Research article
Effects of intravenous furosemide on mucociliary transport and rheological properties of patients under mechanical ventilation
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Introduction
Although mechanical ventilation (MV) is necessary to improve ventilatory support in respiratory failure, it is generally known that this procedure markedly increases the incidence of pulmonary infection and consequently the morbidity and mortality of patients. Mucociliary clearance has been reported to be impaired in patients under MV and this is probably an important underlying mechanism in the pathogenesis of pulmonary infection in these patients [1]. Mucociliary clearance has a pivotal role in the protection of the respiratory tract against inhaled noxious agents that are trapped in the blanket of mucus and transported towards the pharynx by ciliary beating or coughing. The efficiency of the mucociliary system depends not only on the integrity of the epithelium and on ciliary activity but also on the amount of mucus, the depth of the periciliary layer and the viscoelastic properties of mucus [2].

Airway epithelium is an absorptive and secretory type of epithelium [3]; the transepithelial movement of electrolytes generates osmotic gradients that are responsible for the

Abstract
The use of intravenous (IV) furosemide is common practice in patients under mechanical ventilation (MV), but its effects on respiratory mucus are largely unknown. Furosemide can affect respiratory mucus either directly through inhibition of the NaK(Cl)₂ co-transporter on the basolateral surface of airway epithelium or indirectly through increased diuresis and dehydration. We investigated the physical properties and transportability of respiratory mucus obtained from 26 patients under MV distributed in two groups, furosemide (n = 12) and control (n = 14). Mucus collection was done at 0, 1, 2, 3 and 4 hours. The rheological properties of mucus were studied with a microrheometer, and in vitro mucociliary transport (MCT) (frog palate), contact angle (CA) and cough clearance (CC) (simulated cough machine) were measured. After the administration of furosemide, MCT decreased by 17 ± 19%, 24 ± 11%, 18 ± 16% and 18 ± 13% at 1, 2, 3 and 4 hours respectively, \( P < 0.001 \) compared with control. In contrast, no significant changes were observed in the control group. The remaining parameters did not change significantly in either group. Our results support the hypothesis that IV furosemide might acutely impair MCT in patients under MV.

Keywords furosemide, mechanical ventilation, mucociliary transport, mucus rheology
secretion or absorption of water. Pulmonary epithelial ion transport systems are important in the modulation of the ionic content and volume of periciliary fluid, which in turn modulates the physical properties and transportability of mucus. Small changes in the depth of periciliary fluid could greatly alter the efficiency of interaction between mucus and cilia [4]. Diuretics with an action on ionic channels present in the airway epithelium can alter ionic movement and change the physical properties and transportability of mucus. For instance, inhaling amiloride, a diuretic with action on the apical Na⁺ channel, has been reported to increase mucociliary clearance and alter the physical properties of mucus in patients with cystic fibrosis [5–8].

Intravenous (IV) furosemide is frequently used in patients under MV with the aim of equilibrating a cumulative positive fluid balance. However, the possible effects of IV furosemide on respiratory mucus are largely ignored. Furosemide is a potent diuretic that acts by inhibiting the NaK(Cl)₂ co-transporter in the ascending limb of the loop of Henle. Besides its renal action, furosemide can also affect epithelial ion transport in the airway. Earlier studies demonstrated that furosemide inhibits the NaK(Cl)₂ co-transporter in canine airway epithelium [9] and also decreases intracellular Cl⁻ activity in cultured human airway epithelium [10]. The effects of inhaled furosemide have also been investigated. Inhaled furosemide prevents exercise-induced bronchoconstriction in asthmatic patients [11]. Hasani et al. [12] reported that inhaled furosemide had no effects on mucociliary clearance in humans. However, the primary site of furosemide action is the basolateral membrane of the airway, where it inhibits the NaK(Cl)₂ co-transporter. Therefore, the effects of the drug on the respiratory epithelium might depend on the route of administration. The aim of the present study was to investigate the effects of IV furosemide on the transportability and rheological properties of mucus in patients under MV.

Materials and methods

Patients

We studied 26 patients under MV in the Respiratory Intensive Care Unit of the Pulmonary Division, Hospital das Clínicas, University of São Paulo. The study was approved by the Ethics Committee of the University of São Paulo. All patients were clinically and haemodynamically stable for at least 24 hours before the study. In each of these patients we registered their clinical data, including arterial pressure, heart rate, fluid balance, urine output and temperature, during the 24 hours before and during the study. We also registered the mode of MV, tidal volume, respiratory rate, minute volume, fraction of inspired oxygen and system of humidification. The time interval between the initiation of MV and the study was also recorded.

