The β-Agonist Lung Injury Trial (BALTI)
A Randomized Placebo-controlled Clinical Trial

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Rationale: **Experimental data suggest that manipulation of alveolar fluid clearance with β-agonists can accelerate the resolution of alveolar edema and improve survival.**
Objective: **To determine if a sustained infusion of intravenous salbutamol (albuterol) would accelerate the resolution of alveolar edema in adult patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS).**
Methods: **This was a single-center, double-blind, randomized controlled trial. Patients with ALI/ARDS were randomized to treatment with intravenous salbutamol (15 μg kg^{-1} h^{-1}) or placebo for 7 d. The primary endpoint was extravascular lung water measured by thermodilution (PiCCO) at Day 7.**
Measurements and Main Results: **Sixty-six patients were screened; of these, 40 met the inclusion criteria and were enrolled during 2001–2003. Patients in the salbutamol group had significantly lower lung water at Day 7 than the placebo group (9.2 ± 6 vs. 13.2 ± 3 ml kg^{-1}; 95% confidence interval difference, 0.2–8.3 ml kg^{-1}; $p = 0.038$). Plateau airway pressure was lower at Day 7 in the salbutamol group (23.9 ± 3.8 cm H_2O) versus placebo (29.5 ± 7.2 cm H_2O; $p = 0.049$). There was a trend toward lower Murray lung injury score at Day 7 in the salbutamol group (1.7 ± 0.9) versus placebo (2.0 ± 0.6; $p = 0.2$). Patients in the salbutamol group had a higher incidence of supraventricular arrhythmias (26 vs. 10%; $p = 0.2$).**
Conclusion: **Although further research is required to confirm the efficacy and safety of intravenous salbutamol in ALI/ARDS, this trial provides the first proof of principle that, in humans with ALI/ARDS, sustained treatment with intravenous β-agonists reduces extravascular lung water.**

Keywords: adrenergic β-agonists; adult respiratory distress syndrome; albuterol; extravascular lung water; pulmonary edema

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) remain major causes of respiratory failure in critically ill patients (1). Pathophysiologically, ARDS is characterized by inflammatory damage to the alveolar–capillary barrier, leading to the outpouring of proteinaceous fluid into the alveolar space. This leads to the development of noncardiogenic pulmonary edema, which impairs gas exchange, causing refractory hypoxemia and in most cases the need for mechanical ventilation (2).

The resolution of edema from the alveolar space is critical to the recovery from ALI/ARDS. Early resolution is associated with more rapid improvement of lung injury, reduced duration of ventilation, and improved survival (3, 4). The clearance of edema fluid is dependent on the balance between edema formation and reabsorption processes. Edema formation is governed by Starling forces and the integrity of the alveolar–capillary barrier, whereas fluid reabsorption is dependent on the active transport of sodium and electrolytes, which drives water reabsorption (5).

The potential to manipulate endogenous alveolar fluid clearance mechanisms in patients with ALI or ARDS has been the focus of much interest recently (6–8). Experimental studies in *ex vivo* human lung have demonstrated that β-agonists can accelerate the rate of alveolar fluid clearance (9, 10). The mechanism underlying increased alveolar fluid clearance is proposed to be due to an increase in intracellular cyclic adenosine monophosphate (cAMP), resulting in increased sodium transport across alveolar type II cells through up-regulation of the apical sodium and chloride pathways and Na^+/K^+ ATPase. β-Agonists may also reduce alveolar–capillary permeability, thereby reducing edema formation (11). Hyperoxia-induced lung injury in β_2 knockout mice results in increased lung water and worse survival than that in wild-type control animals. This is reversed by adenoviral-mediated transfer of cDNA for the β_2-receptor, confirming a central role for β_2-receptor signaling in the resolution of pulmonary edema and recovery from ALI/ARDS (12). A randomized placebo-controlled clinical trial using inhaled salmeterol, a long-acting β_2-agonist, in volunteers who were known to be at risk of high-altitude pulmonary edema (HAPE) reduced the incidence of HAPE (13). On the basis of these experimental data, augmentation of alveolar epithelial fluid clearance with β_2-agonists seems possible, which could potentially accelerate resolution of pulmonary edema and improve outcome in ALI/ARDS.

