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Aerosolized β_2-adrenergic agonists achieve therapeutic levels in the pulmonary edema fluid of ventilated patients with acute respiratory failure

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Abstract *Objective:* Experimental studies demonstrate that β-adrenergic agonists markedly stimulate alveolar fluid clearance if concentrations of 10^{-6} M are achieved in alveolar fluid. However, no studies have determined whether aerosolized β-adrenergic agonists are delivered to the distal air spaces of the lung in therapeutic concentrations in patients with pulmonary edema. *Design and setting:* This retrospective study measured albuterol levels in the pulmonary edema fluid and plasma from mechanically ventilated patients with pulmonary edema from a hydrostatic mechanism (n=10) or from acute lung injury (n=12). *Measurements and results:* After a total aerosolized albuterol dose of 4.2±3.2 mg in the prior 6 h the median pulmonary edema fluid albuterol level was 1,250 ng/ml (10^{-6} M) in patients with hydrostatic pulmonary edema; after 3.5±2.6 mg the figure was 1,240 ng/ml (10^{-6} M) in patients with pulmonary edema from acute lung injury. Plasma albuterol levels were much lower, with a median of 5.2 ng/ml (0.01×10^{-6} M) in patients with hydrostatic pulmonary edema and 3.1 ng/ml (0.01×10^{-6} M) in patients with pulmonary edema from acute lung injury. *Conclusions:* These results provide the first evidence that levels of β-adrenergic agonists that are physiologically efficacious in experimental models can be achieved with conventional delivery systems in ventilated, critically ill patients with acute respiratory failure from pulmonary edema.

Keywords Adrenergic β-agonists · Albuterol · Alveolar fluid clearance · Pulmonary edema

Introduction

β-Adrenergic agonists are commonly administered to patients with acute pulmonary edema, particularly when auscultation reveals rhonchi, rales, or expiratory wheezes on physical examination. Most studies have indicated that only a small fraction of aerosolized particles are delivered to the proximal airway, with even a smaller proportion reaching distal airways [1, 2, 3, 4, 5]. Interestingly, several animal studies have demonstrated that the rate of clearance of fluid from the alveolar space can be markedly increased by β_2-adrenergic agonists that have been instilled or aerosolized to the distal airspaces of the lung [6, 7, 8, 9, 10, 11, 12]. Recent experimental studies have indicated that β_2-agonists can accelerate the resolution of alveolar edema in the presence of acute lung injury (ALI) [13, 14] or hydrostatic pulmonary edema [11]. The dose-response curve for the effect of β_2-agonists on

up-regulating the rate of alveolar fluid clearance has been defined in the ex vivo human lung [15]. However, it is not known whether aerosolization of a β_2-agonist in intubated, ventilated patients delivers therapeutic levels to the distal airways and alveoli, the primary sites of reabsorption of pulmonary edema [16]. If therapeutic concentrations of an aerosolized β-adrenergic agonist could be delivered to the alveoli in patients with acute pulmonary edema, the resolution of alveolar edema might be accelerated [16].

Data on the pharmacokinetics of albuterol are limited primarily to studies of plasma concentrations measured after inhaled, oral, or intravenous administration [17, 18, 19, 20, 21, 22, 23, 24]. The concentration of albuterol in the pulmonary edema fluid after inhalation therapy has not been determined. Therefore the overall purpose of this study was to measure edema fluid and plasma concentrations of a commonly used β_2-agonist, albuterol, in samples obtained from patients with acute pulmonary edema from either a hydrostatic mechanism or from ALI. The first objective was to determine whether albuterol delivered by aerosol therapy through the inspiratory limb of a mechanical ventilator achieves measurable levels in the alveolar compartment. The second objective was to determine whether conventional β-agonist dosing regimens result in pulmonary edema and plasma fluid albuterol concentrations that are equal to or greater than concentrations required to enhance alveolar fluid clearance in experimental models.

Methods and materials

Patient selection

Patients with acute pulmonary edema who required intubation and mechanical ventilation and had received albuterol in the intensive care units of the University of California San Francisco or San Francisco General Hospital were eligible for inclusion in this study. The patients were classified as having hydrostatic pulmonary edema when the initial pulmonary edema fluid-to-plasma protein ratio was lower than 0.65, and there was clinical evidence of left ventricular failure or volume overload [25]. Patients were classified as having ALI according to the North American–European Consensus Conference statement [26]. The initial pulmonary edema fluid-to-plasma protein ratio was required to be higher than 0.65, consistent with increased permeability pulmonary edema [27]. All patients must have received albuterol by nebulizer or metered dose inhaler.

