Ventilation Patterns Influence Airway Secretion Movement

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BACKGROUND: Retention of airway secretions is a common and serious problem in ventilated patients. Treating or avoiding secretion retention with mucus thinning, patient-positioning, airway suctioning, or chest or airway vibration or percussion may provide short-term benefit. METHODS: In a series of laboratory experiments with a test-lung system we examined the role of ventilator settings and lung-impedance on secretion retention and expulsion. Known quantities of a synthetic dye-stained mucus simulant with clinically relevant properties were injected into a transparent tube the diameter of an adult trachea and exposed to various mechanical-ventilation conditions. Mucus-simulant movement was measured with a photodensitometric technique and examined with image-analysis software. We tested 2 mucus-simulant viscosities and various peak flows, inspiratory/expiratory flow ratios, intrinsic positive end-expiratory pressures, ventilation waveforms, and impedance values. RESULTS: Ventilator settings that produced flow bias had a major effect on mucus movement. Expiratory flow bias associated with intrinsic positive end-expiratory pressure generated by elevated minute ventilation moved mucus toward the airway opening, whereas intrinsic positive end-expiratory pressure generated by increased airway resistance moved the mucus toward the lungs. Inter-lung transfer of mucus simulant occurred rapidly across the "carinal divider" between interconnected test lungs set to radically different compliances; the mucus moved out of the low-compliance lung and into the high-compliance lung. CONCLUSIONS: The movement of mucus simulant was influenced by the ventilation pattern and lung impedance. Flow bias obtained with ventilator settings may clear or embed mucus during mechanical ventilation. *Key words: airway clearance, mechanical ventilation, mucus, secretions.* [Respir Care 2008;53(10):1287–1294. © 2008 Daedalus Enterprises]

Introduction

Retention of airway secretions can present a serious clinical problem during mechanical ventilation because retained mucus narrows or occludes airways, causes breathing discomfort, and, if extensive, leads to atelectasis and gas-exchange impairment. Mucus retention can lead to mortality in chronic bronchitis.[1,2] In the acute-care setting, airway clearance of retained mucus is an acknowledged, important problem for critically ill patients,[3-6] and is associated with significantly higher mortality and morbidity.[7-10] When cough is inhibited and the mucociliary escalator is impaired by intubation, retained secretions are a sequestered growth medium for bacteria, which increases the risk of pneumonia. Though secretions in the proximal large airways are accessible to suctioning, airways beyond the 3rd generation are beyond the suction catheter's reach and must be cleared by other methods.

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There are several approaches to clearing retained secretions, but they are often only marginally or temporarily effective and frequently treat the result rather than the

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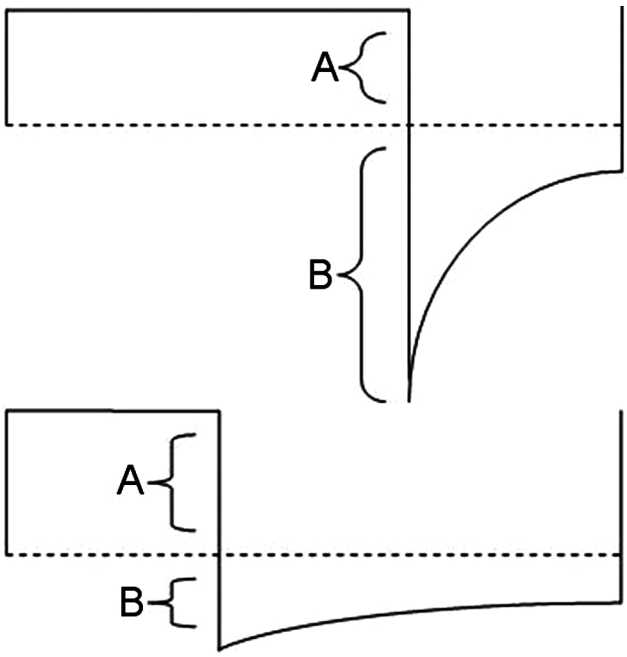

Fig. 1. Method of determining expiratory-inspiratory flow difference and ratio. The upper panel displays an example of a flow pattern that gives a positive value for the expiratory-inspiratory flow difference (ie, B – A > 0) and the expiratory-inspiratory flow ratio (B/A > 1), which would create an expiratory flow bias and therefore tend to expel mucus. In that example, intrinsic positive end-expiratory pressure is generated by the ventilator settings. The lower panel shows a flow pattern where B – A < 0 and B/A < 1, which favors mucus retention because of inspiratory flow bias and increased expiratory resistance. In that example, intrinsic positive end-expiratory pressure is generated by impedance, as in chronic obstructive pulmonary disease.