The aim of this study was to investigate the safety, tolerability, and efficacy of a sustained infusion of the intravenous β_2-agonist salbutamol (albuterol) to accelerate the resolution of pulmonary edema in adult patients with ALI or ARDS. Some of the results of these studies have been previously reported in the form of an abstracts (14, 15).

METHODS

Participants and Setting

Mechanically ventilated adults at Heartlands Hospital, Birmingham, United Kingdom, within 48 h of the onset ALI or ARDS were eligible for inclusion. The study took place between January 2001 and December 2003. ALI and ARDS were defined according to the consensus conference definition (16). The exclusion criteria were as follows: age younger than 18 yr, participation in other intervention trials, severe obstructive airway disease requiring nebulized or intravenous β_2-agonist, treatment with β-blockers within 48 h, neutrophil count of less than 0.3×10^9 L, brainstem death, treatment withdrawal within 24 h, immunosuppression (steroids > 20 mg/d, chemotherapy or other immunosuppressive agents within 2 wk), lobectomy/pneumonectomy, burns over more than 40% of body surface area, or assent declined from the next of kin.

The study was approved by the East Birmingham Local Research Ethics Committee.

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Study Design

This was a single-center, randomized, double-blind, placebo-controlled clinical trial. Block randomization to salbutamol or placebo (1:1) was performed in blocks of four by one of the authors (F.G.). During the study, the size of blocks was unknown to the other investigators. Allocations to treatment or placebo were concealed in opaque, sequentially numbered, sealed envelopes. Enrollment and data collection were performed by another author (G.D.P.). Drug preparation (intravenous salbutamol, 0.2 mg ml^{-1}, or 0.9% saline) was performed by nurses not involved in the study. Infusions were started within 2 h of randomization and run at 0.075 ml kg^{-1} h^{-1} (15 μg kg^{-1} h^{-1}) for 7 d. Our clinical experience and a small pilot study demonstrated this was the highest tolerable dose without significant arrhythmias. A safety protocol (*see* online supplement) allowed dose adjustment if significant tachycardia or arrhythmias were encountered.

Data Collection and Measurements

The gas exchange, organ failure, cause, and associated conditions (GOCA) stratification system was used to record the etiology and severity of lung injury (17). Intensive care unit mortality was predicted by the Acute Physiology and Chronic Health Evaluation II (APACHE II) and Simplified Acute Physiology Score II (SAPS II). These scores were recorded as global markers of disease severity (18). The Murray lung injury score (a composite variable that includes components of oxygenation, compliance, positive end-expiratory pressure, and the appearance of the chest radiograph) (19), Pa_{O_2}:FI_{O_2} ratio, and sequential organ failure assessment (SOFA) (20) scores were recorded daily for the first 7 d. Organ failure was defined by an SOFA score of 3 or more. Daily measurement of hemodynamic variables, ventilation parameters, and extravascular lung water (EVLW) was undertaken between 8:00 and 10:00 A.M. The number of ventilator-free days (number of days free from ventilatory support [for > 48 h] in the first 28 d) (21) and survival status at Day 28 were recorded.

EVLW was measured using the single-indicator transpulmonary thermodilution system (PiCCO; Pulsion Medical Systems, Munich, Germany). A 20-ml bolus of 0.9% saline at 4°C was injected via a central venous catheter into the right atrium. The thermodilution curve was recorded in the aorta and allowed calculation of intrathoracic blood volume index and EVLW index. The average result from three 20-ml bolus injections was used for each measurement. In our study, the coefficient of variation for this system was less than 7% for all parameters.

Outcomes

The primary outcome measure was a reduction in EVLW in the salbutamol group at Day 7. Secondary outcomes were lung injury score, Pa_{O_2}:FI_{O_2} ratio and plateau pressure at Day 7, and ventilator-free days and survival at Day 28. Safety and tolerability were monitored by recording ECG, hemodynamic, electrolyte, and acid-base balance.

Statistical Analysis

On the basis of previous data (22), the study was powered to detect a 30% difference in EVLW between patient treatment and control groups with 80% power at a significance level of 0.05.

Data were analyzed on an intention-to-treat basis using SPSS for Windows 10.0 (SPSS, Inc., Chicago, IL). Data were tested for normality and analyzed by unpaired *t* tests or Mann-Whitney U test. Data are expressed as mean (SD) unless otherwise indicated. A χ^2 or Fisher's exact test was used to compare proportions. A p value of 0.05 was considered significant.

