Mucociliary Clearance Is Impaired in Acutely Ill Patients*

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Objective: This study aimed to investigate nasal mucociliary clearance in acutely ill patients who were clinically stable and had no airway manipulation.

Design: Prospective clinical study.

Setting: Medical ICU.

Patients and participants: Sixteen medical patients admitted to the ICU and 16 healthy subjects were studied. Patients who were receiving airway manipulation, including tracheal suctioning, nasogastric or enteral tubes, noninvasive and invasive mechanical ventilation, were excluded.

Interventions: Mucociliary clearance was evaluated by saccharine transit time (STT) measurements at ICU admission (admission) and 90 days after hospital discharge (recovery). Healthy subjects were also subjected to two measurements 90 days apart.

Measurements and results: The STT of patients was 26.4 ± 11.3 min and 17.9 ± 8.6 min at admission and recovery (p = 0.002) [mean ± SD] but did not change along the 90-day interval in healthy subjects (17.2 ± 10.2 min and 16.7 ± 10.3 min), respectively. Smokers (patients and healthy subjects) presented prolonged STT when compared to nonsmokers (p = 0.026). STT at admission correlated positively with heart rate (r = 0.560; p = 0.024) and hospital stay (r = 0.634; p = 0.008).

Conclusion: Mucociliary clearance is impaired in stable acutely ill patients with no airway manipulation and correlates with simple markers of underlying disease severity. Mucociliary dysfunction may help to explain the increased susceptibility of hospital-acquired respiratory infection in critically ill patients. (CHEST 2005; 128:2772–2777)

Key words: ICU; mucociliary transport; saccharine transit time; tobacco smoking

Abbreviation: STT = saccharine transit time

Patients in ICUs are at increased risk for upper and lower respiratory tract infections.1–3 The risk factors associated with the development of sinusitis and pneumonia in the ICU are airway manipulation, tracheal intubation, tracheostomy, mechanical ventilation, and gastric or enteral tubes.2–5 Therefore, factors that allow microorganisms to access vulnerable areas, often by bypassing or traumatizing body defense mechanisms, are major factors that predispose to nosocomial infection. However, factors that reduce the capacity to resist microbial colonization and invasion may play a significant role. For instance, the severity of the underlying disease has been quoted as a risk factor for hospital-acquired pneumonia.1

Mucociliary clearance plays a pivotal role in defense of the respiratory system, from the nose and upper airways to the lower respiratory tract. Mucociliary clearance is a basic mechanism of the airways, protecting the respiratory mucosa against inhaled particles and microorganisms by transporting them, trapped in mucus, and producing unidirectional mucus flow toward the oropharynx.6 Several factors such as acute infection and long-term smoking may interfere with mucociliary clearance.7–13 Mucociliary clearance has been previously investigated in ICU patients. Konrad et al13 showed that bronchial mucociliary clearance is impaired in patients receiving mechanical ventilation. However, the observed dysfunction may be secondary to treatment-related fac-
tors, including tracheal intubation, mechanical ventilation, and method of artificial airway humidification.

The nose has an epithelium similar to the remaining respiratory airway, and the nose is a useful tool to assess inflammatory events and other pathophysiologic mechanisms in the lower respiratory tract. Mucociliary clearance in the nose and bronchi have been correlated. Saccharine transit time (STT) is defined as the time elapsed between deposition of the saccharine in the nose and the perception of a sweet taste by the subject. STT is a simple and reliable method to determine the overall mucociliary clearance. The use of nasal mucociliary clearance obviates the need for more invasive procedures such as bronchoscopy and is feasible in stable, conscious, and cooperative patients in the ICU.

Mucociliary clearance in the respiratory tract is necessary for health and normal function of the tissue, particularly in resistance to respiratory infection. We hypothesize that mucociliary clearance is primarily impaired in critically ill patients. To test this hypothesis, we determined STT at admission to the ICU and 90 days after hospital discharge in stable patients with no airway manipulation in order to exclude local factors that could directly disturb mucociliary function. We also sought to determine which factors correlate with STT in acutely ill patients, including smoking history and simple markers of disease severity.