cause of secretion retention. Cough effectively clears the major airways, but cough is frequently weakened by illness, and glottis closure is prevented by endotracheal intubation. Repeated catheter suctioning risks airway damage, deoxygenation, and atelectasis.[6] High-frequency chest-wall or airway-pressure vibration has not been proven effective.[11] Bland or muco-active aerosol or direct instillation of fluid can dilute, lubricate, and thin mucus and thus help to centralize secretions.[12,13] Postural drainage is frequently prescribed to enlist the assistance of gravity in moving secretions.[14] Manual lung hyperinflation (an increased tidal volume [V_T] with a slow inspiratory flow and a fast expiratory flow) can aid secretion clearance.[15-17] Chest-wall vibration also improves expiratory flow and, therefore, secretion clearance.[18]

In airways there is a continuous "to and fro" movement of gas that affects the underlying secretion layers. Averaged over several breaths, the net volume of gas moved in either direction must be equal, but the peak or mean flow of the inspiratory and expiratory phases can differ substantially, and this "flow bias" can be toward the lungs or toward the mouth (Fig. 1). Following the lead of investigators of high-frequency oscillation,[19-22] we propose that peak airflow bias (ie, the tidal differential tendency of peak flow and its duration to favor one direction of movement) is an important factor in airway secretion movement. We investigated the effect of ventilator settings and the resulting flow bias on secretion movement.

Fig. 2. Movement of simulated mucus before (A) and after (B) applying a ventilation pattern that favors inspiratory flow (to the left). The image-analysis software colored the changed object (green mucus simulant) red. The center of mass is determined by optical densitometry. The displacement of the center of mass (CM) is the difference between CM1 and CM2. The extreme distance (ED) is the difference between ED1 and ED2. The volume displacement (difference between volume 2 and volume 1) is expressed as the percentage of volume moved in relation to the total initial volume.

Methods

Mucus Simulant

We formulated synthetic solutions with standardized viscoelastic properties similar to human mucus, according to previously described methods.[23] We dissolved either 1.5 g or 3.0 g of polyethylene oxide powder (Sentry Polyox WSR Coagulant, Dow Chemicals, Wilmington, Delaware) in 100 mL of filtered water, at 100°C. The solution thicknesses at the 2 concentrations (1.5% and 3.0%) simulated normal and thick airway mucus. We colored the mucus simulant to allow quantitative photodensitometry, described below.

Mucus-Movement Measurements

We positioned transparent tubing (inner diameter 1 cm, length 30 cm) horizontally on a light box and photographed mucus movement with a 12 megapixel camera (Nikon) fixed 1.30 m above and perpendicular to the light box (Fig. 2). Photographs of mucus simulant position were obtained before and after initiating specific ventilation patterns. We used image-analysis software (Sigmascan, Statistical Solutions, Saugus, Massachusetts) to evaluate mucus movement, by measuring the mucus area in number of pixels. A ruler was positioned next to the tubing to calibrate the area of 1 pixel in square centimeters. The product of 1 pixel area unit and the measured number of pixels gave the mucus area in cm^2. The image-analysis software can also measure the color intensity of each pixel in a

measured object. The color intensity provides an indirect measure of mucus depth. Mucus volume was estimated as the product of the average estimated depth by the corresponding mucus area.

Mucus displacement after applying specific ventilation patterns was evaluated in 3 ways: the displacement of the center of mass; the most extreme distance traveled from the point of mucus injection; and the percent volume displacement from the original center of mass. The image-analysis software calculates the center of mass by determining a central location of the "object" after multiplying all pixels by their relative intensities. The extreme distance was the most distant point of the analyzed object along the major axis of the studied object (see Fig. 2).

Study Protocol

The first stage comprised 3 experiments on the general effects of airflow and airflow bias on mucus movement. The second stage comprised 2 experiments in which we tracked mucus displacement following specific clinical ventilation scenarios. A test lung (Training and Test Lung, Michigan Instruments, Grand Rapids, Michigan) was ventilated via transparent tubing (inner diameter 1.0 cm, length 30 cm, held horizontal on the light box) with a mechanical ventilator (model 840, Puritan Bennett/Tyco, Carlsbad, California).

In each experiment, 1 mL of mucus simulant was injected into the center of the tubing and was allowed to settle for 3–5 min before taking the initial photograph. Then we connected the tubing to the mechanical ventilator. After applying a specific ventilation pattern for 5 min we took another photograph. We analyzed the photographs to assess the ventilation pattern's effect on mucus movement. In the stage-1 experiments we tested both mucus simulant concentrations. In the stage-2 experiments we used only the 1.5% mucus. After each experiment the tube was washed, air-dried, and repositioned on the light box for the next experiment. Inspiratory and expiratory flows and V_T were measured with a pneumatic sensor (NICO, Respironics, Murrysville, Pennsylvania). In experiment 2 of stage 2 we used a separate pneumatic sensor for each test-lung chamber to detect pendelluft with its respective effect on interlung mucus transfer.