RESULTS

Sixty-six patients were identified during the screening process. Forty of these patients fulfilled the criteria for inclusion in the study; 26 patients were excluded. Twenty-five of these patients were excluded because they met one or more of the exclusion criteria; in one case, Assent was withheld by the patient's next of kin. Therefore, 40 patients were finally enrolled and treated. Nineteen patients were randomized to treatment with intravenous salbutamol and 21 patients were randomized to placebo. Two patients died after enrollment but before the initiation of treatment (one in each group). Patients were analyzed on an intention-to-treat basis. The patient flow is summarized in Figure 1.

Patient Baseline Demographics

The baseline severity data and etiology of lung injury are summarized in Tables 1 and 2. Patients in the two groups were well matched in terms of the severity of lung injury (Pa_{O_2}:FI_{O_2} ratio and lung injury score) and the global severity of illness (APACHE II and SAPS II scores). Patients in the salbutamol-treated group were significantly older than those in the placebo group (mean age, 68.7 ± 16 vs. 57 ± 14.7 yr; p = 0.021; 95% confidence interval difference [CI diff], 1.8–21.5). There were no statistically significant differences in the etiology of lung injury. However, 52% of the patients randomized to placebo had direct lung injury compared with 16% in the salbutamol group. Lung injury related to infection (pneumonia and sepsis) is associated with impaired alveolar fluid clearance (3). The numbers of patients with lung injury secondary to infection were similar (salbutamol group = 16, placebo group = 17; Fisher's exact test, p = 0.6).

Primary Outcome

Patients in the salbutamol-treated group had significantly lower lung water at Day 7 than the those in the placebo group (9.2 ± 6 vs. 13.2 ± 3 ml kg^{-1}; 95% CI diff, 0.2–8.3 ml kg^{-1}; p = 0.04; Figure 2). Separation of the groups is seen from Day 2 through to Day 7 (Figure 3). To allow for possible imbalances between groups at baseline, an analysis of Day 7 EVLW stratified by baseline levels was also performed. A treatment effect of 3.9 ± 8.2 ml kg^{-1} (95% CI, 0.01–7.8; p = 0.05) was present. To take into account data from patients that died during the study, we performed a secondary *post hoc* analysis, carrying the last recorded value of EVLW forward to Day 7. EVLW was still lower in the treatment group compared with placebo (10.5 ± 3.4 vs. 14.4 ± 6.8; 95% CI diff, 0.5–7.33; p = 0.027). There were no significant differences in cardiac index or pulmonary blood volume (Table 3), suggesting that salbutamol had a specific effect on lung water rather than a nonspecific effect on pulmonary blood flow or cardiac output. Medications with the potential to manipulate alveolar edema were similar between the two groups. Inotrope requirements (adrenaline and noradrenaline) were well balanced throughout the study (Table 3). No patients received dobutamine or dopexamine or other inotropic drugs. There was no difference in the use of diuretics or glucocorticoids between groups (data not shown). No patient received inhaled or nebulized β-agonists.

Secondary Outcomes

There was a trend toward lower lung injury at Day 7 in the salbutamol group (1.7 ± 0.9) versus the placebo group (2.0 ± 0.6; p = 0.2). The treatment effect was unchanged after adjustment for baseline differences in lung injury score. Plateau airway pressures were significantly reduced in the salbutamol group at Day 7 (23.9 ± 3.8 vs. 29.5 ± 7.2 cm H_2O; 95% CI diff, 0.2–11.2; p = 0.049; Table 3). There was no difference in the Pa_{O_2}:FI_{O_2} ratio at Day 7 (salbutamol, 171 ± 68, vs. placebo, 161 ± 68 mm Hg; p = 0.738), the organ-failure SOFA score (salbutamol median [IQR], 10 [6–13], vs. placebo median [IQR], 11 [5–14]; p = 0.4), the number of ventilator-free days (salbutamol, 6.2 ± 8.9, vs. placebo, 5.3 ± 8.6 d; p = 0.6). There was no difference in 28-d mortality in the salbutamol-treated group (58%) compared with placebo (66%; p = 0.4).