Materials and Methods

Subjects

Patients were recruited consecutively from the ICU of Hospital Nossa Senhora da Penha (São Paulo, Brazil) during a 6-month period. All medical patients admitted to the ICU were considered for inclusion into the study. The criteria for exclusion were disturbance of consciousness, hemodynamic instability, use of vasoactive drugs, airway suctioning, use of invasive or noninvasive mechanical ventilation, presence of tracheal, gastric or enteral tube, inability to taste saccharine, and expected ICU stay < 48 h. Tobacco smoking (number of packs of cigarettes/years), diagnosis at ICU admission, respiratory infection, use of oxygen, and ICU and hospital stay were recorded. In addition, simple markers of disease severity, including heart rate, BP, and respiratory rate, were recorded. Healthy subjects enrolled into the study were members of the ICU staff. Subjects receiving long-term medication, except for contraceptives, who presented inability to taste saccharine and nasal dysfunction, including vasomotor rhinitis, chronic purulent rhinitis, allergic rhinitis (within 4 weeks before the experiments) or previous nasal surgery, were excluded. This study was approved by the local Ethical Committee and by the Ethical Committee of University of São Paulo City, São Paulo, Brazil. The study was performed according to the standards of good clinical practice. The purpose and all procedures of this study were explained to the involved subjects. Each subject gave their informed written consent according to the Declaration of Helsinki of the World Medical Association.

Measurement of Mucociliary Clearance by STT

Measurements of STT were performed between 3 PM and 5 PM to eliminate the influence of circadian and nasal rhythms. Patients and healthy subjects were seated in bed (elevation of 60°) and allowed to rest for 30 min before STT measurement. Saccharine powder, 5 mg, was deposited under visual control 2 cm inside the nonobstructed nostril. The subject was instructed to breathe through the mouth, allowed to swallow freely, and oriented to maintain a normal ventilation, avoiding deep breaths, talking, coughing, sneezing, sniffing, or eating. Patients receiving humidified nasal catheter oxygen had the delivery changed to a humidified distal tube, kept 30 cm away from the nose, 30 min before the STT measurement.

Study Design

Each patient took part in two STT measurements. The first measurement was performed within 48 h after ICU admission (admission), followed by a second measurement performed at patient’s home, 90 days after hospital discharge (recovery). Healthy subjects also took part in two measurements of STT, 90 days apart, also named admission and recovery for the sake of simplicity.

Statistical Analysis

The summary statistics are given as mean ± SD. Demographic data of patients and healthy subjects were compared by Student t test or χ² test when appropriate. Patients at hospital admission were categorized according to sex, tobacco smoking, respiratory infection, and use of oxygen, and STT results were compared by Student t test. STT values in patients and healthy subjects according to tobacco smoking and time (admission and recovery) were compared by analysis of variance for repeated measures. Pearson coefficient was applied to correlate STT at admission with age, heart rate, respiratory rate, arterial BP, pulse oximetry, ICU stay, and hospital stay. A p value of < 0.05 was considered statistically significant.

Results

Eighteen patients and 18 healthy subjects were enrolled into the study. Two patients were excluded. One patient died during ICU stay, and one patient refused the second measurement after hospital discharge. Two healthy subjects were also excluded. They presented acute upper airway infection at the time of the second measurement. Therefore, 16 patients and 16 healthy subjects were included in the statistical analysis. The group of 16 patients included 8 men and 10 smokers. The group of 16 healthy subjects included 5 men and 8 smokers. The mean age of the patients and healthy subjects was 52 ± 19 years and 32 ± 14 years, respectively (p = 0.002). Demographic data of the patients, diagnosis of ICU admission, associated illness, tobacco smoking, ICU stay, and hospital stay are presented in Table 1. All patients were clinically stable at the time of STT measurement. Mean body temperature was 36.7 ± 1°C, heart rate was 89 ± 10 beats/min, respi-
ratory rate was 18 ± 3 breaths/min, pulse oximetry was 96 ± 1%, systolic BP was 139 ± 19 mm Hg, and diastolic BP was 77 ± 10 mm Hg. Ten patients were receiving oxygen, and 4 patients presented respiratory infection.

