Terbutaline stimulates alveolar fluid resorption in hyperoxic lung injury

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Alveolar fluid resorption occurs by active epithelial sodium transport and is accelerated by terbutaline in healthy lungs. We investigated the effect of terbutaline on the rate of alveolar fluid resorption from rat lungs injured by hyperoxia. Rats exposed to >95% O₂ for 60 h, sufficient to increase wet-to-dry lung weight and cause alveolar edema, were compared with air-breathing control rats. After anesthesia, the animals breathed 100% O₂ for 10 min through a tracheostomy. Ringer solution was instilled into the alveoli, and the steady-state rate of volume resorbed at 6 cmH₂O pressure was measured via a pipette attached to the tracheostomy tubing. Ringer solution in some animals contained terbutaline (10⁻³ M), ouabain (10⁻³ M), or both. Normoxic animals resorbed 49 ± 6 µl·kg⁻¹·min⁻¹; ouabain reduced this by 39%, whereas terbutaline increased the rate by 75%. The effect of terbutaline was blocked by ouabain. Hyperoxic animals absorbed 78 ± 9 µl·kg⁻¹·min⁻¹; ouabain reduced this by 44%. Terbutaline increased the rate by a mean of 39 µl·kg⁻¹·min⁻¹, similar to the absolute effect seen in the normoxic group, and this was blocked by ouabain. Terbutaline accelerates fluid resorption from both normal and injured rat lungs via its effects on active sodium transport.

**METHODS**

Fluid resorption measurement. Measurement of fluid resorption was based on a model described by Vejsstrup et al. (28) in which fluid resorption was monitored by following the change in a calibrated system attached to a fluid-filled rabbit lung. In our experiments, male Sprague-Dawley specific pathogen-free rats (Harlan, Madison, WI), weight 175–250 g, were anesthetized with pentobarbital sodium (80 mg/kg ip), and a tracheostomy was performed. Inspired O₂ fraction of 1.0 was administered with 2–4 cmH₂O constant positive airway pressure for 10 min to facilitate subsequent degassing of the lungs. Ringer solution that previously had been bubbled for 10 min with 100% O₂ was instilled via the tracheostomy; cardiac arrest occurred within a few minutes of instillation. The composition of the Ringer solution was as follows (in mM): 137 NaCl, 2.68 KCl, 1.25 MgSO₄, 1.82 CaCl₂, 5.55 glucose, and 12 N-2-hydroxyethylpiperazine-N’-2-ethanesulfonic acid. The pH was adjusted to 7.4 and sufficient blue dextran (mol wt 2 × 10⁶) was added to color the solution, with a resulting osmolality of 270–290 mosmol. The tracheostomy tubing was then attached to a graduated 1-ml fluid-filled pipette supported in a horizontal position at a height of 6 cm above the table top. Thoracotomy was performed to document adequate degassing and filling of the lungs with the Ringer solution. The temperature in the thorax was monitored and maintained at 37°C with a heating blanket placed below the animal. Volume measurements were taken every 10 min following the meniscus in the pipette. These values were recorded through the initial equilibration period and for 40 min with a stable rate of clearance, as defined by interval measurements varying by no more than 25%. The volume of >95% O₂ or chronic (7 days of 85% O₂) hyperoxia increases Na⁺-K⁺-ATPase mRNA, protein, and activity (4, 14, 15, 25) as well as sodium-channel protein and activity (10). Upregulation of Na⁺-K⁺-ATPase also occurs in type II cells isolated from rats ventilated with high pressures for 25 min (26). Recent human data suggest that patients with lung injury who resorb fluid have a better prognosis (13). However, there is little published data demonstrating that active sodium transport, and thus net fluid resorption, can be accelerated pharmacologically in an injured lung (12, 22). Because acceleration of fluid clearance in lung injury may improve outcome, we have used a recently developed model to test the hypothesis that terbutaline will accelerate net fluid resorption in an injured lung. Hyperoxia was chosen as a method of inducing lung injury because the morphological changes associated with 60 h of 100% O₂ are well described (27) and include alveolar edema accompanied by increased wet-to-dry lung weight (14); in addition, increases in Na⁺-K⁺-ATPase mRNA and protein have been demonstrated in this model (4, 14).