Stage 1: Flow Effects and Relationships

Experiment 1-1: Mucus Displacement Flow Thresholds. This experiment was designed to identify the flow threshold required to move the mucus simulant. We used a single-lung circuit, volume-control ventilation, square-wave inspiratory flows of 5, 10, 15, 20, 40, and 60 L/min, a respiratory frequency of 12 breaths/min, and V_T of 375 mL and 750 mL. To isolate the influence of unidirectional flow, we added one-way valves and a separate expiratory limb to the circuitry.

Experiment 1-2: Effect of Peak Flow. This experiment compared the effects of mean and peak inspiratory flow, V_T, and inspiratory time (T_I) on mucus movement. We used flow-controlled, volume-cycled ventilation, a respiratory rate of 12 breaths/min, and V_T of 375 mL and 750 mL. At identical T_I, constant square-wave and decelerating inspiratory flow patterns were tested at mean flows of 20, 40, 60, and 80 L/min.

Experiment 1-3: Flow Bias. This experiment studied the relationship between inspiratory and expiratory flow and mucus displacement. We used a respiratory rate of 15 breaths/min and a V_T of 750 mL. To adjust the differences (and ratios) between the inspiratory and expiratory flows, we kept compliance constant at 0.04 L/cm H_2O) to maintain a peak expiratory flow of approximately 60 L/min, with 10 inspiratory flows from 35 L/min to 117 L/min. We report the averages of ≥ 2 measurements for each test condition.

Stage 2: Simulated Clinical Conditions

Experiment 2-1: Dynamic Hyperinflation. This experiment investigated the effects of dynamic hyperinflation (and associated intrinsic positive end-expiratory pressure [auto-PEEP]) generated by a high minute ventilation (ventilator-generated auto-PEEP) or elevated airway resistance (impedance-generated auto-PEEP). In both experiments the settings were: compliance 0.08 L/cm H_2O, V_T 1,000 mL, constant inspiratory flow 30 L/min, and $T_I = 2.00$ s. Auto-PEEP values of 7, 11, and 17 cm H_2O were induced with respiratory rates of 18, 20, and 21 breaths/min, respectively. Similar levels of impedance-generated auto-PEEP were generated at a rate of 12 breaths/min by adjusting a variable resistor.

Experiment 2-2: Inter-Lung Mucus Transfer. This experiment studied the possibility that mucus might move between lungs of different compliance under certain ventilation patterns. We tested 3 compliance combinations: one lung was set at a compliance of 0.01 L/cm H_2O and the other lung was set 0.02, 0.04, or 0.08 L/cm H_2O. The ventilator settings were: V_T 1,000 mL, respiratory rate 12 breaths/min, and T_I 0.5 s.

Statistical Analysis

In experiment 1-1, differences in response between the 2 mucus preparations were tested with repeated-measures analysis of variance with post hoc contrasts to identify

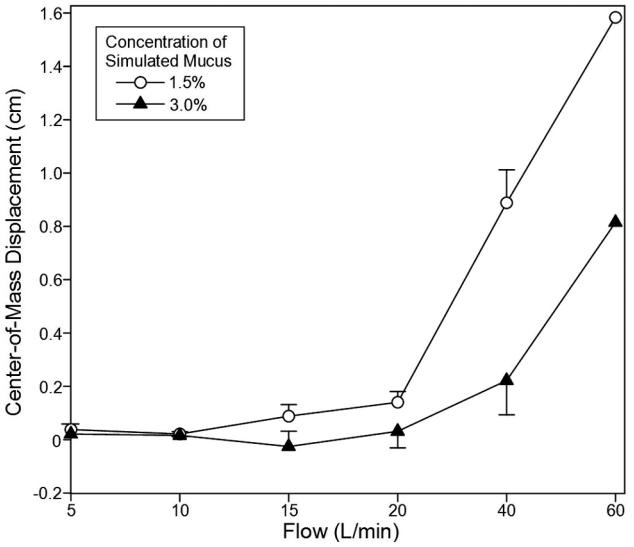

Fig. 3. Center-of-mass displacement with various flows. The 1.5% mucus simulant moved significantly more than the 3.0% mucus simulant at 40 L/min and 60 L/min ($P < .007$).

thresholds. We used univariate and multivariate linear regression analyses to study the influence of mucus thickness, inspiratory and expiratory flow, V_T, and T_I on mucus movement. For all comparisons, $P \leq .05$ was considered significant. Analysis was performed with statistics software (SPSS 12.0, SPSS, Chicago, Illinois).