Ten patients with pulmonary edema secondary to a hydrostatic mechanism had received albuterol. Nine had pulmonary edema fluid samples, and three had plasma samples available for analysis and were included in the study. Twelve patients with pulmonary edema secondary to ALI had received albuterol. Eleven had pulmonary edema fluid samples, and 12 had plasma samples available for analysis and were included in the study. Control pulmonary edema fluid samples were collected from three patients who had not received albuterol, and control plasma samples were obtained from two patients with pulmonary edema who had not received albuterol and one healthy volunteer. The clinical characteristics of the patients are summarized in Table 1. This study was approved by the Committee on Human Research of the University of California San Francisco.

Table 1 Clinical characteristics of patients with hydrostatic pulmonary edema and pulmonary edema from acute lung injury (*ALI* acute lung injury, *SAPS II* Simplified Acute Physiology Score II)

	Hydrostatic (n=10)	ALI (n=12)	p
Male (%)	50	66	0.72
Age (years)	68±15	48±19	0.01
Hospital mortality (%)	30	75	0.03
SAPS II score	52±18	57±25	0.63
Unassisted ventilation (days)	17±12	4±9	0.01
Sepsis (%)	0	58	0.01

Pulmonary edema fluid collection and classification

Pulmonary edema fluid was collected by a well validated method [6, 7] by trained respiratory therapists or the authors of this study as previously described [25, 27]. The Simplified Acute Physiology Score II [28] was used to assess severity of illness upon admission to the intensive care unit [25].

Measurement of albuterol levels

Pulmonary edema fluid and plasma albuterol levels were measured by high-performance liquid chromatography [29]. Albuterol levels reported in this study are the sum of the (*R*)- and (*S*)-enantiomer levels and were measured at Sepracor (Marlborough, Mass., USA).

Calculation of administered albuterol dose

The medical records of all patients were reviewed, and the time and quantity of all doses of albuterol administered in the 24 h prior to collection of each edema fluid or plasma sample were recorded. Albuterol was administered through the ventilator circuit by nebulization of 2.5 cc of a 5% albuterol solution (2.5 mg) or by a metered dose inhaler (four to six puffs at 90 µg/puff). Patients with pulmonary edema from a hydrostatic mechanism were intubated for a median of 2.5 h prior to collection of the first edema fluid sample. Patients with pulmonary edema from ALI were intubated for a median of 12.75 h prior to collection of the first edema fluid sample. The total albuterol dose administered within the previous 6, 12, and 24 h was calculated so that albuterol levels could be evaluated with regard to the total administered dose. To control for differences in administered dose the absolute pulmonary edema fluid and plasma albuterol levels were divided by the total dose of albuterol administered in the previous 6 h. Statistical analysis was performed on absolute fluid albuterol levels as well as fluid levels per milligram of albuterol administered in the previous 6 h.

Statistics

Pulmonary edema fluid and plasma albuterol levels are presented as median (25–75 percentiles). Drug doses administered are presented as mean ±SD. Statistical analysis was carried out by Mann-Whitney test, Pearson's correlation coefficient, or χ^2 where appropriate using In Stat 2.03. Results were considered statistically significant at $p<0.05$.

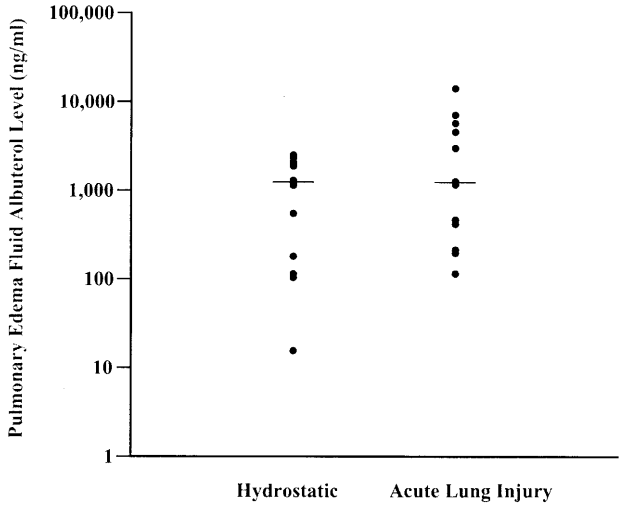

Fig. 1 Albuterol levels in the pulmonary edema fluid from patients with acute pulmonary edema. Patients with acute pulmonary edema from a hydrostatic mechanism (9 patients, 12 samples) had a median albuterol level of 1,250 ng/ml (10^{-6} M) after receiving 4.2±3.2 mg albuterol in the previous 6 h. Patients with acute lung injury (9 patients, 11 samples) had a median albuterol level of 1,240 ng/ml (10^{-6} M) after receiving 3.5±2.6 mg albuterol in the previous 6 h. *Horizontal bar* Median