**ALTHOUGH** it previously was thought that sodium and fluid movement across the alveolar epithelium was entirely due to passive diffusion driven by hydrostatic and osmotic pressure gradients, there is now ample evidence that active sodium transport across the alveolar epithelium plays a key role in driving isotonic fluid resorption. Vectorial active sodium transport has been demonstrated in cultured type II cells in monolayers (5, 8), isolated perfused lungs (1, 5, 6, 8, 16), and whole animals (3, 11, 16, 20, 23). Furthermore, lungs from sheep and humans actively resorb fluid despite the absence of blood flow or ventilation (19, 20). Active transport in these models is stimulated by β-agonists (3, 5–9, 11, 16, 18) and adenosine 3’,5’-cyclic monophosphate (cAMP) analogues (5, 8), showing that it is possible to pharmacologically accelerate clearance, at least in normal lungs. In these models, transport also is inhibited by amiloride (1, 4, 5, 9, 11, 23) and ouabain (1, 9, 11, 19, 20), consistent with the idea that both the apical sodium channel and basolateral Na⁺-K⁺-adenosinetriphosphatase (ATPase) are critical for active transepithelial transport.

The effects of lung injury on net sodium and fluid resorption are less clear. In rats, injury due to acute (60 h of >95% O₂) or chronic (7 days of 85% O₂) hyperoxia increases Na⁺-K⁺-ATPase mRNA, protein, and activity (4, 14, 15, 25) as well as sodium-channel protein and activity (10). Upregulation of Na⁺-K⁺-ATPase also occurs in type II cells isolated from rats ventilated with high pressures for 25 min (26). Recent human data suggest that patients with lung injury who resorb fluid have a better prognosis (13). However, there is little published data demonstrating that active sodium transport, and thus net fluid resorption, can be accelerated pharmacologically in an injured lung (12, 22). Because acceleration of fluid clearance in lung injury may improve outcome, we have used a recently developed model to test the hypothesis that terbutaline will accelerate net fluid resorption in an injured lung. Hyperoxia was chosen as a method of inducing lung injury because the morphological changes associated with 60 h of 100% O₂ are well described (27) and include alveolar edema accompanied by increased wet-to-dry lung weight (14); in addition, increases in Na⁺-K⁺-ATPase mRNA and protein have been demonstrated in this model (4, 14).

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resorbed during the latter time period was plotted vs. time. As the experiment progressed, additional Ringer solution with blue dextran was added to the tubing to maintain the meniscus within the calibrated section of the pipette. Similar to the findings of Vejstrup et al. (28), the equilibration period consistently lasted 100–150 min and then was followed by a steady rate of fluid resorption, as illustrated by a representative time curve (Fig. 1). In some rats, fluid resorption was measured for up to a total of 4 h, with steady fluid resorption for >120 min.

For each rat, a line was fit by linear least-squares methods to the volume vs. time data; the \( r^2 \) value was >0.97 in all cases. The slope of the line provided a value for the fluid resorption rate, which was normalized to weight. Leakage of blue fluid from the tracheostomy site or into the pleural space invalidated the results from that animal, and the data were excluded from analysis. Experimental design. A total of 66 animals were studied; data from 9 of these rats either were not obtained or were discarded due to anesthetic death before instillation of Ringer solution without blue dextran (4 animals), or hydrothorax (4 animals), or hydrothorax plus ouabain (1 animal). No rats died in the exposure chamber or before anesthesia. Eight of the nine experiments with technical difficulties occurred in the first 23 animals. Of the remaining 57 animals, 27 were exposed to 60 h of 100% \( O_2 \); the details of the exposure protocol have been described previously (29).