Table 2 presents comparisons of STT in patients at admission according to sex, tobacco smoking, respiratory infection, and use of oxygen. STT of smoking patients was different from nonsmoking patients (p = 0.033). STT of patients at admission was prolonged and returned at recovery to values similar to those of healthy subjects (p = 0.002, Fig 1). Mucociliary clearance dysfunction was present at admission in both smokers and nonsmokers patients (Fig 2). STT of patients at admission did not correlate with the following variables: ICU stay (r = 0.434, p = 0.092), age (p = 0.293), respiratory rate (p = 0.950), oxygen flow (p = 0.373), systolic arterial BP (p = 0.102), and diastolic arterial BP (p = 0.998). In contrast, STT correlated positively with heart rate (r = 0.560, p = 0.024; Fig 3) and hospital stay (r = 0.634, p = 0.008; Fig 4), and negatively with pulse oximetry (r = −0.583, p = 0.018). However, the results of pulse oximetry should be interpreted with caution because 10 patients were receiving oxygen.

**DISCUSSION**

The current study shows that stable medical patients admitted into the ICU presented with significant upper airway mucociliary clearance dysfunction, which was not dependent on airway manipulation and was reversible 90 days after hospital discharge. Our data confirm previous findings of prolonged mucociliary clearance in smokers. The additional information is that mucociliary clearance dysfunction associated with acute illness is of similar magnitude as dysfunction associated with long-term smoking. Acutely ill smokers presented a twofold increase in STT when compared to healthy nonsmokers. We also found that STT at ICU admission correlated positively with simple markers of disease severity (namely heart rate and hospital stay), suggesting that mucociliary clearance dysfunction may well reflect the ongoing systemic disease.

Patients in the ICU have an increased risk of upper and lower respiratory infection.1–3 External factors are well recognized, which include airway suctioning, tracheal intubation, tracheostomy, mechanical ventilation, and nasogastric or enteral tubes.2–5 However, host factors may also play an

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**Table 1—Demographic Data, Diagnosis at ICU Admission, Associated Illness, Tobacco Smoking, ICU Stay, and Hospital Stay of Patients**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age, yr</th>
<th>Diagnosis at ICU Admission</th>
<th>Associated Illness</th>
<th>Tobacco Smoking, pack-yr</th>
<th>ICU Stay, d</th>
<th>Hospital Stay, d</th>
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<tbody>
<tr>
<td>Male</td>
<td>75</td>
<td>Congestive heart failure</td>
<td>Hypertension, diabetes mellitus</td>
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<td>9</td>
<td></td>
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<tr>
<td>Female</td>
<td>72</td>
<td>Pneumonia</td>
<td>Hypertension, COPD</td>
<td>50</td>
<td>3</td>
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<tr>
<td>Male</td>
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<td>Congestive heart failure</td>
<td>Hypertension, diabetes mellitus</td>
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<td>12</td>
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<tr>
<td>Male</td>
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<td>Hypertension, diabetes mellitus, COPD</td>
<td>7</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>42</td>
<td>Decompensated diabetes</td>
<td>Hypertension, diabetes mellitus</td>
<td>15</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Female</td>
<td>25</td>
<td>Decompensated diabetes</td>
<td>diabetes mellitus</td>
<td>2</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>55</td>
<td>Pneumonia</td>
<td>Hypertension, diabetes mellitus</td>
<td>3</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Male</td>
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<td>Hypertension, diabetes mellitus</td>
<td>13</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
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<td>Hypertension, COPD</td>
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<td>14</td>
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<tr>
<td>Male</td>
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<td>Coronary artery disease</td>
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<tr>
<td>Female</td>
<td>45</td>
<td>Decompensated diabetes</td>
<td>Diabetes mellitus</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>32</td>
<td>Pneumonia</td>
<td>COPD</td>
<td>16</td>
<td>2</td>
<td>8</td>
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<tr>
<td>Male</td>
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<td>Hypertension</td>
<td>70</td>
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<tr>
<td>Female</td>
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<td>3</td>
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<tr>
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<td>26</td>
<td>Decompensated diabetes</td>
<td>Diabetes mellitus</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Male</td>
<td>42</td>
<td>Pneumonia</td>
<td>Hypertension</td>
<td>23</td>
<td>5</td>
<td>10</td>
</tr>
</tbody>
</table>

