Removal of excessive bronchial secretions by asymmetric high-frequency oscillations

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FREITAG, LUTZ, WILLIAM M. LONG, CHONG S. KIM, AND ADAM WANNER. Removal of excessive bronchial secretions by asymmetric high-frequency oscillations. J. Appl. Physiol. 67(2): 614-619, 1989. — The present study evaluated whether high-frequency oscillations (HFO) with biased flow profiles applied at the airway opening are capable of altering mucus clearance. In eight anesthetized sheep, artificial mucus (100 P) was infused continuously (1 ml/min) into the left main bronchus via a cannula inserted through the dorsal wall of the left main bronchus after thoracotomy. Outcoming mucus was collected every 10 min from the end of a cuffed orotracheal tube. Animals were ventilated with a Harvard respirator at a low frequency with superimposed HFO at 14 Hz with asymmetrical waveforms generated by a digitally controlled electromagnetic piston pump (expiratory bias: peak expiratory flow 3.8 l/s, peak inspiratory flow 1.3 l/s; inspiratory bias: reverse of expiratory bias). The influence of posture and of HFO airflow bias on mucus clearance was determined. In the horizontal position, mucus clearance with expiratory biased HFO was 3.5 ± 2 (SD) ml/10 min. Head-down tilt produced a clearance of 3.1 ± 3 ml/10 min; addition of HFO with expiratory bias increased clearance to 11.0 ± 2.0 ml/10 min (P < 0.05). No clearance occurred with inspiratory biased HFO during head-down tilt. These results indicate that expiratory biased HFO at the airway opening can clear excessive airway secretions and augment clearance by postural drainage.

MUCUS CLEARANCE IN AIRWAYS is achieved normally by a combination of factors including ciliary beating and cough. When the rate of mucus production exceeds the capacity of normal clearance mechanisms, mucus accumulates in the airways; this can impair respiratory function. Mucolectasis is a frequent complication of acute inflammatory diseases such as bronchitis, pneumonia, cystic fibrosis, and bronchiectasis (14). Additionally, prolonged artificial ventilation may depress mucociliary function and increase the susceptibility to infection. Although postural drainage, chest percussion, and breathing and coughing maneuvers are used in the treatment of excessive airway mucus (15), these techniques may be ineffective in treating patients receiving artificial ventilation.

Clinical case reports and early studies indicated that mucus clearance could be improved by using orally applied symmetric high frequency oscillations (HFO) of airflow (3, 13). Other studies could not show enhanced mucus clearance even though similar methods were used (9, 11). Because increased mucus clearance in airway models has been demonstrated to occur only when asymmetric airflow oscillations were applied (2, 5-7), the variable results of the in vivo studies may have depended on the degree of asymmetric airflow oscillations achieved within the airway. The purpose of the present study was to determine the clearance of excessive airway mucus by orally applied asymmetric HFO in an animal model. We also examined the effects of asymmetric HFO when combined with postural drainage.

MATERIALS AND METHODS

Eight healthy adult sheep (average weight 25 kg, range 23-29 kg) were anesthetized with pentobarbital sodium (30 mg/kg iv, with subsequent doses to maintain deep anesthesia) and intubated with a 10-mm cuffed orotracheal tube by using a fiber-optic bronchoscope. A Harvard respirator was used to ventilate the sheep at a frequency of 12 breaths/min with warm humidified air and supplemental O2. The tidal volume was adjusted to maintain an arterial PCO2 between 35 and 45 Torr (Radiometer, Copenhagen, Denmark). Under most experimental conditions, this required a tidal volume <250 ml. An end-expiratory pressure of 5 cmH2O was applied to prevent lung collapse after thoracotomy. Expiration was passive. A left thoracotomy was performed through the sixth intercostal space, and a 14-gauge cannula was inserted through the dorsal wall of the left main bronchus into the bronchial lumen close to the carina. The position of the cannula was confirmed with the fiber-optic bronchoscope before and after each experiment. To simulate bronchial secretions, an artificial mucus, a 1.6% solution of polyethylene oxide powder (Polyox, Union Carbide, Danbury, CT) in phosphate-buffered saline, was infused through the bronchial cannula by means of a Harvard infusion pump. The rheological properties of this artificial mucus (viscosity 100 P at a shear rate of 1 s-1 at 23°C, elastic modulus 72 dyn/cm2) were comparable to natural mucus. A preweighed flask was attached to the proximal end of the orotracheal tube in a fashion of a sidearm (Fig. 1). Outcoming mucus was collected and the volume measured periodically by weighing the flask and replacing it with a new one.