The patients were distributed in two groups: the furosemide group consisted of 12 patients (8 female and 4 male) who received IV furosemide; the control group consisted of 14 patients (3 female and 11 male) who did not receive any diuretic during the study. Their ages (means ± SD) in the furosemide and control groups were, respectively, 66 ± 15 years with a range of 30–82 years, and 49 ± 20 years with a range of 20–76 years. The indication and dose of furosemide were determined by each patient’s clinical conditions and in all cases were because of a positive fluid balance. The aim of including a control group was to make sure that there were no time-dependent changes in the variables analysed. When recruiting patients for the control group, our main goal was to match them in terms of the MV parameters.

Collection of mucus

Respiratory mucus was collected from the endotracheal tube by sterile technique with a suction catheter. The samples were extracted from the catheter with a sterile needle and were immediately immersed in mineral oil to prevent mucus dehydration. The suction conditions were kept to a minimum to decrease the degree of shear thinning and the incorporation of air bubbles [13]. Mucus samples were stored at −70°C in sealed plastic containers for later analysis.

We collected mucus at 0, 1, 2, 3 and 4 hours. The first sample (0 hours) in the furosemide group was just before the administration of the diuretic.

Mucus analysis

Mucus transportability by cilia

Mucociliary transport (MCT) was determined in vitro in the frog palate preparation, which possesses an epithelium that is similar to that in the upper airways in humans [14]. All animals were cared for in compliance with the Guide for Care and Use of Laboratory Animals published by the National Institutes of Health (NIH publication 85-23, revised 1985). To deplete the palate mucus, the palate was stored for 2 days at 4°C in a humidified chamber covered with plastic wrap [15]. Ciliary activity is maintained under these experimental conditions. The frog mucus was collected and used as a control for measurements of transport rate. Measurements of transport rate were determined with a stereomicroscope (Zeiss) equipped with a reticulated eyepiece. We timed the displacement of the mucus samples across a segment between the anterior and posterior parts of the palate. During the experiments the palate was kept at ambient temperature (20–25°C) and 100% humidity, provided by ultrasonic nebulization [13,16]. The results were expressed as relative transport velocity and corresponded to the ratio of velocity of the test mucus sample to that of the control frog mucus.

Contact angle (CA)

Respiratory mucus is a complex material that possesses both rheological properties, which are directly involved in the transportability of mucus, and physical properties such as wettability, which is an important property in the interaction between the mucus and the respiratory epithelial surface. Wettability is the tendency of a biological fluid to spread when deposited
on a solid plane surface owing to the interaction between the surface and the molecules of the mucus. The degree of wet-
tability is determined by the contact angle between the
tangent to the liquid–air interface and the horizontal at the
triple point where the three phases meet [17].

CA was determined by an eyepiece that had a goniometer
with a scale of 0° to 180°. Mucus samples were placed on a
plate pretreated with sulphochromic acid to remove electrical
charges, which interfered with measurements. During the
experiments a water bath kept at 37°C allowed humidification
to prevent the dehydration of mucus [13,16].

Mucus transportability by cough
Cough clearance (CC) experiments were performed in vitro in
a simulated cough machine adapted from King et al. [18]. This
machine consisted of a cylinder of compressed air serving as
gas supply, a solenoid valve that controlled the release of gas,
and a cylindrical acrylic tube 4 mm in internal diameter and
133 mm in length as a model trachea. Mucus was introduced
into the tube and connected to the simulated cough machine.
The solenoid valve released the air for 0.5 s under a pressure
of 280 kPa. Clearance was quantified by determining the dis-
placement of mucus in millimetres [13,16].

Rheological properties
The rheological properties of mucus samples were deter-
mined in the present study with a magnetic microrheometer
as described by King and Macklem [19] and modified by Sil-
veira et al. [20]. The microrheometer measured the displace-
ment, resulting from a sinusoidal oscillating magnetic field, of
a small steel ball inserted in the mucus sample. The motion of
the ball was opposed by viscous and elastic forces.