**Table 2—STT Comparison Between Groups in Patients at ICU Admission According to Sex, Tobacco Smoking, Respiratory Infection, and Use of Oxygen**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients, No.</th>
<th>STT, min</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.613</td>
</tr>
<tr>
<td>Male</td>
<td>8</td>
<td>27.9 ± 9.4</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>8</td>
<td>24.9 ± 13.4</td>
<td></td>
</tr>
<tr>
<td>Tobacco smoking</td>
<td></td>
<td></td>
<td>0.033†</td>
</tr>
<tr>
<td>Smoker</td>
<td>6</td>
<td>18.8 ± 10.4</td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>10</td>
<td>24.9 ± 13.4</td>
<td></td>
</tr>
<tr>
<td>Respiratory infection</td>
<td></td>
<td></td>
<td>0.317</td>
</tr>
<tr>
<td>No</td>
<td>9</td>
<td>24.0 ± 14.3</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7</td>
<td>24.9 ± 13.4</td>
<td></td>
</tr>
<tr>
<td>Oxygen</td>
<td></td>
<td></td>
<td>0.373</td>
</tr>
<tr>
<td>No</td>
<td>6</td>
<td>23.0 ± 7.5</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10</td>
<td>28.4 ± 13.0</td>
<td></td>
</tr>
</tbody>
</table>

*p = 0.092, age (p = 0.293), respiratory rate (p = 0.950), oxygen flow (p = 0.373), systolic arterial BP (p = 0.102), and diastolic arterial BP (p = 0.998). In contrast, STT correlated positively with heart rate (r = 0.560, p = 0.024; Fig 3) and hospital stay (r = 0.634, p = 0.008; Fig 4), and negatively with pulse oximetry (r = −0.583, p = 0.018). However, the results of pulse oximetry should be interpreted with caution because 10 patients were receiving oxygen.

**Table 2**—STT Comparison Between Groups in Patients at ICU Admission According to Sex, Tobacco Smoking, Respiratory Infection, and Use of Oxygen

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*Data are presented as mean ± SD.
†p < 0.05.
important role but are poorly recognized. The respiratory epithelium is the first barrier to potential injury agents, and mucociliary clearance plays a pivotal role in the pulmonary defense mechanism. Konrad et al showed that patients receiving mechanical ventilation in the ICU have impaired mucus transport at the level of the main bronchus and trachea. However, the dysfunction observed may be secondary and induced by local factors, such as airway manipulation, mechanical ventilation, and artificial system of inspired air humidification. In contrast, the current study avoided and excluded all of these local factors that could induce mucociliary dysfunction. Therefore, our results extend the data previously reported by demonstrating that mucociliary dysfunction is present at ICU admission even in clinically stable patients with no airway manipulation.

The nose and tracheal mucosa share common mucociliary apparatus and similar responses to aggression. The nose has been considered a useful tool to assess inflammatory events and other pathophysiologic mechanisms in the lower respiratory tract. Furthermore, changes in nasal and bronchoalveolar lavage fluid have been associated with mucociliary dysfunction. The current study showed that mucociliary dysfunction was present at ICU admission even in clinically stable patients with no airway manipulation.

**Figure 1.** STT data of patients and healthy subjects are presented as mean ± SE. STT of patients at admission was prolonged and returned to similar values of healthy subjects at recovery (*p = 0.002).