Safety and Tolerability

Treatment was generally well tolerated. There was a trend toward higher heart rates in the salbutamol group at Day 4 (103 ± 22)

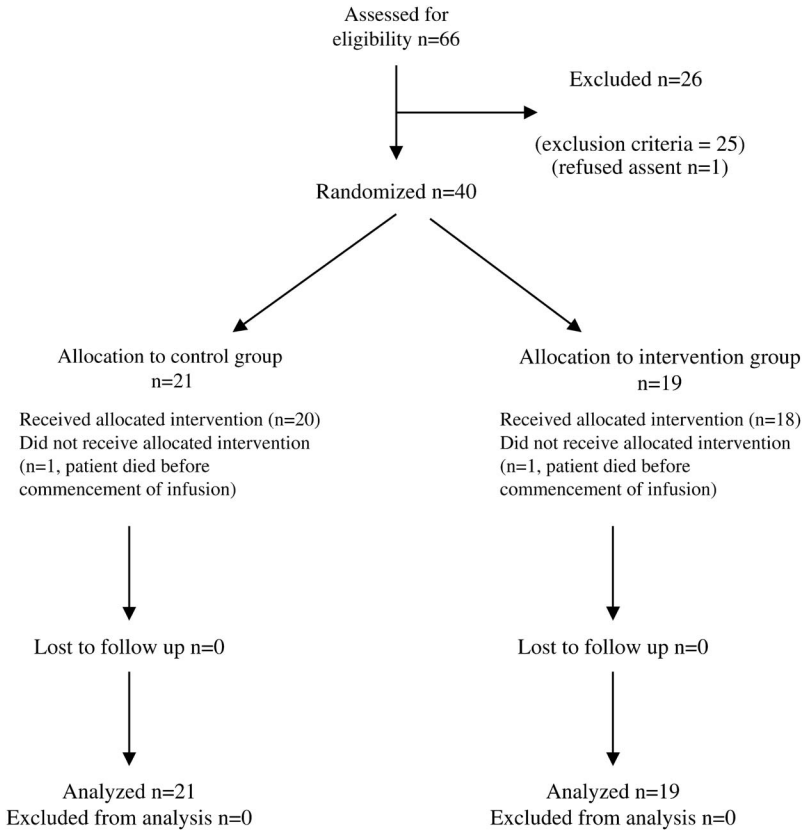

Figure 1. Consort flow diagram showing participant progress.

versus placebo (88 ± 16, p = 0.06) and Day 7 salbutamol (94 ± 14) versus placebo (86 ± 22; p = 0.3; Table 3). Nineteen patients received intravenous salbutamol for a total of 2,148 h. During these infusions, five patients developed new onset of supraventricular tachycardia, which required adjustment of the dose of salbutamol according to the safety protocol. These arrhythmias did not cause significant hemodynamic compromise and were short lived. In comparison, two patients in the placebo group had similar problems (p = 0.2). No patients sustained serious ventricular arrhythmias.

There were no substantial differences in electrolyte concentrations between salbutamol and placebo for potassium at Day 4 (4.1 ± 0.3 vs. 4.6 ± 0.7 mmol L^{-1}, p = 0.03) or Day 7 (4.3 ± 0.6 vs. 4.8 ± 0.9 mmol L^{-1}, p = 0.1), or magnesium at Day 4 (0.98 ± 0.2 vs. 1.0 ± 0.3 mmol L^{-1}, p = 0.9) or Day 7 (0.98 ± 0.2 vs. 0.92 ± 0.1 mmol L^{-1}, p = 0.6; Table 3). Glycemic control was similar between groups: Day 4 (salbutamol, 10.1 ± 5, vs. placebo, 8.3 ± 2 mmol L^{-1}; p = 0.5); Day 7 (7.0 ± 2 vs. 8.5 ± 2 mmol L^{-1}, p = 0.4). There was no difference in acid-base balance: Day 4 (salbutamol H^+, 41 ± 8, vs. placebo, 44 ± 9 nmol L^{-1}; p = 0.4), Day 7 (37 ± 9 vs. 38 ± 6 nmol L^{-1}, p = 0.789); or lactate: Day 4 (2.0 ± 1 vs. 2.1 ± 1 mmol L^{-1}, p = 0.4); Day 7 (1.7 ± 0.6 vs. 1.9 ± 1 mmol L^{-1}, p = 0.9).