The plexiglass container with the drop of mucus sample and
the steel ball was placed into the gap of a magnetic toroid
that was mounted on the stage of a projecting microscope
and driven by a sine-wave generator. The shadow of the ball
was projected onto two photocells that captured its oscilla-
tory movement and provided an electrical output in proportion
to the displacement of the moving ball. The toroid current and
the output of the photocells were transmitted to a digital
oscilloscope connected to an IBM-compatible personal com-
puter for storage and off-line processing [13,16].

Measurements were made at two different frequencies:
1 radian/s (ciliary movement) and 100 radians/s (cough) [21].
Two parameters were obtained: first, the relation between
stress and strain, representing the overall impedance of the
mucus (G*), and second, the phase lag between stress and
strain, representing the ratio between viscosity and elasticity
(tan δ).

Statistical analysis
Statistical analysis was performed by profile analysis [13],
which takes into account time correlation between different
sampling times (0, 1, 2, 3 and 4 hours). This is a multivariate
method in which only one statistical model is applied. This
method considers the group along the time and basic
hypotheses can be tested enabling post hoc corrections to
be performed through contrasts so as to identify, or discrimi-
nate, significant differences. Basic hypotheses are the follow-
ing: H$_{01}$, in which there is no interaction between the factors
group and time (parallelism); H$_{02}$, in which there is no differ-
ence between the use of either control or furosemide group
(coincidence); and H$_{03}$, in which there is no time effect.

When H$_{01}$ was accepted, hypotheses H$_{02}$ and H$_{03}$ were
tested. When H$_{01}$ was rejected, hypotheses H$_{02}$ and H$_{03}$
were not tested and post hoc corrections for multiple com-
parisons were performed through contrasts.

P < 0.05 was considered statistically significant.

Results
Demographic and MV parameters are described in Tables 1
and 2. The time lag between the initiation of MV and the
study was 9 ± 6 and 9 ± 6 days for the furosemide and
control groups, respectively (P = 0.9). In the furosemide
group, two patients were using the heat and moisture
exchanger (HME), and 10 were using the heated humidifier.
In the control group, six patients were using the HME and
eight were using the heated humidifier.

The results of mucus transportability in the frog palate (MCT)
and cough (CC) are presented in Figs 1 and 2, respectively.
MCT decreased significantly after furosemide administration
and did not recover to baseline values by 4 hours
(P = 0.0001). In contrast, MCT remained constant in the
control group (Fig. 1). There was a trend that did not reach
statistical significance for a decrease in CC in the furosemide
group (Fig. 2).

The results of the remaining parameters, contact angle, log G*
and tan δ measured at 1 and 100 radians/s, are presented in
Table 3. There were no significant differences between groups.

Discussion
To our knowledge this is the first study to investigate the
effects of IV furosemide on mucus transportability in vitro and
the physical properties of mucus from patients under MV. Our
results suggest that IV furosemide might acutely impair MCT
for up to 4 hours after administration.

The mucociliary escalator of the lungs is an important protec-
tive transport system by means of which inhaled particles and
microorganisms are removed from the tracheobronchial
system. Lung mucociliary clearance is influenced by several
factors, including the integrity of the ciliated epithelium and
the thickness and physical properties of the periciliary or
mucous layer [12]. Under normal circumstances, active ion
transport in the respiratory epithelium is important in the pro-
duction and regulation of the volume and composition of the respiratory tract secretion, which in turn is important for adequate mucociliary interaction [22]. Pharmacological interference in ionic transport is caused by a new class of drugs that can change MCT. For instance, inhalation of amiloride increases MCT in patients with cystic fibrosis by inhibiting the active absorption of salt and water from airway surfaces [23,24].

The effects of furosemide on the respiratory epithelium have attracted interest in the decade since Bianco et al. [11] reported that inhaled furosemide prevents exercise-induced bronchoconstriction in asthmatic patients. The mechanism of this protective effect remains to be established. The effects of inhaled furosemide on mucociliary clearance have been investigated and the results are controversial. Hasani et al. [12] reported that nebulized furosemide does not affect mucociliary clearance measured with a radioaerosol technique in healthy and asthmatic subjects. It must be stressed that the primary site of furosemide action is the basolateral membrane of the airway, where it inhibits the NaK(Cl)2 co-transporter. Inhaled furosemide might therefore not reach the basolateral membrane of airway epithelial cells in vivo [11,25]. In fact, experimental studies have demonstrated that, in contrast with the serosal application of furosemide, mucosal application has no effect on co-transporter function [26]. Winters and Yeates [27] have reported an increase in lung mucociliary clearance in vivo after the inhalation of aerosolized furosemide and the IV administration of furosemide in dogs and baboons. However, in this study the