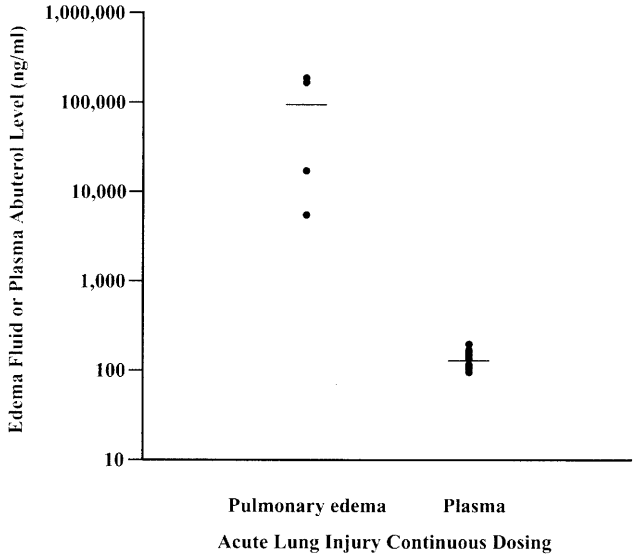

Fig. 2 Pulmonary edema fluid and plasma albuterol levels in patients receiving continuous albuterol nebulizers. Two patients with acute lung injury who were receiving 10–20 mg/h continuous nebulized albuterol in the 24 h prior to collection of pulmonary edema fluid (n=4) and plasma (n=10) had a median pulmonary edema fluid albuterol level of 94,415 ng/ml (100×10^{-6} M) and a median plasma fluid albuterol level of 129 ng/ml (0.1×10^{-6} M). *Horizontal bar* Median

Results

Albuterol levels in pulmonary edema fluid

Hydrostatic edema

Nine patients (12 samples) who had received 4.2±3.2 mg albuterol in the previous 6 h (4.7±3.4 in the previous 12 h and 5.8±4.1 in the previous 24 h) had a median albuterol level of 1,250 ng/ml (378–5,000, 10^{-6} M; Fig. 1).

Acute lung injury

Nine patients (11 samples) who had received 3.7±2.8 mg albuterol in the past 6 h (7.3±4.5 in the previous 12 h and 29±41 in the previous 24 h) had a median albuterol level of 1,240 ng/ml (186–2,000, 10^{-6} M; Fig. 1). There was no difference in absolute pulmonary edema fluid albuterol levels between the hydrostatic edema and ALI groups (p=0.3).

Dose-adjusted edema fluid levels

The median pulmonary edema fluid drug level per milligram of albuterol administered in the previous 6 h was 500 ng ml^{-1} mg^{-1} (156–2,000) in the hydrostatic group and 288 ng ml^{-1} mg^{-1} (178–1,036) in the ALI group. There was no significant difference between dose corrected pulmonary edema fluid albuterol levels between the hydrostatic edema and ALI groups (p=0.5)

Continuous nebulizer treatment

Two patients (four samples) with ALI who were receiving 10–20 mg/h continuous nebulized albuterol had a median edema fluid level of 94,415 ng/ml (14,670–176,520, 100×10^{-6} M; Fig. 2).

Albuterol levels in plasma

Hydrostatic edema

Three patients (five samples) who received 4.5±2.8 mg albuterol in the previous 6 h (5.3±3 in the previous 12 h and 5.8±4.1 in the previous 24 h) had a median plasma albuterol level of 5.2 ng/ml (4.9–39, 0.01×10^{-6} M; Fig. 3).