Results

Validation of Photometric Method

We evaluated 190 mucus volumes (1 mL injected) via our photometric method. The mean calculated volumes before and after application of the ventilation patterns were 0.94 ± 0.02 mL and 1.03 ± 0.02 mL, respectively, which indicates that that the calculated mucus volume was well estimated by this technique.

Stage 1: Flow Effects and Relationships

Experiment 1-1: Mucus Displacement Flow Thresholds. Figure 3 suggests a mucus-movement unidirectional flow threshold of 10–20 L/min. The center-of-mass displacement of the 1.5% mucus simulant was more evident than with the 3.0% preparation ($P = .007$ for the overall difference, and $P = .013$ for the interaction between the mucus-concentration and flow factors). Compared to the 5 L/min condition, the center-of-mass mucus-displacement only occurred at $\geq$ 40 L/min with the 1.5% mucus simulant ($P < .001$) and at 60 L/min with the 3.0% preparation ($P = .007$). However, the 1.5% mucus formed waves on its surface layer with all flows $\geq$ 15 L/min. The 3.0% mucus formed waves on its surface layer with all flows $\geq$ 20 L/min. The extreme-distance and volume-displacement data show tendencies similar to the center-of-mass displacement data.

Table 1. Univariate and Multivariate Analysis of Variables Associated With Mucus Simulant Displacement as the Dependent Variable

	Univariate Analysis			Multivariate Analysis		
Variable	r	b*	*P*	r	b*	*P*
Peak flow	0.938	0.048	< .001	0.976	0.049	< .001
Mean flow	0.853	0.057	< .001	0.196	0.006	.268
T_I	–0.585	–1.241	< .001	0.011	0.008	.949
V_T	0.193	0.527	.245	0.121	0.292	.496
Waveform	0.342	0.461	.036	–0.150	–0.047	.398

* slope of the regression line
T_I = inspiratory time
V_T = tidal volume

Experiment 1-2: Effect of Peak Flow. A total of 38 measurements (4 per condition) were made of each variable: peak inspiratory flow (PIF), mean inspiratory flow, T_I, V_T, and waveform. Table 1 shows the results for the univariate and multivariate analysis with mucus center-of-mass displacement as the dependent variable. During univariate analysis, PIF, mean inspiratory flow, T_I, and waveform each correlated with mucus displacement. Multivariate analysis, however, revealed that only PIF significantly correlated with center-of-mass displacement ($r = 0.976$, $P < .001$). The strong association between PIF and mucus movement suggested that:

- After adjusting the regression model for PIF, other variables did not provide additional information to explain mucus displacement.
- On the contrary, when the regression model was preadjusted for the influence of these variables (mean inspiratory flow, T_I, V_T, and waveform), PIF always emerged as an important variable, which explains a significant portion ($P < .001$) of the residual difference in mucus movement. The extreme-distance and volume-displacement variables had a similar relationship to PIF. However, multivariate analysis showed that the center-of-mass displacement ($r^2 = 0.952$) produced the most consistent results, compared to the extreme-distance ($r^2 = 0.922$) and volume-displacement ($r^2 = 0.703$). Figure 4 illustrates the correlation curve between PIF and mucus center-of-mass displacement. Waveform effects were not identified in this experiment.

Experiment 1-3: Flow Bias. The tested expiratory/inspiratory flow ratio (E/I) range was 2.4–0.7, and the ex-

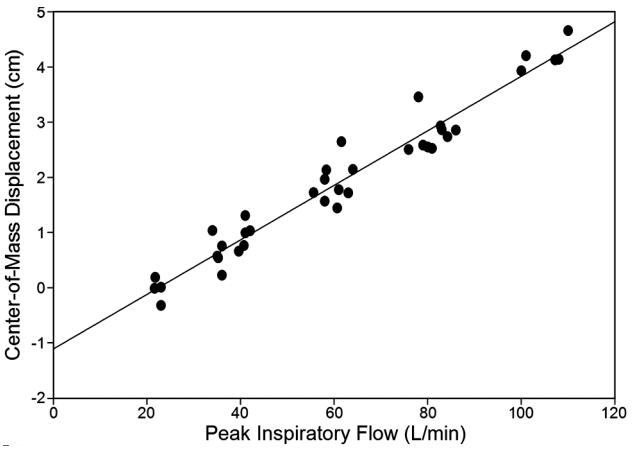

Fig. 4. The center-of-mass displacement of the mucus simulant was directly related to the inspiratory peak flow in experiment 1-2 (r = 0.94).