<table>
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<tr>
<th>Sex</th>
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<th>Diagnosis</th>
<th>Mode</th>
<th>FIo2 (%)</th>
<th>VE (L/min)</th>
<th>Vasoactive drugs</th>
<th>Tracheal secretion</th>
<th>Fluid balance (ml)</th>
<th>Diuresis (ml)</th>
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<td>Dobutamine, Dopamine</td>
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<td>Lung neoplasm, COPD, acute renal insufficiency</td>
<td>PS</td>
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<td>+183</td>
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<td>Drug intoxication, pneumonia</td>
<td>PC/SIMV</td>
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<td>7.7</td>
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<td>S. aureus</td>
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<td>–98</td>
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<td>8.3</td>
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<td>PC/SIMV</td>
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<td>Noradrenaline</td>
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<td>–59</td>
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<td>Mean</td>
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<td></td>
<td>±4</td>
<td>±1.7</td>
<td></td>
<td></td>
<td>±1169</td>
<td>±212</td>
</tr>
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</table>

Abbreviations: AMV, assisted mechanical ventilation; COPD, chronic obstructive pulmonary disease; FIo2, fraction of inspired oxygen; PC, pressure-controlled ventilation; PS, pressure-support ventilation; SIMV, synchronized intermittent mandatory ventilation; VAPS, volume-assured pressure support, VE, minute volume. *P < 0.05.
properties and in vitro transportability of mucus were not determined.

In our study we observed a decrease in MCT after furosemide administration that did not recover to the baseline by 4 hours. Furosemide inhibits the NaK(Cl)\textsubscript{2} co-transporter, which is one of the physiological mechanisms involved in the respiratory hydration of mucus; its inhibition could therefore interfere in the rheological properties of mucus [4,28]. The ionic concentration of Na\textsuperscript{+} and Cl\textsuperscript{2–} in mucus can also influence the rheology and transportability of mucus independently of its total water content [6,29]. In addition, diuresis might lead to systemic dehydration and impairment of mucociliary clearance [30,31]. In our study, furosemide administration was a clinical decision based on cumulative positive fluid balance and determined by the medical staff. Interestingly, the furosemide and control groups had similar fluid balance in the 24 hours before the onset of the study. As expected, furosemide promoted increased diuresis. It must be stressed that in our study the patients were not monitored invasively. Fluid balance, diureses and haemodynamic status can give only gross estimates of fluid balance. In summary, from this study it is not possible to determine the mechanism involved in the effects of furosemide on MCT.

The mode of humidification was not uniform between the groups. Nakagawa et al. [13] have recently compared the effects of two systems of humidification (HME with a Pall BB 100 F, and a heated humidifier) on respiratory mucus and its transportability in patients under MV. The effects were evaluated for up to 72 hours of MV. They observed a decrease in CC in the HME group only after 72 hours of MV. Because the present study was limited to an intervention in a short period (4 hours), baseline clinical conditions, including age, MV parameters and the mode of humidification, probably did not influence the results. Indeed, our control group showed no time-dependent changes in all parameters studied. Infection also affects respiratory mucous and epithelium. However, the occurrence of pulmonary infection was similar in both groups (10 patients in the control group and 9 in the furosemide group), suggesting that this factor did not influence our results.

Table 2

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Mode</th>
<th>F\textsubscript{O2} (%)</th>
<th>V\textsubscript{E} (L/min)</th>
<th>Vasoactive Drugs</th>
<th>Tracheal secretion</th>
<th>Fluid balance (ml)</th>
<th>Diuresis (ml)</th>
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<td>Dobutamine</td>
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</table>

Mean 66.2 ±SD ±14.7

Abbreviations: AC, assist/control ventilation; AMV, assisted mechanical ventilation; CMV, controlled mechanical ventilation; COPD, chronic obstructive pulmonary disease; F\textsubscript{O2}, fraction of inspired oxygen; PC, pressure-controlled ventilation; PE, pulmonary embolism; SIMV, synchronized intermittent mandatory ventilation; CPAP, continuous positive airway pressure; VAPS, volume-assured pressure support, V\textsubscript{E}, minute volume.

