survival of 8 of the 10 patients with ventilator scores >80 suggest that the outcome of these patients is better than expected. In Smith and Gordon's series (Fig. 1) the 13 patients with ventilator scores >80 all died from respiratory failure, whereas of the 17 patients with scores <80 only 2 died, neither from respiratory failure. In contrast in this study only 2 of the 10 patients with ventilator scores >80 died, neither from respiratory failure. Had the PIP not been limited in our patients their ventilator scores would presumably have been even higher. Although the numbers in Smith and Gordon's study were small, these authors have continued to collect data and have still found that a ventilator score >80 universally predicts death from respiratory failure (personal communication).

It is conceivable that the 24 patients on whom we had records of PIP and thus were able to calculate ventilator scores were in some way a biased group. However, as far as we could determine, whether or not the ventilator charts containing this information had been filed in the patient's case notes had been random depending on Medical Records Staff. In addition there were no significant differences in any of the recorded parameters between patients who did and those who did not have scores calculated, and the mortality was virtually identical in each group. Therefore we believe these patients were representative of the whole group.

Our assessment that deaths were due to the underlying illness or sepsis rather than respiratory failure, other than in the patient who died from pneumocystis pneumonia, is supported by the lack of significant differences in lung injury score, ventilator score, worst PaO_2/FiO_2, maximum $PaCO_2$, and maximum PIP between survivors and non survivors. In other studies of patients with ARDS a variable proportion of the deaths have been due to respiratory failure, most recent studies suggesting that only a minority of deaths result from this cause [20, 22]. Respiratory failure has been a more common cause of death in other studies however, and it was clearly the major cause of death in Smith and Gordon's series. These authors state in their discussion that "twenty years experience of this unit taught us that three physiological observations indicated irreversible lung damage in ARDS. These were a sustained high PaW, hypoxemia despite high inspired oxygen, and hypercapnia despite a large minute volume ventilation". We suggest that it is very important to question whether this statement is true simply because these observations indicate very severe ARDS with an unavoidably high mortality, or because the sustained high PIP, minute volume and Vt result in progressive ventilator induced lung injury and themselves determine the fatal outcome from progressive respiratory failure. We believe that our results, along with much associated evidence, suggest that the latter may well be the case, and that an alteration in the ventilatory management along the lines we have suggested may avoid the fatal outcome in such patients.

It may appear unlikely that the ventilatory management could affect mortality other than that due to respiratory failure in patients with ARDS. However Montgomery et al. [20] showed that the development of ARDS clearly appeared to predispose to the development of sepsis, the incidence of sepsis in patients with ARDS being 6 times that in patients with a similar initial severity of illness who did not develop ARDS, and in most cases the sepsis occurred following the development of ARDS. Thus if the ventilatory management results in a worsening of the lung injury, it is conceivable that this may increase the probability of the subsequent development of sepsis and mortality. The demonstration in a number of studies of supply dependency of oxygen consumption in ARDS [23–25] also suggests that ARDS is a multi-system illness not restricted to the lungs, and thus worsening of the ARDS related to the ventilatory management may affect other organs.

We have previously reported an additional 38 patients with severe aspiration pneumonia who were managed in a similar manner, and who also had a mortality less than half of that predicted by Apache II (21% vs 43%, $p<0.01$), although we did not detail the ventilatory management in that paper [26]. In that study also only 1 death was directly related to respiratory failure. Even if the mortality in our patients is lower than may have been the case with different management, we can not be certain that it is the ventilatory management that has been responsible for this, and indeed several aspects of management may have contributed. We believe that our generous fluid replacement, rather than severe fluid restriction and diuretic therapy as has been advocated by others [27, 28] may also have contributed to the favourable outcome in these patients. We have discussed previously our reasons for using this approach to fluid therapy [26].

In summary we believe that the results of this study suggest that the mortality in these patients was substantially lower than would be expected from 3 independent prognostic scoring systems. If this is the case, it is not possible to know which aspects of management were responsible, but we believe that the ventilatory management may have been an important factor. Other authors have also published good results using limitation of PIP in patients with ARDS [29, 30], although the aim appears always to have been to maintain $PaCO_2$ within the normal range. We believe that in view of our results and those of these other studies, in addition to the compelling evidence from animal studies, the hypothesis that pressure limitation in the ventilatory management of ARDS prevents or reduces ventilator induced lung injury and improves outcome must be considered seriously, and perhaps should be tested in a multi-centre randomised trial.

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