The normoxic and hyperoxic animals were divided into four groups: those with no drug in the instillate, those with terbutaline \((10^{-3} \text{ M})\), those with ouabain \((10^{-3} \text{ M})\), and those with both. This concentration of terbutaline has been used by several investigators, although no additive effect of using terbutaline in concentrations \(>10^{-3} \text{ M}\) has been reported (8, 11, 19). To determine the active transport of fluid, we used ouabain because of its inhibition of \(\text{Na}^+\text{-K}^+\text{-ATPase}\), the only known basolateral exit pathway for intracellular sodium. Most investigators have used ouabain in the vascular space (1, 9), sometimes in combination with intra-alveolar ouabain (11, 20), but we used it only in the alveolar space based on the report of Sakuma et al. (19) of a 49% reduction in alveolar liquid clearance when \(10^{-3} \text{ M}\) ouabain was instilled into the alveoli of resected human lung. Although our model has no ventilation or perfusion, Sakuma and co-workers (19, 20) demonstrated that active transport occurs in the absence of blood flow or perfusion for 4 h in both sheep and humans.

Lung histology. Tissue for histology was obtained immediately and 4 h after instillation of Ringer solution without blue dextran in both hyperoxic and normoxic animals; volume resorption data were not collected from these animals. At both time points, 4% Formalin in phosphate-buffered saline was instilled via the tracheostomy tubing, and after mixing, the pressure was readjusted to 6 cmH\(_2\)O. The trachea was tied off and the lungs were removed. The lungs were immersion fixed in 4% Formalin in phosphate-buffered saline for 15 min. Tissue slices were submitted in Formalin for paraffin embedding and staining with hematoxylin and eosin. Lung sections were analyzed by a pathologist (L. S. Schmitz) blinded to the treatment conditions. They were graded for inflammation, interstitial edema, and congestion.

Data analysis. Fluid resorption rates were analyzed using analysis of variance for a three-factor completely randomized design, fixed-effects model (11a) with SPSS (14a). Pairwise comparisons were performed using the Mann-Whitney test.

RESULTS

Histology. Representative lung histology from both exposed and unexposed rats, obtained immediately and 4 h after degassing and instillation of Ringer solution, is shown in Fig. 2. There was no light-microscopic evidence of degradation of the tissue after 4 h of ex vivo fluid measurements. There was no major difference between the groups with regard to congestion or neutrophil infiltration. Little alveolar edema was noted in the hyperoxic animals, as this was eliminated by the intratracheal fixation method. However, after 4 h ex vivo for the normoxic lungs and at both times for the hyperoxic lungs, there was interstitial edema. This was an expected finding, as one would predict that fluid cleared from the alveoli would collect in the interstitium. There was no marked increase in edema in the hyperoxic lungs after 4 h ex vivo.

Normoxic animals. As shown in Fig. 1, each preparation typically resorbed very little fluid for up to 2 h but then achieved a steady rate of fluid resorption shortly thereafter. Figure 3 shows the distribution of fluid resorption rates for each rat in the four normoxic groups. There was an even distribution of values in all groups, with somewhat tighter clustering in the ouabain group. The average fluid resorption rates for the four groups of normoxic animals are shown in Table 1. The control animals resorbed \(49 \pm 6 \mu\text{l} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\), or \(-0.6 \text{ ml/h}\), which is consistent with previously published values for rats (11). Terbutaline increased fluid resorption by a mean of \(37 \mu\text{l} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\) (75%), whereas ouabain reduced resorption by a mean of \(19 \mu\text{l} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\) (39%) and prevented the acceleration of fluid resorption by terbutaline. These results are very similar to those of Jay et al. (11) using a ventilated rat model, who had 30% inhibition of fluid resorption with combined intravascular and alveolar ouabain. Figure 4 is a plot of volume vs. time for the normoxic animals, demonstrating the acceleration of alveolar fluid resorption with terbutaline and the reduction with ouabain.
Hyperoxic animals. Figure 5 shows the distribution of fluid resorption rates for each rat in the four hyperoxic groups. Again, the ouabain group is more tightly clustered. A similar pattern of response to terbutaline and ouabain was seen in the normoxic and hyperoxic rats (Table 1). Although the percentage increase in fluid resorption in response to terbutaline (50%) was not as great as in the normoxic group (75%), the absolute increase was similar (39 vs. 37 µl·kg⁻¹·min⁻¹). Ouabain reduced the rate of fluid resorption by a mean of 34 µl·kg⁻¹·min⁻¹ (44%) and prevented the stimulation by terbutaline. As expected, the fluid movement out of the alveolus with ouabain present was greater in the hyperoxic than normoxic rats, presumably due to increased paracellular permeability. Figure 6 is a plot of volume vs. time for the hyperoxic animals, again demonstrating the acceleration of alveolar fluid resorption with terbutaline and the reduction with ouabain. Prevention of the terbutaline effect by ouabain confirmed the role of increased active transport in the acceleration of fluid resorption rates by terbutaline in both normoxic and hyperoxic animals.