*P < 0.05.
In our study, impairment in MCT was not matched with significant changes in other physical properties of mucus. It is possible that MCT is a more sensitive method for detecting mucociliary impairment. Because our study involved a relatively small number of patients, we cannot discard a type 2 error to explain the absence of furosemide effect on other mucus parameters. An alternative explanation is that furosemide has direct effects on the ciliary beating frequency of the frog palate.

### Table 3

**Mucus analysis (means ± SD)**

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>MCT (relative speed)</th>
<th>CA (degrees)</th>
<th>CC (mm)</th>
<th>logG*, 1 radian/s</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>F</td>
<td>C</td>
<td>F</td>
</tr>
<tr>
<td>0</td>
<td>0.83 ± 0.22</td>
<td>1.01* ± 0.21</td>
<td>44.14 ± 8.78</td>
<td>37.75 ± 8.13</td>
</tr>
<tr>
<td>1</td>
<td>0.88 ± 0.24</td>
<td>0.81 ± 0.16</td>
<td>45.43 ± 8.53</td>
<td>41.25 ± 10.9</td>
</tr>
<tr>
<td>2</td>
<td>0.85 ± 0.21</td>
<td>0.77 ± 0.2</td>
<td>44.93 ± 8.11</td>
<td>40.92 ± 7.8</td>
</tr>
<tr>
<td>3</td>
<td>0.88 ± 0.2</td>
<td>0.82 ± 0.22</td>
<td>45 ± 10.2</td>
<td>41.75 ± 9</td>
</tr>
<tr>
<td>4</td>
<td>0.88 ± 0.18</td>
<td>0.82 ± 0.2</td>
<td>44.29 ± 6.29</td>
<td>39.92 ± 11.4</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td></td>
<td>0.88</td>
<td></td>
<td>0.0001*</td>
</tr>
</tbody>
</table>

**logG*, 100 radians/s**

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>C</th>
<th>F</th>
<th>C</th>
<th>F</th>
<th>C</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.65 ± 0.24</td>
<td>1.61 ± 0.42</td>
<td>0.51 ± 0.12</td>
<td>0.51 ± 0.19</td>
<td>0.73 ± 0.22</td>
<td>0.84 ± 0.41</td>
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<td>1</td>
<td>1.68 ± 0.3</td>
<td>1.71 ± 0.38</td>
<td>0.57 ± 0.14</td>
<td>0.54 ± 0.25</td>
<td>0.75 ± 0.23</td>
<td>0.79 ± 0.34</td>
</tr>
<tr>
<td>2</td>
<td>1.67 ± 0.35</td>
<td>1.69 ± 0.26</td>
<td>0.49 ± 0.13</td>
<td>0.61 ± 0.26</td>
<td>0.86 ± 0.27</td>
<td>0.78 ± 0.26</td>
</tr>
<tr>
<td>3</td>
<td>1.40 ± 0.36</td>
<td>1.71 ± 0.32</td>
<td>0.47 ± 0.15</td>
<td>0.63 ± 0.36</td>
<td>0.63 ± 0.17</td>
<td>0.72 ± 0.16</td>
</tr>
<tr>
<td>4</td>
<td>1.51 ± 0.23</td>
<td>1.62 ± 0.25</td>
<td>0.6 ± 0.15</td>
<td>0.57 ± 0.14</td>
<td>0.66 ± 0.22</td>
<td>0.82 ± 0.39</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td></td>
<td>0.16</td>
<td></td>
<td>0.16</td>
<td></td>
<td>0.14</td>
</tr>
</tbody>
</table>

**tanδ, 1 radian/s**

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>C</th>
<th>F</th>
<th>C</th>
<th>F</th>
<th>C</th>
<th>F</th>
</tr>
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</tr>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>0.16</td>
<td></td>
<td>0.16</td>
<td></td>
<td></td>
<td>0.14</td>
</tr>
</tbody>
</table>

**Abbreviations:** C, control group; CA, contact angle; CC, cough clearance; F, furosemide group; MCT, mucociliary transport. *P < 0.05.
In conclusion, our preliminary results support the hypothesis that IV furosemide might acutely impair mucociliary clearance. In patients with respiratory failure and MV, many factors can potentially impair MCT, such as ventilation with a high concentration of oxygen, the activation of inflammatory mediator systems, colonization by bacteria, suction-induced lesions of the mucus membrane, infections and drugs [1]. The mechanisms and the clinical relevance of our findings remain to be established.

Competing interests
None declared.

References