HFO were generated by an electromagnetic piston pump. The waveforms were produced by a digital step generator with an analog-to-digital converter; control of the waveform was achieved using 16 different potentiometers that allowed an independent control of frequency...
and amplitude. The wave signal of the device was amplified by a modified audio power amplifier (Grigelat model 200; 200 W RMS) and was fed into an electromagnetic-mechanical transducer (Schmidt KG model TG51). The piston head was in the form of a vaulted aluminum plate (24 cm diam) and attached to the outer cylinder (30 cm diam) via a circumferential rubber diaphragm. The vaulted aluminum plate and the curved cylinder head have the advantage of reducing both airflow turbulence and chamber capacitance (Fig. 2). At the smoothly edged opening of the cylindrical chamber, a maximum peak flow of 10 l/s could be achieved at frequencies to 20 Hz.

The oscillatory airflow was transmitted to the orotracheal tube via a short rigid tube and a screen type pneumotachograph (E. Jaeger, Wurzburg, FRG). The airflow signal from the pneumotachograph was amplified and conditioned by a Validyne modulator and displayed on a storage oscilloscope (Fig. 3). A low-frequency ventilatory airflow provided by the Harvard respirator was connected to the orotracheal tube via a T piece proximal to the pneumotachograph.

Four sheep were placed on a tilting table in the right lateral decubitus position. Another four sheep were placed in the prone position. Artificial mucus was infused at a rate of 1 ml/min and continued without interruption throughout the experiments. In each experiment, seven maneuvers each lasting 20 min were done in the following sequence: 1) HFO at 14 Hz with expiratory bias (peak expiratory flow 3.8 l/s, peak inspiratory flow 1.3 l/s) with the animals in the horizontal position, 2) expiratory biased HFO with a 15° head-down tilt, 3) a repetition of maneuver 1, 4) a repetition of maneuver 2, 5) head-down tilt without HFO, 6), a repetition of maneuver 2, and finally 7) HFO with inspiratory bias and head-down tilt. The rate of mucus clearance was measured at 10 and 20 min after beginning each of the seven maneuvers; the value obtained at the end of the second period was used for data analysis. After the experiment the sheep were killed, the bronchial system was dissected and was examined for the presence of mucus plugs. Some data points were missed because of temporarily kinked or plugged tubes. Three sheep died during maneuver 7, presumably because of complete plugging of central airways.

In preliminary studies in two horizontally positioned sheep, no clearance of artificial mucus (infused for 30–40 min) was observed during mechanical ventilation. Further attempts using this maneuver were not repeated because pooling artificial mucus compromised gas exchange. Thus, any positive clearance with HFO or tilt was considered as an improvement from mechanical ventilation alone.

Statistical analysis. Differences in mucus removal from the tracheobronchial tree were examined by two-way analysis of variance with repeated measures. Identical maneuvers, i.e., 1 and 3 and 2, 4, and 6, were averaged. The data were expressed as means ± SD. P < 0.05 was considered significant.

RESULTS

Clearance rates of infused artificial mucus measured for 10-min periods for each of the seven maneuvers in
FIG. 4. Clearance of artificial mucus under various conditions of airflow oscillation and tilt in individual animals (prone position). Each line (either solid or dashed) indicates serial data obtained in 1 sheep. Each body position was held for 20 min, and clearance rate of mucus was measured at 10-min intervals.

FIG. 5. Clearance of artificial mucus under various conditions of airflow oscillation and tilt in individual animals (right lateral decubitus position). Each line (either solid or dashed) indicates serial data obtained in 1 sheep. Each body position was held for 20 min, and clearance rate of mucus was measured at 10-min intervals.
either the prone (Fig. 4) or the right lateral decubitus (Fig. 5) position were summarized in Table 1. Because clearance rates were not different between the two body positions, the data were combined and averaged (Table 1) and are depicted in Fig. 6. After an initial 10-min infusion period, which lined the airways with artificial mucus, expiratory HFO in the horizontal position cleared mucus at a rate of 3.5 ± 2 ml/10 min (mean of 2 runs; maneuvers 1 and 3). This value was not significantly different from 15° head-down tilt without HFO (3.1 ± 3 ml/10 min). Application of expiratory biased HFO with 15° head-down tilt cleared mucus at a rate of 11 ± 2 ml/10 min (mean of 3 runs; maneuvers 2, 4, and 6). This value was significantly greater than that of head-down tilt alone and expiratory biased HFO without tilt. Applying inspiratory biased HFO in the head-down tilt position stopped mucus clearance. Mechanical ventilation alone produced expiratory flow velocities slightly less than or equal to inspiratory flow velocities. This was attributable in part to loss of expiratory force in this open-chest model. No effective mucus clearance was observed by mechanical ventilation alone with the Harvard pump; the sheep (n = 2) were in the horizontal position.