Effect of hyperoxia on active transport independent of terbutaline. Hyperoxia increased fluid resorption rates in all treatment subgroups (Table 1). Some of this
increase resulted from increased paracellular permeability (4, 29). It is possible, as previously suggested (14), that hyperoxia upregulates active sodium and fluid resorption independent of the terbutaline effect. To examine this question, it would not be statistically valid to compare the differences between mean fluid resorption rates in the presence and absence of ouabain for the normoxic and hyperoxic rats. Instead, the graphs in Fig. 7 plot the fluid resorption rates as a function of exposure to hyperoxia. The ouabain-sensitive fluid resorption rate is defined as the difference between the ouabain-treated and untreated groups; because ouabain inhibits Na\(^{+}\)-K\(^{+}\)-ATPase, the ouabain-sensitive rate represents the component of fluid resorption due to active transport. In Fig. 7, top, without terbutaline present in any of the animals, the ouabain-sensitive fluid resorption rate increased from 19 to 34 µl·kg\(^{-1}\)·min\(^{-1}\). In Fig. 7, bottom, with terbutaline present in all animals, the ouabain-sensitive rate increased from 41 to 69 µl·kg\(^{-1}\)·min\(^{-1}\). When an analysis of variance was performed on the combined data from Fig. 7, top and bottom, a trend towards significance (P = 0.09) was demonstrated, suggesting, but not proving, that hyperoxia upregulates active sodium transport and net fluid resorption.

**DISCUSSION**

Although upregulation of Na\(^{+}\)-K\(^{+}\)-ATPase mRNA, protein, and activity, as well as sodium-channel protein, occurs in several models of lung injury, including hyperoxia (4, 10, 14, 15, 25, 26), it is unclear whether this results in increased alveolar fluid resorption in the face of a leaky alveolar-capillary membrane. The model we used measures alveolar volume resorption and thus answers this question directly. Our data demonstrate that terbutaline further stimulated net alveolar fluid resorption in the hyperoxia-exposed animals through a Na\(^{+}\)-K\(^{+}\)-ATPase-dependent mechanism. It is interesting to note that the absolute increase in fluid resorption caused by terbutaline was the same in the normoxic and hyperoxic groups. Thus stimulation of active transport effected net alveolar fluid removal despite the increased paracellular permeability of the alveolar capillary membrane that occurs with hyperoxia and that was previously seen in our studies of this model (4). Secondly, the results suggest, but do not prove, that hyperoxia stimulated active sodium transport with a resultant increase in net fluid clearance. If this were correct, then the mechanism is not certain, but the increased active sodium transport in response to hyperoxic lung injury would serve as a homeostatic response.