Acute lung injury

Ten patients (11 samples) who received 4.3±2.8 mg albuterol in the previous 6 h (7.3±3.6 in the previous 12 h

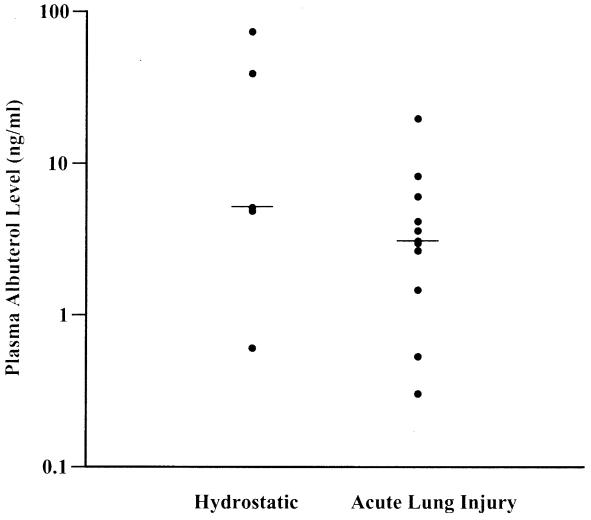

Fig. 3 Albuterol levels in plasma from patients with acute pulmonary edema. Patients with acute pulmonary edema from a hydrostatic mechanism (three patients, five samples) had a median albuterol level of 5.2 ng/ml (0.01×10^{-6} M) after receiving 4.5±2.8 mg albuterol in the previous 6 h. Patients with acute lung injury (10 patients, 11 samples) had a median albuterol level of 3.1 ng/ml (0.01×10^{-6} M) after receiving 4.3±3 mg albuterol in the previous 6 h. *Horizontal bar* Median

and 21±34 in the previous 24 h) had a median plasma albuterol level of 3.1 ng/ml (2.1–5.1, 0.01×10^{-6} M; Fig. 3). There was no significant difference in absolute plasma fluid albuterol levels between the hydrostatic edema and ALI groups (p=0.2).

Dose-adjusted plasma levels

The median plasma fluid drug level per milligram of albuterol in the previous 6 h was 2 ng ml^{-1} mg^{-1} (0.9–4.6) in the hydrostatic group and 0.8 ng ml^{-1} mg^{-1} (0.4–4.3) in the ALI group. There was no significant difference between dose corrected plasma fluid albuterol levels between the hydrostatic edema and ALI groups (p=0.4).

Continuous nebulizer treatment

Two patients (ten samples) with ALI who were receiving 10–20 mg/h continuous nebulized albuterol