**TABLE 1. Artificial mucus output by asymmetric airflow oscillations with and without head-down tilt**

<table>
<thead>
<tr>
<th>Ventilation Maneuver</th>
<th>Position</th>
<th>HFO bias</th>
<th>Angle, degrees</th>
<th>Lateral (n = 4)</th>
<th>Prone (n = 4)</th>
<th>Mean (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Expiratory</td>
<td>0</td>
<td>1.5±3</td>
<td>4.0±1</td>
<td>2.8±3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Expiratory</td>
<td>15</td>
<td>10.5±1</td>
<td>10.0±2</td>
<td>10.3±2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Expiratory</td>
<td>0</td>
<td>5.0±2</td>
<td>3.3±1</td>
<td>4.0±2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Expiratory</td>
<td>15</td>
<td>11.2±3</td>
<td>10.5±2</td>
<td>10.9±2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 No HFO</td>
<td>15</td>
<td>1.5±2</td>
<td>4.7±2</td>
<td>3.1±3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Expiratory</td>
<td>15</td>
<td>12.0±3</td>
<td>11.8±2</td>
<td>11.9±2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 Inspiratory</td>
<td>15</td>
<td>0.0</td>
<td>0.8±1</td>
<td>0.6±1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD expressed as ml/10 min; n, no. of sheep/group. HFO, high-frequency oscillation.

**DISCUSSION**

The mechanisms by which airway secretions are cleared are complex. The ciliary escalator is usually sufficient to clear the normal amount of fluid reaching the airways by epithelial secretion, an estimated 10 ml/24 h (14). Under conditions of hypersecretion and/or impaired ciliary clearance, coughing assumes an important secondary clearance mechanism based on two-phase gas-liquid interaction (8, 10, 12). Proper conditions for such gas-liquid interaction could also exist when forced expiratory maneuvers or HFO are applied at times when mucus depth in the airway is increased (5-8). Using in vitro models, Kim et al. (5-7) identified several important factors for mucus transport by two-phase gas-liquid interaction. These include the expiratory to inspiratory airflow ratio (I/E), peak expiratory flow velocity, the rheological properties of the mucus, and mucus layer thickness. They found that two-phase transport occurs only if the mucus layer thickness exceeds a certain critical value after which transport rate rises with increasing peak expiratory flow velocity. Thus, for given rheological properties of mucus, peak expiratory flow velocity and mucus layer thickness are the most important factors affecting two-phase transport. Recent studies by Chang et al. (2) have also shown effective mucus transport in a tracheal model by using asymmetric airflow oscillations of 7-13 Hz. However, mucus clearance studies in vivo have shown variable results depending on the method of applying airflow oscillations to the airways. King et al. (3) have shown that tracheal mucus clearance increases with high-frequency chest wall compressions in the frequency range of 5-15 Hz. With orally applied HFO with symmetric wave patterns, some investigations showed enhanced mucus clearance (3), whereas others found no change or even retrograde movement of the mucus blanket (9, 11). Although a few potential mechanisms have been proposed that might affect mucus clearance under HFO, i.e., stimulation of ciliary action, alteration of mucus viscoelastic properties and biased airflow pattern, the reasons for the variable results are unclear. Furthermore the role of two-phase flow interaction in these studies is unlikely to be a significant factor because the studies were done in normal lungs in which the mucus layer thickness is extremely thin (~10 μm). However, our previous studies using fluoroscopic video imaging have demonstrated wave motion of excessive mucus in the sheep trachea during normal spontaneous breathing and effective net clearance of accumulated mucus by expiratory biased tidal breathing with E/I of 1.9 and 3.0 (1, 4). In the present study, artificial mucus was infused continuously in sheep to maintain a sufficient mucus layer thickness permitting sustained two-phase gas-liquid interactions. The present study therefore demon-
strates that HFO with expiratory biased airflow promotes mucus clearance by two-phase gas-liquid flow mechanism under conditions simulating excessive mucus in vivo. A frequency of 14 Hz was used in the present study because the oscillator could produce a relatively stable expiratory biased waveform at this frequency and because previous animal experiments have shown this to be an ideal frequency (9). Our previous in vitro studies (5-7) using normal breathing frequencies (<1 Hz) showed that mucus could be transported through a 1-cm-diam glass tube with peak expiratory flow rates ranging from 0.3 to 1.0 l/s with a peak E/I >1.2. Chang et al. (2) used HFO and an E/I of 1.5 to demonstrate effective mucus transport in a trough. Although the peak expiratory flow rate used in the present study was much higher than those of the in vitro studies, because the diameter of the sheep trachea was larger (~2 cm), the actual flow velocity was comparable with those used in vitro. The present E/I used was also in line with the previous studies.