**Table 1. Alveolar fluid resorption rates**

<table>
<thead>
<tr>
<th></th>
<th>Normoxic, µl·kg(^{-1})·min(^{-1})</th>
<th>Hyperoxic, µl·kg(^{-1})·min(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>49 ± 6 (8)</td>
<td>78 ± 9 (7)</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>86 ± 13*(9)</td>
<td>117 ± 10* (8)</td>
</tr>
<tr>
<td>Ouabain</td>
<td>30 ± 3* (7)</td>
<td>44 ± 6* (6)</td>
</tr>
<tr>
<td>Terbutaline + ouabain</td>
<td>45 ± 6 (6)</td>
<td>48 ± 9 (6)</td>
</tr>
</tbody>
</table>

Values are means ± SE. Nos. in parentheses are no. of rats. Two-tailed P values were determined using Mann-Whitney test. *Significantly different compared with control values, P < 0.03.

**Fig. 5.** Histogram showing distribution of fluid resorption rates for all hyperoxic rats. †, Mean value.
In this model of hyperoxic lung injury at 60 h of exposure, there was alveolar edema with significantly increased wet-to-dry lung weight ratio (11.5 vs. 2.7 for control) and paracellular permeability (4, 14), but the alveolar epithelium was intact, as shown by electron microscopy at that time point (14, 27). It is possible that more severe disruption of the alveolar epithelium would prevent an increase in net fluid clearance by upregulated active sodium transport.

Vejlstrup et al. (28) used this method to study fluid resorption in rabbits with intact perfusion. Because of the technical difficulties presented by working with smaller animals, we modified their method so that perfusion ceased before the experiment. Sakuma et al. (19, 20) demonstrated that active transport occurs in the absence of ventilation or perfusion for 4 h in both sheep and humans, providing justification for our technique. Another technical issue with our method is that we added ouabain to the alveolar side of the epithelium. We chose to use ouabain because it blocks the single basolateral route of exit for sodium from the cell. Amiloride has been used in similar fashion, but it may not block all the apical entry of sodium into epithelial cells and there is discrepancy in the literature reports about the amiloride binding affinity of the alveolar epithelium. Using ouabain is difficult because the binding affinity of the rat Na\(^{+}\)-K\(^{+}\)-ATPase for ouabain is relatively low (24), but high ouabain concentrations rapidly cause cell death with disruption of tissue architecture. Although most investigators have instilled ouabain into the vascular space (1, 9, 11, 20), Sakuma et al. (19) demonstrated a 49% reduction in alveolar liquid clearance when 10\(^{-3}\) M ouabain was instilled into the alveoli of resected human lung. In the isolated perfused rat lung, 50 \(\mu\)M ouabain in the perfusate reduced the sodium permeability-surface area product (PS) by 18% (9). Thus, although we cannot say definitively that we have blocked all active transport, the percent inhibition we observed with ouabain is
within the range of reported values. Another technical concern is the reproducible lag of 100–150 min before steady fluid resorption occurred. Vejlstrup et al. (28) noted a similar lag before a stable rate of fluid resorption occurred; we also do not have a clear explanation for this delay. Finally, it would be optimal to confirm the fluid resorption measurements of this model with another technique, such as simultaneous measurement of the concentration of a low-permeability marker. However, given the need to add additional fluid as the experiment progresses, there would be only very small changes in the concentration of this marker, making this estimate of fluid resorption imprecise.

The validity of our results in this rat model is supported by the similarity of our measured rates of fluid resorption in the presence of slight positive pressure (6 cmH₂O) to those measured in rats by other investigators. The baseline rate of fluid resorption in our experiments was 49 ± 6 µl·kg⁻¹·min⁻¹, whereas Basset et al. (1) found 26.8 ± 3.7 µl·kg⁻¹·min⁻¹ by measurement of alveolar protein concentration and Jayr et al. (11) found a mean of 37.6 µl·kg⁻¹·min⁻¹.