piratory-inspiratory flow difference (E-I) range was +50 to −45 L/min. Univariate analysis revealed that both E/I ratio ($r^2 = 0.766$, $P < .001$) and E-I difference ($r^2 = 0.845$, $P < .001$) were important correlates of mucus movement. In multivariate analysis, however, with both ratio and difference variables forced into the regression model, the E-I difference showed a stronger correlation with center-of-mass displacement (r = 0.91, $P < .001$), whereas E/I no longer correlated with mucus movement (r = 0.09, $P = .637$). Moreover, the curve-fitting analysis suggests a linear relationship between E-I difference and mucus displacement, whereas the E/I ratio plot suggests a curvilinear relationship (Fig. 5). These observations held true for both tested mucus viscosities, which suggests a slightly better behavior for the E-I difference as an explanatory variable for mucus displacement. An E-I flow difference of 17 L/min with the 1.5% mucus seems to be a threshold for mucus movement (center of mass) to change direction. Differences moved mucus toward the mouth if E-I was > 17 L/min, or toward the lungs if I-E was > 17 L/min (see Fig. 5). With the 3% mucus simulant the E-I difference threshold was slightly higher. There was also a strong interaction between flow bias and mucus thickness ($P < .001$): a smaller flow bias difference moved the thinner mucus.

Stage 2: Simulated Clinical Conditions

Experiment 2-1: Dynamic Hyperinflation. Similar levels of auto-PEEP generated in different ways (ventilator-generated or impedance-generated) produced I-E flow differences (see Figure 1). As a result, auto-PEEP caused by increasing ventilatory frequency produced an expiratory flow bias that moved mucus out of the simulated lung. In contrast, auto-PEEP generated by increasing expiratory resistance caused an inspiratory flow bias that moved mucus into the simulated lung (Table 2). In agreement with the results of experiment 1-3, a greater E-I flow difference tended to displace mucus further.

Experiment 2-2: Inter-Lung Mucus Transfer. The first compliance combination tested was 0.01 L/cm H_2O and 0.02 L/cm H_2O, which had mean observed E-I flow differences of 29 L/min with the test lung set at 0.01 L/cm H_2O and −13 L/min for the test lung set at 0.02 L/cm H_2O. The second combination was compliances of 0.01 L/cm H_2O and 0.04 L/cm H_2O, which had E-I flow differences of 27 L/min and –28 L/min, respectively. The last combination was compliances of 0.01 L/cm H_2O and 0.08 L/cm H_2O, which had observed E-I peak flow differences of 40 L/min and −45 L/min, respectively. After 5 min of ventilation the leading edge of mucus had moved

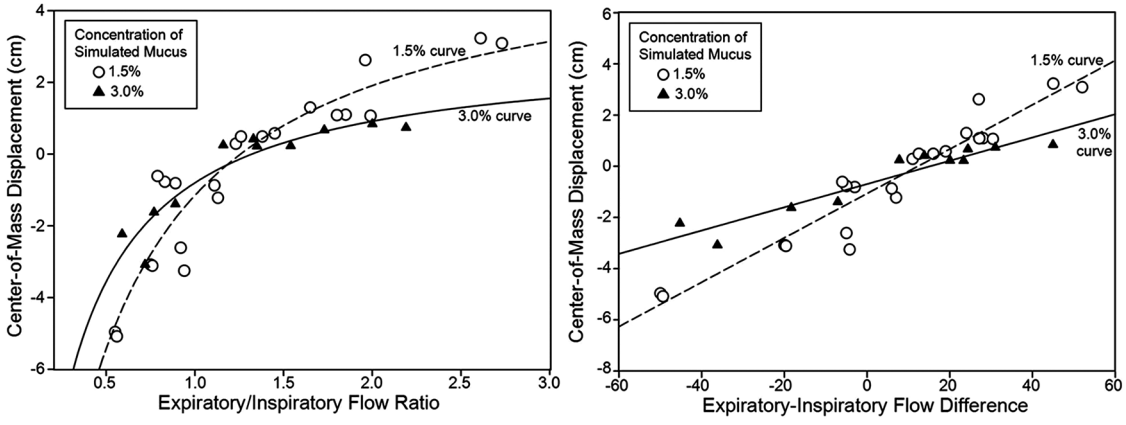

Fig. 5. Relationship of center-of-mass displacement to expiratory/inspiratory flow ratio and expiratory-inspiratory flow difference. A negative displacement indicates mucus movement toward the test lungs. Across the tested range there is a curvilinear relationship between the expiratory/inspiratory flow ratio and mucus movement, whereas the relationship between mucus movement and the expiratory-inspiratory flow difference is linear.