DISCUSSION

Despite focused attention on treatments for ALI/ARDS over the last three decades, to date only a small number of pharmacologic therapies have been shown to be efficacious (23). This randomized, double-blind, placebo-controlled trial provides the first proof of principle that in humans with ALI/ARDS, sustained treatment with an intravenous β_2-agonist can reduce EVLW. This was associated with a significant reduction in plateau airway pressures and a trend toward improved lung injury.

Alveolar flooding leading to noncardiogenic pulmonary edema is a common feature of ALI/ARDS, despite a wide variety

TABLE 1. BASELINE PATIENT DEMOGRAPHICS

Parameter	Salbutamol	Placebo	p Value	95% CI
Age, yr	68.7 (16.0)	57.0 (14.7)	0.021	1.8–21.5
Pa_{O_2}:$F_{I_{O_2}}$ ratio, kPa	15.6 (6.6)	13.7 (4.9)	0.326	
LIS	2.8 (0.7)	3.0 (0.4)	0.447	
APACHE II	24.9 (6.4)	22.5 (6.5)	0.243	
APACHE predicted mortality	51.8 (19.1)	44.6 (20.4)	0.257	
SAPS II	55.6 (15.1)	49.3 (14.7)	0.198	
SAPS predicted mortality	56.7 (27.3)	49.3 (14.7)	0.204	

Definition of abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation II; CI = confidence interval; LIS = Murray lung injury score; SAPS II = Simplified Acute Physiology Score II.

Data are presented as mean and SD.

TABLE 2. ETIOLOGY AND SEVERITY OF LUNG INJURY

Parameter	Salbutamol n (%)	Placebo n (%)	p Value
Gas exchange			
Pa_{O_2}/FI_{O_2}, kPa			
26.8–40	1 (5.3)	0 (0)	
13.46–26.8	10 (52.6)	10 (47.6)	0.501
< 13.46	8 (42.1)	11 (52.4)	
PEEP, cm H_2O			
0–5	7 (36.8)	4 (19)	
6–10	7 (36.8)	10 (47.6)	0.453
> 10	5 (26.3)	7 (33.3)	
Organ failure			
Lung + 1 organ	13 (68.4)	16 (76.2)	
Lung + 2 organs	6 (31.6)	5 (23.8)	0.442
Cause			
Direct			
Pneumonia	3 (15.8)	9 (43)	
Aspiration	0 (0)	2 (9.5)	
Indirect			
Sepsis	13 (68.4)	8 (38)	
Trauma	1 (5.3)	0 (0)	0.105
Transfusions	1 (5.3)	2 (9.5)	
Other	1 (5.3)	0 (0)	
Associated diseases			
No coexisting diseases	13 (68.4)	16 (76.2)	
Coexisting disease that will cause death within 5 yr	6 (31.6)	5 (23.8)	
Coexisting disease that will cause death within 6 mo	0 (0)	0 (0)	

Definition of abbreviation: PEEP = positive end-expiratory pressure.

of different etiologies of lung injury (24). The reabsorption of edema fluid from the alveolar space is critical in the resolution of ALI/ARDS. Clinical studies in humans have shown that alveolar fluid clearance mechanisms are impaired in most patients with ALI/ARDS (3, 25) in contrast to patients with cardiogenic pulmonary edema, where 75% have intact alveolar fluid clearance (26). In a small study (n = 15), we previously reported that patients who cleared EVLW early in the course of ALI/ARDS had more rapid resolution of lung injury, a shorter duration of ventilation, and improved survival (4). In a series of 79 patients with ALI/ARDS, Ware and Matthay (3) found patients with maximal alveolar fluid clearance (n = 10) had significantly better hospital survival than patients with submaximal or impaired fluid clearance. These data support the hypothesis that therapies

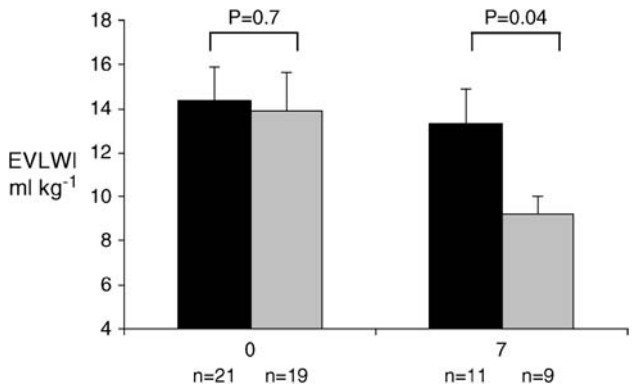

Figure 2. Extravascular lung water (EVLW) at Day 7 is significantly reduced in patients treated with intravenous salbutamol. *Black bars,* placebo; *gray bars,* salbutamol. EVLWI = EVLW index. Data shown are mean and SE.

targeted at accelerating alveolar fluid clearance may be of clinical benefit to patients with ALI/ARDS.