Both expiratory biased HFO at the airway opening and head-down tilt promoted mucus transport equally well in our study. Head-down tilt (postural drainage) has been used with some success in patients with airway disease for a long time (12-15). However, our results suggest that mucus clearance can be further enhanced when postural drainage is combined with biased HFO (Figs. 4-6). It is noteworthy that our findings showing similar clearance rates between expiratory biased IIFO and postural drainage may be fortuitous because of the particular properties of the artificial mucus used. Postural drainage may not be as effective for mucus with high viscosities as biased HFO (5, 6). Thus differences between the two clearance mechanisms may have become apparent at higher mucus viscosities.

There was no significant difference in tracheal mucus clearance between the lateral decubitus and prone positions that indicates that in the lateral decubitus position the contralateral lung did not serve as a "mucus sink." The cessation of mucus clearance during inspiratory biased HFO proved that expiratory biased airflow is the dominant factor in clearing mucus. Mucus movement was unlikely to achieve steady-state flow conditions because the clearance rate in a given maneuver was affected by the previous maneuver, i.e., a fast clearance rate after a slow clearance maneuver and vice versa. Therefore, mucus output may not necessarily equal the amount infused. However, this did not invalidate our observations that asymmetrical oscillations enhance mucus clearance.

The total recovery of mucus during expiratory biased airflow was approximately two-thirds of that infused (80 ml of 120 ml). Our previous glass tube studies showed that the minimal mucus layer depth required for two-phase transport was 5-10% of the tube diameter for mucus with similar properties to the mucus used in the present study (5, 6). However, because of the uneven surface of the sheep trachea, the minimum mucus layer in vivo is much greater than that predicted by the glass tube studies. Therefore, we estimate that at least 30 ml of mucus were needed to coat the tracheal and orotracheal tube surface. Additionally, because of nonsteady-state flow condition, a substantial portion of the infused mucus could have accumulated in foci. The remaining portion of unrecoverable mucus was probably located near the distal cuff of the orotracheal tube.

With the exception of the artificial mucus residing in the airway lumen, the tracheobronchial tree of our sheep was normal. In patients with excessive mucus secretion, airway obstruction can alter the E/I peak flow ratio and the absolute peak flow velocity generated by the simple pressure device used in our experiment. For example, in the sheep receiving inspiratory biased HFO, mucus accumulated in the airways and increased the resistance such that the waveform could not be maintained. Mucus plugging of several airways caused a breakdown of the oscillatory flow signal, and pressure swings from the volume-limited Harvard respirator drove the oscillatory coil out of the center of its magnetic field. A stable oscillatory flow generator instead of an oscillatory pressure source that is dependent on the compliance and resistance of the tandem-arranged compartments would therefore be required for a clinically useful device. However, the possibility that oscillations with these relatively high flow rates, tensions, and shearing forces can cause bronchial constriction by unspecific stimulation may have to be ruled out. Additional experiments are also needed to determine the optimal frequency range and to test the effects of asymmetrical oscillations on the circulatory as well as respiratory systems.

The present study demonstrates a beneficial effect of expiratory biased airway oscillation on artificial mucus clearance in intubated sheep and suggests that similar results may be obtainable in intubated humans. Use of a mask or a mouthpiece to apply these oscillations would expand their therapeutic potential to the larger number of nonintubated patients with excessive airway secretions.

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