Table 2. Effect of Auto-PEEP on Mucus Movement*

Type of Auto-PEEP	Amount of Auto-PEEP (cmH_2O)	Flow Bias (PEF–PIF) (L/min)	Center-of-Mass Displacement (cm)	Extreme Distance (cm)	Volume (%)
Impedance-generated	8	–4	–0.8	–1.5	–47
	12	–5	–0.8	–1.1	–45
	18	–5	–0.6	–0.9	–36
Ventilator-generated	7	27	2.6	3.4	46
	11	45	3.2	5.3	61
	17	51	3.1	4.5	68

* Negative values indicate mucus movement toward the test lung.
auto-PEEP = intrinsic positive end-expiratory pressure
PEF = peak expiratory flow
PIF = peak inspiratory flow

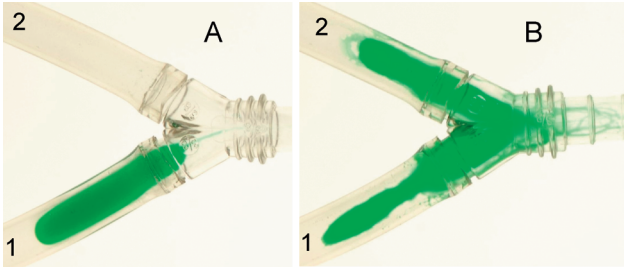

Fig. 6. Tubing circuitry primed with 1 mL of mucus simulant before (A) and after (B) 10 min of mechanical ventilation with a heterogeneous lung model. Tube segment 1 was connected to the lung chamber set to a compliance of 0.01 L/cm H_2O. Tube segment 2 was connected to the lung chamber set to a compliance of 0.08 L/cm H_2O. Ventilation transferred the mucus that was injected into the lower-compliance circuit from the lower-compliance lung to the higher-compliance lung.

from the lower-compliance lung into the higher-compliance lung in each case. As expected, E-I peak flow differences of 29, 27, and 40 L/min (bias to expel mucus) moved the mucus simulant toward the ventilator. Mucus that reached the artificial carina (Y-piece) moved into the more compliant lung with the E-I differences −13, −28, and −45 (the negative values indicate a bias to retain mucus). With greater E-I differences, the extreme distance moved further into the more compliant lung: 1.3 cm, 2.5 cm, and 3.1 cm for the 3 conditions, respectively. Figure 6 displays mucus displacement during the third compliance combination.

Discussion

Our results suggest that ventilation settings and lung impedance affect secretion mobilization. Once the flow-magnitude and phase-differential thresholds are exceeded, the relationship of tidal expiratory flow to peak inspiratory flow (factors affected by the ventilation mode, flow profile, V_T, and breathing frequency) may move mucus toward or away from the airway opening. Moreover, flow differences resulting from mechanical heterogeneity can transfer secretions between lung regions.

In intubated patients, few problems are more prevalent than secretion retention, because intubation compromises both cough ability and the mucociliary escalator.[7,24] Intubation also contaminates the lower airway with inoculates from the oropharynx.[24] Although the consequences of intubation on impaired gas exchange, increased breathing work load, and ventilator-associated pneumonia have been well recognized, the role of ventilation pattern in secretion retention has not. In selecting the ventilation mode and settings, clinicians usually target specific values for inflation pattern (PEEP and plateau pressure and/or flow profile and magnitude). Quantitatively studying secretion movement in the setting of critical illness is difficult, which partly explains why so little information on the topic is solidified. With the paucity of data for guidance, perhaps it is not surprising that clinicians seldom consider the implications of ventilator settings on secretion clearance. Yet, when viewed against the background of the existing intriguing but largely ignored experimental work, our findings strongly suggest that this subject needs a closer look.[19-22]

Our initial experiments led to predictable associations between flow-specific bias conditions and mucus movement. The lower-viscosity mucus simulant moved further than the high-viscosity mucus simulant under otherwise identical conditions, which verifies the previously reported importance of secretion viscosity.[6,13] This effect was clearly shown in the flow-threshold study (experiment 1-1, see Fig. 3) and the E-I ratio/E-I difference study (experiment 1-3, see Fig. 5). Thus, thinning secretions should encourage secretion mobility, and, logically, increasing the PIF should drive mucus deeper, and, conversely, increasing the expiratory flow (ie, under reduced-compliance conditions) should expel mucus from the airways. This might explain the impression that there are fewer secretion problems in

acute respiratory distress syndrome (ARDS), which involves low compliance and elevated expiratory flow. Retarding expiratory flow with an airway resistor has the opposite effect.