**Figure 2.** STT data of patients and healthy subjects according to tobacco smoking at admission and recovery are presented as mean values ± SE. Smokers, patients, and healthy subjects presented with prolonged STT as compared to nonsmokers (#p = 0.026). STT was significantly prolonged in patients at admission compared to recovery (*p = 0.002). In contrast, no significant STT changes occurred in healthy subjects.

**Figure 3.** Correlation between STT and heart rate at admission. bpm = beats per minute.
chial mucociliary clearance are correlated.\textsuperscript{17} We have to acknowledge however, that mucociliary clearance was only measured at the level of the nose. Therefore, the observed mucociliary dysfunction could be a local phenomenon induced by factors such as upper respiratory tract infection\textsuperscript{12,13} or supplemental oxygen delivered by nasal catheter.\textsuperscript{14} However, we observed acute mucociliary dysfunction not only in the four patients presenting with acute respiratory infection but also in patients admitted with a variety of underlying diseases, including congestive heart failure and decompensated diabetes. Patients who were receiving oxygen delivered by a humidified nasal catheter were changed to a humidified system placed 30 cm from the nose before STT measurement. Moreover, STT was not different between patients with the two factors (infection and oxygen) present or absent (Table 2).

Mucociliary clearance may be disturbed by factors including increased mucus production, abnormal mucus rheology, abnormal ciliary activity, and loss of ciliated cells.\textsuperscript{20,21} In the present study, an overall measurement of mucociliary clearance was assessed by STT\textsuperscript{15,18} and therefore does not allow the distinction of the exact mechanism responsible for the mucociliary dysfunction. Of note, the studied patients were clinically stable and had no symptoms or signs of increased mucus production. The observation that STT correlated positively with simple markers of disease severity, namely heart rate and hospital stay, suggests that mucociliary clearance dysfunction is associated with systemic factors. We speculate that systemic inflammation and tissue mucosal hypoperfusion\textsuperscript{22,23} present even in hemodynamically stable patients could interfere with ciliary beating frequency. This hypothesis should be tested in further studies.

The STT values obtained in nonsmokers healthy subjects (approximately 11.5 min) fits nicely with that determined by Liote\textsuperscript{e}ta\textsuperscript{l}\textsuperscript{18} (approximately 13.6 min) and Ho et al\textsuperscript{24} (approximately 12.5 min). We also replicated the observation that mucociliary clearance is impaired in smokers.\textsuperscript{3,8,10,11} Long-term exposure to tobacco smoking is responsible for tracheobronchial epithelial changes associated with mucous cell and glandular hyperplasia.\textsuperscript{9,11} Agius et al\textsuperscript{10} showed a decreased nasal ciliary beat frequency as a major cause of the delayed mucociliary clearance in smokers. During general anesthesia, long-term smokers present impairment in bronchial mucociliary clearance, which is associated with a high risk for the development of postoperative atelectasis and nosocomial pneumonia.\textsuperscript{8} Smokers have increased admission into the ICU,\textsuperscript{25} they are hospitalized more frequently,\textsuperscript{26,27} and they may stay longer in the hospital\textsuperscript{28,29} than nonsmokers. Our study showed that acute illness impairs mucociliary clearance in smoking and nonsmoking subjects. The association of the two conditions (smoking and acute illness) adds up to an already impaired mucociliary clearance and raises the hypothesis that this particular group of patients would be at an increased risk of nosocomial pneumonia in ICU. To the best of our knowledge, we did not find evidence in the literature that smokers are at increased risk for nosocomial pneumonia in the nonsurgical ICU.

In conclusion, mucociliary clearance is impaired in stable acutely ill patients with no airway manipulation. Therefore, mucociliary dysfunction must be regarded as a potential mechanism to explain the increased susceptibility of hospital-acquired respiratory infection and subsequent increased morbidity and mortality in critically ill patients.

\textbf{REFERENCES}