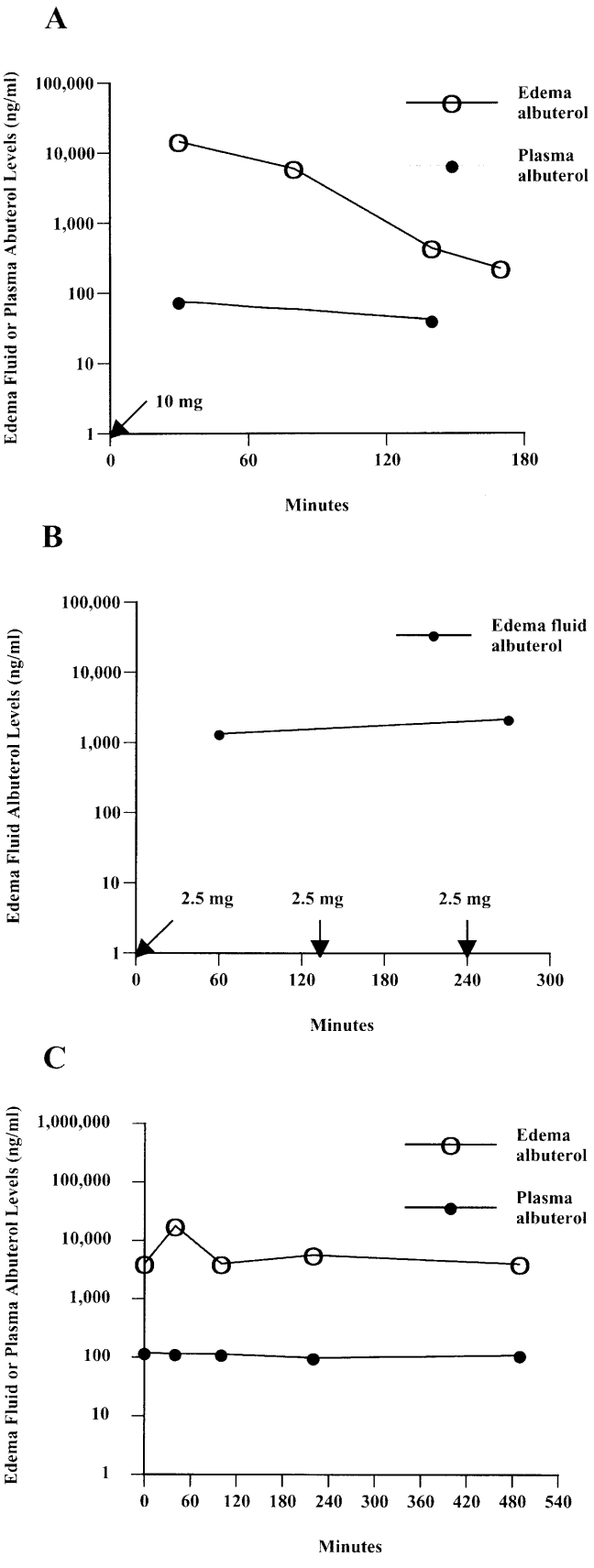

Fig. 4A–C Albuterol levels in pulmonary edema fluid and plasma over time. **A** Sequential pulmonary edema fluid and plasma albuterol levels after 10 mg was administered over 15 min in a patient with hydrostatic pulmonary edema. **B** Sequential pulmonary edema fluid levels in a patient with acute lung injury receiving nebulizers every 2 h. **C** Sequential pulmonary edema fluid and plasma albuterol levels in an acute lung injury patient receiving 10 mg/h continuously nebulized albuterol. The three edema fluid data points at 4,000 ng/ml represent minimum estimates as these samples were beyond the upper limit of quantification

had a median plasma fluid level of 129 ng/ml (113–154 ng ml^{-1} mg^{-1}, 0.1×10^{-6} M; Fig. 2).

Albuterol levels in pulmonary edema fluid and plasma over time

One patient with hydrostatic edema received 10 mg nebulized albuterol during a 15-min period and had sequential samples of pulmonary edema fluid and plasma collected (Fig. 4A). The edema fluid drug levels were initially 100-fold higher than those of plasma. The ratio of (*R*)- and (*S*)-enantiomers of albuterol in this patient's edema fluid samples was 1, while in the plasma samples the (*S*)-enantiomer predominated. This same pattern of enantiomer ratios was found in all patients (data not shown). One patient with ALI received 2.5 mg nebulized albuterol every 2 h and had serial edema fluid albuterol levels above 10^{-6} M (Fig. 4B). One patient with ALI who received continuous albuterol nebulizers had serial edema fluid and plasma sample albuterol levels measured and consistently had edema fluid levels that were either above the limit of quantification or above 10×10^{-6} M (Fig. 4C).

Correlation between pulmonary edema fluid and plasma albuterol levels

Edema fluid and plasma albuterol levels were measured simultaneously in ten patients (three from the hydrostatic group, seven from the ALI group). The correlation coefficient in these samples was r=0.8 (p=0.005)

Control studies

The seven control samples (four pulmonary edema fluid, three plasma) had undetectable levels of albuterol.

Discussion

The concentration of albuterol in pulmonary edema fluid after aerosolization has never been measured in human subjects. This is an important issue because experimental data demonstrate that β_2-adrenergic agonists can accelerate the resolution of alveolar edema, providing adequate concentrations are achieved in the distal airspaces and the alveolar compartment where the pulmonary edema fluid accumulates.

The beneficial effect of β-adrenergic agonist therapy on the up-regulation of alveolar fluid clearance has been convincingly demonstrated in sheep, dogs, and rats and in ex vivo human lung studies [6, 7, 8, 9, 10, 11, 12, 15, 30, 31]. In the in vivo rat model the instillation of salmeterol at a concentration of 10^{-7} M resulted in a 100% increase in alveolar fluid clearance from 15% to 30%/h, with a further increase to 34%/h with 10^{-5} M salmeterol [15]. The ex vivo rat lung demonstrated a dose-dependent increase in alveolar fluid clearance from 90% to 150% above control values as the instilled dose of salmeterol was raised from 10^{-8} M to 10^{-5} M. In the ex vivo human lung the instillation of 10^{-7} M salmeterol had no effect on alveolar fluid clearance, while 10^{-6} M concentration resulted in a 70% increase in alveolar fluid clearance above baseline [15]. Thus a concentration of 10^{-6} M β-adrenergic agonist augments alveolar fluid clearance in three different experimental systems.