Several aspects of the present study generate provocative points of consideration regarding mucus movement in ventilated patients. As reported in previous laboratory studies, settings that invert the I-E ratio tend to produce an expiratory flow bias that directs mucus away from the lungs.[19,20] We observed that effect in experiment 1-3 (see Fig. 5). Manipulating the I-E ratio with the ventilator settings to direct mucus movement is not a common clinical practice, but the present study confirms a rationale for that strategy. The effects of induced flow bias (due to auto-PEEP) on the simulated mucus appeared to depend on the cause of the auto-PEEP. Auto-PEEP generated by elevated minute ventilation under normal impedance conditions caused flow bias that directed mucus away from the lungs (experiment 2-1, see Table 2)—an effect of induced expiratory flow bias. When expiratory resistance was imposed (as in obstructive disease) to increase auto-PEEP, mucus migrated toward the lungs—an effect of the relatively high inspiratory flow bias. That mechanism could contribute to secretion retention in patients with airway obstruction, which is a serious, common problem caused by persistent inspiratory flow bias.

To summarize, the role of auto-PEEP and expiratory flow intensity and duration may be the direct factor related to secretion expulsion, however controlled or effected. And our experiment on the potential for inter-lung mucus transfer found that mucus moved from the lower-compliance lung to the higher-compliance lung. Mucus is propelled from the lower-compliance units toward the carina because of the relatively high expiratory flow, but is then driven into the higher-compliance lung by the relatively rapid inspiratory flow to that side. We contend that inter-lung, interlobe, and intersegmental transfer of infectious materials could be accelerated by this mechanism, which might explain pneumonia propagation and/or occlusion of major airways (especially in heavily sedated or paralyzed patients).

That ventilation pattern influences secretion movement has been reported in laboratory experiments with high-frequency ventilation—a setting in which I-E ratio influences the flow direction of mucus simulant.[5] Our work confirms and extends that of Benjamin et al[19] and Kim et al,[19,20] who emphasized the importance of expiratory-to-inspiratory peak flow bias in their high-frequency-ventilation model. Undeniably important as a cofactor is the powerful gravitational effect of body positioning,[14] which was not tested in our study. Panigada and colleagues illustrated this principle convincingly in sheep.[25] Postural drainage is the central tenet of chest physiotherapy, and in the acute-care setting postural drainage is often an unintended benefit of prone positioning.[26] Recent work from Schortgen and colleagues demonstrated the potential for ventilation patterns to either reinforce or offset the fluid-mobilizing effects of adverse gravitational orientation.[27] Given that perhaps two thirds or more of ARDS cases begin on the airway side of the alveolus (ie, primary or pulmonary ARDS, as opposed to secondary or extrapulmonary ARDS[28]), it is a point of interest and concern that the low-V_T, lung-protection ventilation strategy would retain rather than expel secretions.

Limitations

Our experiment, designed as a step in establishing conceptual, qualitative principles to direct further research into an important set of clinical problems, was not undertaken to definitively answer them. The clinical relevance of our findings should be questioned on several fronts. Our simulated mucus, although previously used by others,[23] is not equivalent to real mucus, which differs and varies markedly in consistency and composition in and among patients. Our mucus simulant does not have a sol and gel layer, it does not have the same cohesion and adherence properties of pathological mucus, and it was not applied to a dynamic, corrugated, lubricated mucosal surface. Only a single tube diameter similar in overall dimension to the trachea was examined, and the behavior of our mucus simulant in a biologically branched network was not studied and should be considered a limitation, because a suction catheter can often be employed to evacuate the central airways.

Secretion movement depends on the secretions' adherence to the airway surface, the cohesiveness and stickiness of the secretions, and the forces that compete to move the secretions in one direction or the other. The shearing and propelling forces depend on overall flow rate and the diameter of the airway. Inferences drawn from our experiments with a larger-diameter tube of uniform diameter may not apply to smaller distal airways, where velocities, resistances, and pressure gradients are different. We also did not investigate the role of position, gravity, or cough on mucus movement, and those are likely cofactors in the expulsion or embedding of mucus.

Conclusions

Although we hope our work will raise awareness and stimulate interest among clinical investigators and clinicians, we are not advocating direct application of these results to the care of patients. The principles of clearance and retention developed here, however, are consistent with

the findings of prior studies of ventilation pattern and secretion movement. When considered together with physical principles and experimental reports, our data strongly suggest untapped therapeutic potential and the opportunity to avoid iatrogenesis. Well-conceived biological experiments must now be conducted to confirm or refute those possibilities.