The principal finding of this study was that patients treated with intravenous salbutamol had significantly lower EVLW than those in the placebo group at Day 7. The primary mechanism through which β-agonists are believed to enhance alveolar fluid clearance is through the up-regulation of sodium transport mechanisms located on the alveolar epithelial cells (5). However, there are alternative or parallel mechanisms through which β-agonists could also enhance fluid clearance. β-Agonists are pulmonary vasodilators and could have acted to reduce pulmonary pressures, thereby reducing one of the driving forces for edema formation (27, 28). However, there were no changes in pulmonary blood volume measured by thermodilution between groups, a finding that makes large changes in pulmonary hemodynamics less likely. We did not, however, measure pulmonary artery occlusion pressures, so we cannot rule out that the drug may have acted at a microvascular level to reduce pulmonary capillary pressures. *In vitro* (29, 30) and *in vivo* animal studies in sheep (31) and rats (32, 33) have shown that β-agonists can reduce endothelial permeability. These experimental findings are supported by a small nonrandomized study in humans where administration of intravenous terbutaline to 10 patients with ARDS was associated with a significant reduction in lung vascular permeability (measured by radiolabeled transferrin) and improved survival (11). The mechanism appears to be related to inhibition of endothelial cell contraction and increased force between endothelial cell tight junctions. Other effects of salbutamol that could have indirectly reduced EVLW include modulation of neutrophil activation, surfactant processing, and the inflammatory cascade (34).

In our patients, separation of the EVLW curves are not seen until 48 h after the initiation of treatment. This was unexpected because in animal and *ex vivo* human lungs, salbutamol increases alveolar fluid clearance rates within a few hours of starting treatment (33, 35). One possible explanation is that the alveolar microenvironment, early in the course of ALI/ARDS, may reduce the ability of salbutamol to up-regulate alveolar fluid clearance. Elevated reactive oxygen and nitrogen species within the lung in the early stages of lung injury (36) can down-regulate alveolar epithelial sodium transport by type II alveolar cells, probably by damaging the apical epithelial sodium channels (37–39). This observation is supported by clinical data that found a correlation between alveolar fluid clearance rates and nitrate and nitrite levels in edema fluid (40). Profound cellular hypoxia is a potent inhibitor of alveolar fluid clearance in rats, although the inhibitory effect of hypoxia could be reversed with supraphysiologic doses of β-agonists (41). Acidosis, attributed to tissue hypoperfusion, is also associated with reduced alveolar fluid clearance in humans (26). Apart from the alveolar milieu adversely affecting fluid clearance, the extensive damage to the alveolar epithelium barrier seen in postmortem studies of patients with ARDS (42) suggests ongoing alveolar flooding could overcome any beneficial effect on fluid clearance (43, 44). The delay in response observed could reflect the time taken for regeneration and repair of the damaged alveolar–capillary barrier.

Despite significant reductions in the amount of lung water in the salbutamol-treated group, we found no improvement in oxygenation as measured by the Pa_{O_2}:FI_{O_2} ratio. The Acute Respiratory Distress Syndrome Network (ARDSNet) study, investigating low tidal volume ventilation, demonstrated a worsening in oxygenation despite a significant improvement in survival in the low tidal volume treatment arm (45). One possibility is that because of the intrinsic high degree of variability of oxygenation measures such as the Pa_{O_2}:FI_{O_2} ratio, the study was underpowered to detect a difference between groups. Alternatively, measurements