To date there has only been one animal study in which pulmonary edema fluid levels of β-adrenergic agonists were measured after aerosol administration. Campbell et al. [8] delivered 5 mg nebulized salmeterol through a mechanical ventilator to intubated sheep and measured plasma and pulmonary edema levels 4 h after drug treatment. The mean edema fluid level was 700 ng/ml (10^{-6} M) and the mean plasma level was 4 ng/ml (10^{-9} M). The current study provides the first direct measurement of a β-agonist concentration in pulmonary edema fluid of human subjects after aerosol delivery. Most patients in this study had edema fluid levels of albuterol well above the 10^{-6} M threshold with conventional albuterol dosing (600 ng/ml=10^{-6} M).

These results demonstrate that levels of β-adrenergic agonists that are physiologically efficacious in experimental models can be effectively delivered to the distal airspaces of the lung by standard aerosol delivery through a mechanical ventilator circuit. The dose and frequency of albuterol administration necessary to sustain 10^{-6} M edema fluid levels is difficult to predict because of the retrospective nature of this study. However, as demonstrated in Fig. 4B, conventional 2- to 4-h dosing regiments of 2.5–5 mg nebulized albuterol would probably suffice. Continuous nebulizer therapy will likely maintain alveolar edema concentrations well above 10^{-6} M, although the high plasma and edema albuterol concentrations that result (Fig. 4C) raise concerns about the risk-benefit ratio of continuous treatment. Furthermore, high levels of edema fluid β-agonists might be more likely to induce down-regulation of the β-receptors.

One limitation of this observational study was that a dose-response analysis of the effects of albuterol on alveolar fluid clearance was not possible. However, the finding that an aerosolized β-agonist can be delivered in potentially therapeutic concentrations to the pulmonary edema fluid, in combination with prior studies that reported no significant hemodynamic changes in ventilated patients receiving β-agonist therapy [17, 32], indicates that future studies of the ability of inhaled adrenergic agonists to increase the resolution of pulmonary edema should be safe and feasible in ventilated patients.

Previous analysis of the proportional lung deposition of aerosolized drugs has been limited mostly to radionucleotide studies of ambulatory asthmatic and normal subjects, with only a few studies in mechanically ventilated patients [32, 33, 34]. These studies estimate parenchymal aerosol deposition to range from 3% to 12% of the administered dose. In order to determine the efficiency of delivery of albuterol to the edema fluid compartment we estimated extravascular lung water using previously published approximations. In critically ill patients without radiological evidence of pulmonary edema, normal extravascular lung water is estimated to be 4–6 ml/kg [35, 36, 37, 38]. Patients with radiographically evident cardiogenic pulmonary edema have estimated extravascular lung water volumes of 10 ml/kg, while patients with noncardiogenic pulmonary edema have estimated lung water volumes of 15 ml/kg [37, 38]. In this study four patients with hydrostatic edema who received a single 2.5-mg dose of albuterol had a mean edema fluid albuterol level of 2,600 ng/ml. Assuming these patients had an average weight of 60 kg, they would have a mean extravascular lung water of approximately 600 ml. Subtracting 300 ml for normal extravascular lung water leaves a volume of 300 ml, and we can estimate that approximately two-thirds would be in the airspaces as alveolar edema. Thus an edema fluid level of 2,600 ng/ml multiplied by 200 ml indicates that 520 µg or approximately 20% of the administered dose of albuterol was delivered to the edema fluid in the distal airspaces of the lung. This may be a conservative estimate because the samples in this study do not necessarily measure peak edema fluid albuterol levels. These data suggest that a higher proportion of aerosolized β_2-agonists is delivered to the edema fluid than predicted by the radionucleotide studies of intubated patients [32, 33, 34].

There are some limitations to this observational study. Although high levels of albuterol were measured in both the plasma and the pulmonary edema samples, the stability of albuterol in human plasma has been documented only up to 5.5 months (P. Koch, personal communication). Since most of our samples had been stored at –70°C for more than 12 months, it is possible that the levels measured in this study could underestimate the true levels. This, however, does not alter our conclusions. If anything, our data would underestimate the therapeutic levels of β-adrenergic agonists that can be achieved in edema fluid and plasma after standard aerosol delivery to the mechanically ventilated patient. This was not a formal prospective study, and therefore the data cannot be used to calculate exact dosing and time interval requirements.

In summary, this is the first study to demonstrate that aerosolized delivery of standard doses of a commonly used β-adrenergic agonist through a mechanical ventilator circuit results in pulmonary edema fluid drug levels that are sufficient to augment alveolar fluid clearance based on ex vivo human lung studies as well as other experimental studies.

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