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REFERENCES

1. Ekberg-Aronsson M, Pehrsson K, Nilsson JA, Nilsson PM, Löfdahl CG. Mortality in GOLD stages of COPD and its dependence on symptoms of chronic bronchitis. Respir Res 2005;6:98.
2. Ekberg-Aronsson M, Lofdahl K, Nilsson JA, Lofdahl CG, Nilsson PM. Hospital admission rates among men and women with symptoms of chronic bronchitis and airflow limitation corresponding to the GOLD stages of chronic obstructive pulmonary disease–a population-based study. Respir Med 2008;102(1):109-120.
3. Airway clearance: physiology, pharmacology, techniques, and practice. Respir Care 2007;52(9):1070-1238.
4. Airway clearance: physiology, pharmacology, techniques, and practice. Respir Care 2007;52(10):1239-1405.
5. Airway Clearance Techniques. Respir Care 2002;47(7):737-848.
6. Branson RD. Secretion management in the mechanically ventilated patient. Respir Care 2007;52(10):1328-1347.
7. Konrad F, Schreiber T, Brecht-Kraus D, Georgieff M. Mucociliary transport in ICU patients. Chest 1994;105(1):237-241.
8. Henke MO, Shah SA, Rubin BK. The role of airway secretions in COPD – clinical applications. COPD 2005;2(3):377-390.
9. Rogers DF. Airway mucus hypersecretion in asthma: an undervalued pathology? Curr Opin Pharmacol 2004;4(3):241-250.
10. Rogers DF. The role of secretions in COPD: pathophysiology, epidemiology and pharmacotherapeutic options. COPD 2005;2(3):341-353.
11. Chatburn RL. High-frequency assisted airway clearance. Respir Care 2007;52(9):1224-1235.
12. Rogers DF. Mucoactive agents for airway mucus hypersecretory disease. Respir Care 2007;52(9):1176-1193.
13. Nakagawa NK, Macchione M, Petrolino HM, Guimarães ET, King M, Saldiva PH, Lorenzi-Filho G. Effects of a heat and moisture exchanger and a heated humidifier on respiratory mucus in patients undergoing mechanical ventilation. Crit Care Med 2000;28(2):312-317.
14. Pryor JA. Physiotherapy for airway clearance in adults. Eur Respir J 1999;14(6):1418-1424.
15. Maxwell L, Ellis ER. The effects of three manual hyperventilation techniques on pattern of ventilation in a test lung model. Anesth Intensive Care 2002;30(3):283-288.
16. Denehy L. The use of manual hyperinflation in airway clearance. Eur Respir J 1999;14(4):958-965.
17. Savian C, Paratz J, Davies A. Comparison of the effectiveness of manual and ventilator hyperinflation at different levels of positive end-expiratory pressure in artificially ventilated and intubated intensive care patients. Heart Lung 2006;35(5):334-341.
18. McLean D, Drummond G, Macpherson C, McLaren G, Prescott R. Maximum expiratory airflow during chest physiotherapy on ventilated patients before and after the application of an abdominal binder Int Care Med 1989;15(6):396-399.
19. Benjamin RG, Chapman GA, Kim CS, Sackner MA. Removal of bronchial secretions by two-phase gas-liquid transport. Chest 1989; 95(3):658-663.
20. Kim CS, Iglesias AJ, Sackner MA. Mucus clearance by two-phase gas-liquid flow mechanism: asymmetric periodic flow model. J Appl Physiol 1987;62(3):959-971.
21. Freitag L, Long WM, Kim CS, Wanner A. Removal of excessive bronchial secretions by asymmetric high-frequency oscillations. J Appl Physiol 1989;67(2):614-619.
22. Patrinos ME, Balaraman V, Ku T, Meister J, Rubin B, Stenzler A, Easa D. Promoting meconium clearance from the lungs of a neonatal piglet with asymmetric high frequency oscillation. Paediatr Res 1997; 42(3):342-347.
23. Shah S, Fung K, Brim S, Rubin BK. An in vitro evaluation of the effectiveness of endotracheal suction catheters. Chest 2005;128(5): 3699-3704.
24. Jaber S, Amraoui J, Lefrant JY, Arich C, Cohendy R, Landreau L, et al. Clinical practice and risk factors for immediate complications of endotracheal intubation in the intensive care unit: a prospective, multiple-center study. Crit Care Med 2006;34(9):2355-2361.
25. Panigada M, Berra L, Greco G, Stylianou M, Kolobow T. Bacterial colonization of the respiratory tract following tracheal intubation-effect of gravity: an experimental study. Crit Care Med 2003;31(3): 729-737.
26. Easby J, Abraham BK, Bonner SM, Graham S. Prone ventilation following witnessed pulmonary aspiration: the effect on oxygenation. Intensive Care Med 2003;29(12):2303-2306.
27. Schortgen F, Bouadma L, Joly-Guillou ML, Ricard JD, Dreyfuss D, Saumon G. Infectious and inflammatory dissemination are affected by ventilation strategy in rats with unilateral pneumonia. Intensive Care Med 2004;30(4):693-701.
28. Gattinoni L, Pelosi P, Suter PM, Pedoto A, Vercesi P, Lissoni A. Acute respiratory distress syndrome cause by pulmonary and extrapulmonary disease: different syndromes? Am J Respir Crit Care Med 1998;158(1):3-11.