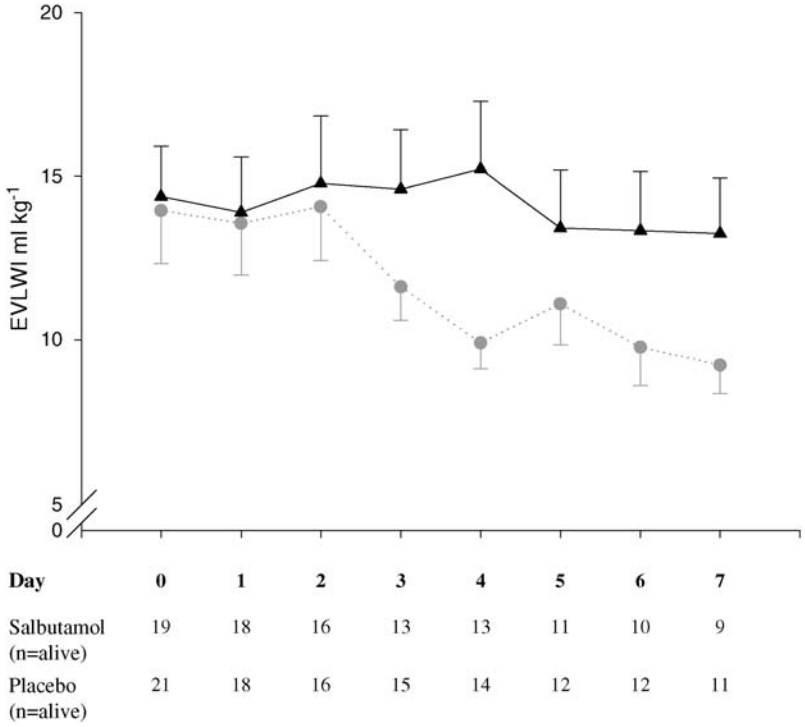

Figure 3. Serial EVLW measurements in salbutamol- and placebo-treated groups. *Circles* (*dashed line*) represent salbutamol group and *triangles* (*solid line*) represent placebo group. Data shown are mean and SE.

of oxygenation may be poor markers of resolution of lung injury. It is possible that salbutamol, as a pulmonary vasodilator, inhibited hypoxic pulmonary vasoconstriction, thereby increasing shunt and overcoming a beneficial effect on oxygenation from the reduction in alveolar edema. The finding that plateau airway pressures were lower in the salbutamol treatment group is consistent with the reduction in EVLW through an improvement in pulmonary compliance.

This study has certain limitations. The mortality rate (60%) is substantially higher than those reported in recent randomized controlled trials (ARDSNet tidal volume study: treatment group mortality, 31% [45]; surfactant study mortality, 34% [46]). However, the severity of illness measures (APACHE II, SAPS II, and SOFA) suggests that patients recruited to the present study were sicker than those recruited to similar trials reported in the literature. The actual mortality in the present study is concordant with the mortalities predicted by APACHE II and SAPS II, reflecting the severity of illness of our patients. This mortality rate is consistent with the recent European multicenter epidemiology and outcome study in ARDS, where mortality rates were 55%. The high mortality rate in the present study significantly reduced the quantity of patient data that could be evaluated at

TABLE 3. HEMODYNAMIC VARIABLES, VENTILATOR PARAMETERS, AND OTHER CLINICAL PARAMETERS FOR SALBUTAMOL AND PLACEBO GROUPS AT DAYS 0, 1, 4, AND 7

	Day 0		Day 1		Day 4		Day 7	
	Placebo (*n = 21*)	Treatment (*n = 19*)	Placebo (*n = 18*)	Treatment (*n = 18*)	Placebo (*n = 13*)	Treatment (*n = 11*)	Placebo (*n = 11*)	Treatment (*n = 9*)
HR, min^{-1}	105 (17)	102 (20)	98 (17)	109 (27)	88 (16)	103 (22)	86 (22)	94 (14)
SBP, mm Hg	131 (27)	125 (15)	127 (11)	134 (16)	133 (18)	131 (15)	136 (27)	136 (17)
CI, L min^{-1} m^{-2}	4.5 (1.2)	4.0 (1.3)	4.3 (1.4)	4.4 (1.1)	4.6 (0.7)	4.6 (1.2)	4.7 (1)	5.2 (0.9)
PBV ml	337 (110)	370 (122)	322 (98)	263 (95)	347 (94)	359 (97)	326 (74)	387 (79)
Adrenaline, mg 24 in h	0 (0–109)	20 (0–117)	0 (0–109)	0 (0–275)	0 (0–186)	0 (0)	0 (0)	0 (0)
Noradrenaline, mg in 24 h	59 (6–451)	232 (38–636)	246 (135–649)	259 (32–546)	105 (20–282)	105 (0–413)	0 (0–113)	0 (0–89)
Daily fluid balance, L	2.1 (1.5)	1.7 (1.8)	1.7 (1.8)	2.8 (1.7)	2.1 (9)	0.2 (1.4)	−0.3 (1.2)	−0.3 (1.4)
Pl airw, cm H_2O	30 (7)	29 (7)	32 (8)	29 (8)*	30 (6)	24 (5)*	29 (4)	24 (7)*
Pa_{O_2}: FI_{O_2} ratio, mm Hg	104 (38)	118 (46)	127 (46)	147 (53)	150 (46)	172 (53)	161 (68)	171 (68)
kPa	13.7 (5)	15.5 (6)	16.1 (6)	19.4 (7)	19.9 (6)	22.6 (7)	21.2 (9)	22.5 (9)
LIS	2.9 (0.4)	2.8 (0.8)	3 (0.6)	2.6 (1)	2.5 (0.5)	2.2 (0.7)	2.0 (0.8)	1.7 (0.9)
SOFA	14 (11–17)	15 (12–17)	14 (12–17)	15 (13–16)	12 (9–17)	14 (12–17)	11 (5–14)	10 (6–13)