An issue in interpreting our results is whether the β-agonist-induced increases in alveolar fluid resorption may be mediated by an increase in paracellular permeability rather than in active transepithelial transport. Previous studies of isolated perfused rat lungs using this model of hyperoxic lung injury demonstrated a clear increase in paracellular permeability as measured by the sucrose PS (4). However, the available data regarding effects of β-agonists on the paracellular permeability of normal rat lungs is contradictory (2, 21), and there are no data available regarding the effects of terbutaline on the paracellular permeability of hyperoxia-injured rat lungs. The effect of β-agonists on paracellular permeability has been postulated to occur through cAMP effects on cytoskeletal organization and tight junction function. The reduction of fluid resorption by ouabain and its prevention of the terbutaline effect in the normal and injured lungs strongly support the idea that terbutaline is acting predominantly via effects on active sodium transport and not paracellular permeability.

Our results from directly measuring alveolar fluid resorption in uninjured rats are very similar to those reported in multiple other species using different measurement techniques. Although rabbits have a very rapid basal rate of clearance, there is no further increase with terbutaline (23). Rats clear alveolar fluid nearly as rapidly as rabbits, but resorption can be stimulated further. Using ventilated live rats, Jayr et al. (11) demonstrated a 50% increase in alveolar fluid resorption with terbutaline and a 30% reduction with ouabain. Goodman et al. (9) found a 28% increase in total sodium PS with 24 µM terbutaline in the perfusate of isolated perfused rat lungs (9). Dogs and humans resorb alveolar fluid at a slower rate than rabbits or rats, but both species double their clearance rates with terbutaline (3, 19). The inhibition of the effects of terbutaline by ouabain in our experiments suggests that the mechanism involves active transport, including upregulation of Na⁺-K⁺-ATPase activity, although a concurrent effect on apical sodium channel is likely present. β-Agonists can affect bronchial tone but given the large alveolar-to-bronchial surface area ratio and the minimal change in surface area with bronchodilatation, this would be expected to have minimal effect in this system.

We were uncertain whether terbutaline would be able to accelerate fluid resorption when there is increased permeability due to injury, although several studies support our concept that fluid resorption can be stimulated. After intratracheal instillation of polyethylene glycol increased paracellular movement of mannitol in isolated perfused rat lungs, cAMP derivatives and isoproterenol augmented alveolar fluid resorption (22). In mild edema in rat lungs due to intravenous infusion of Pseudomonas bacteria, endogenous catecholamines increased alveolar fluid resorption (16). Both models had relatively mild injury without increased protein leakage into the alveolar space but support the concept that β-adrenergic agonists can stimulate fluid resorption in the face of lung injury. In sheep infused continuously with intravenous Pseudomonas bacteria for 8 h, there was an increase in extravascular lung water (17). The majority of sheep did not have significant protein leakage into the alveolar space and had accelerated alveolar fluid resorption, whereas a minority of sheep had more severe systemic and lung injury with greater extravascular lung water and could not resorb alveolar fluid. In preliminary data using an injury model of 40 h of 100% O₂ exposure of rats, terbutaline increased alveolar liquid clearance (12), again supporting the idea that pharmacological acceleration of fluid clearance is possible in the mildly to moderately injured lung.

The demonstration that terbutaline accelerates the clearance of alveolar fluid in the face of lung injury has potential therapeutic implications, especially given the prominent effect of terbutaline on fluid resorption by the human lung (19). Patients with lung injury who clear fluid more rapidly are believed to have a better prognosis (13); however, it is possible that this reflects a lesser severity of injury rather than the degree of stimulation of alveolar epithelial transport. Still, it is tempting to speculate that the use of terbutaline in patients with adult respiratory distress syndrome (ARDS) might improve survival. It is important to remember, however, that ARDS survival may be related less to lung function than to the function of other failed organs or secondary infection. Further work with large animals is needed to confirm these findings and to determine the physiological benefits of the terbutaline effect and the dose-response relationship. Other models of lung injury also should be studied, such as pressure-induced injury, to determine the generality of this effect and to determine the degree of barrier damage beyond which net fluid resorption cannot be achieved. The demonstration of physiological benefit in large animals would provide support for the study of β₂-adrenergic agonist treatment of patients with ARDS.
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