Definition of abbreviations: CI = cardiac index; HR = heart rate; LIS = Murray lung injury score; PBV = pulmonary blood volume; Pl airw = plateau airway pressure; SBP = systolic blood pressure; SOFA = sequential organ failure assessment.

Data are mean (SD) with the exception of adrenaline, noradrenaline, and SOFA, which are median (interquartile range).

* $p < 0.05$.

the primary endpoint of Day 7. In retrospect, a larger patient cohort should have been recruited to account for the number of drop-outs before the study primary outcome measure. This limitation was partially addressed by the *post hoc* analysis, where the last recorded value of lung water was imputed forward to Day 7. Despite this, we cannot rule out that we may not have seen a significant effect on EVLW if all the patients had survived until Day 7.

Although our finding of a reduction in EVLW is promising, the study was not powered to detect a difference in mortality. Observational data suggest that improvements in lung water are associated with improved clinical outcomes (3, 4); however, this needs to be confirmed in an appropriately powered randomized controlled trial. The PiCCO thermodilution system is a useful noninvasive tool for the assessment of EVLW. In animal models of direct and indirect lung injury, it shows close agreement to gravimetric measurements of lung water (47). However, its use in patients with ARDS has certain limitations. The technique is based on a number of theoretical assumptions and approximations. To our knowledge, no patients in the present study had intracardiac shunts, valvular heart disease, or large abdominal aortic aneurysms, which could lead to an underestimation of the volume of lung water. Another important consideration is that the volume of EVLW is dependent on pulmonary perfusion—the greater the area of lung perfused, the greater the amount of EVLW (48). We consider it unlikely that differences in pulmonary perfusion influenced our results because cardiac output and pulmonary blood volume were similar between groups. Furthermore, if salbutamol (as a pulmonary vasodilator) had influenced pulmonary perfusion, it would have increased, rather than reduced EVLW.

In the closely monitored environment of a critical care unit, with strict adherence to the safety protocol, treatment with salbutamol (15 $\mu g\ kg^{-1}\ h^{-1}$) was tolerated without serious complications. However, the high incidence of arrythmias (26%) in the salbutamol group, albeit in this study without significant hemodynamic compromise, is a concern. Nebulized salbutamol or long-acting β_2-agonists are efficacious in animal models of ARDS (33) and have less systemic side effects than intravenous formulations (49). Since commencing this study, Atabai and coworkers (50) have reported that nebulized albuterol can achieve clinically relevant concentrations of the drug in the edema fluid of patients with ARDS, and Sartori and colleagues (13) demonstrated the efficacy of the inhaled route for the prevention of HAPE in healthy volunteers. These promising findings support the need to explore the efficacy of this route of administration for enhancing alveolar fluid clearance in ARDS.

In conclusion, this double-blind, randomized, placebo-controlled trial provides the first proof of principle that, in humans with ARDS, sustained treatment with an intravenous β-agonist reduces EVLW. This was associated with a reduction in plateau airway pressure and a trend toward reduced lung injury in the salbutamol-treated group. These findings support the need for an appropriately powered multicenter clinical trial to test the effect of salbutamol for improving clinical outcomes in ALI/ARDS.

Conflict of Interest Statement: None of the authors have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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