Effects of duty cycle and positive end-expiratory pressure on mucus clearance during mechanical ventilation*

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Objectives: **During mechanical ventilation, air flows may play a role in mucus transport via two-phase gas liquid flow. The aim of this study was to evaluate effects of duty cycles and positive end-expiratory pressure on mucus clearance in pigs using mechanical ventilation, and to assess their safety.**

Design: **Prospective randomized animal study.**

Setting: **Animal research facility, University of Barcelona, Spain.**

Subjects: **Eight healthy pigs.**

Interventions: **Pigs were intubated and on volume-control mechanical ventilation for up to 84 hrs. After 4, 24, 48, and 72 hrs of mechanical ventilation, six levels of duty cycle (0.26, 0.33, 0.41, 0.50, 0.60, and 0.75) with no associated positive end-expiratory pressure or 5 cm H_2O of positive end-expiratory pressure were randomly applied. Surgical bed was oriented 30 degrees in the reverse Trendelenburg position, as in the semirecumbent position.**

Measurement and Main Results: **Inspiratory and expiratory flows and hemodynamics were measured after each 30-min ventilation period. Mucus movement was assessed through fluoroscopy tracking of radio-opaque markers. Mucus velocity was described by a positive vector (toward the glottis) or negative vector (toward the lungs). No effect of positive end-expiratory pressure was found; however, as duty cycle was increasingly prolonged, a trend toward reduced velocity of mucus moving toward the lungs and increased outward mucus velocity was found ($p = .064$). Two clusters of mucus velocities were identified as duty cycle was prolonged beyond 0.41. Thus, duty cycle >0.41 increased mean expiratory–inspiratory flow bias from -4.1 ± 4.6 to 7.9 ± 5.9 L/min ($p < .0001$) and promoted outward mucus velocity from -0.22 ± 1.71 mm/min (range, -5.78 to 2.42) to 0.53 ± 1.06 mm/min (-1.91 to 3.88; $p = .0048$). Duty cycle of 0.75 resulted in intrinsic positive end-expiratory pressure (2.1 ± 1.1 cm H_2O [$p < .0001$] vs. duty cycle 0.26–0.5), with no hemodynamic compromise.**

Conclusions: **In the semirecumbent position, mucus clearance is improved with prolongation of the duty cycle. However, in clinical practice, positive findings must be balanced against the potentially adverse hemodynamic and respiratory effects. (Crit Care Med 2012; 40:895–902)**

KEY WORDS: intensive care; intrinsic positive end-expiratory pressure; mechanical ventilation; mucociliary clearance; peak expiratory flow rate; positive end-expiratory pressure

Critically ill patients often develop retention of airways secretions (1, 2). Tracheal intubation is one of the most important risk factors for impairment of mucus clearance (3). We previously demonstrated in sheep that after intubation, mucus is regularly transported by cilia toward the glottis and ultimately accumulates on the dependent tracheal regions, proximal to the endotracheal tube cuff (4). However, when the trachea is obliquely oriented, as in the semirecumbent position, the retained mucus eventually flows backward, toward the lungs.

Mucus transport also can be influenced by inspiratory and expiratory flows via a two-phase gas–liquid flow mechanism (5). Thickness of the mucus layer, inspiratory/expiratory air velocity, and viscosity of mucus are the critical factors that influence movement of mucus through flow of air (6). There is evidence that outward clearance of mucus can be achieved when expiratory flow exceeds inspiratory flow (5, 7). During mechanical ventilation, flow rates can be modified by adjusting the duty cycle (T_I/T_{TOT}) or by applying positive end-expiratory pressure (PEEP). In volume-controlled mechanical ventilation, the prolongation of T_I/T_{TOT} decreases the inspiratory flow rate,

***See also p. 1013.**

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which consequently increases the expiratory–inspiratory flow bias. Differently, PEEP can improve expiratory flow through the increase of expiratory lung volume and prevention of the premature airways closure during expiration.

The primary aim of our 84-hr study in mechanically ventilated healthy pigs positioned in a model of the semirecumbent position was to explore whether the difference between expiratory and inspiratory flow rates, generated by T_I/T_{TOT} prolongation and PEEP, can counteract effects of gravity on retained mucus and improve mucus clearance. Furthermore, safety of T_I/T_{TOT} prolongation and PEEP was studied.

MATERIALS AND METHODS

This study was conducted at the Animal Research Laboratories of the University of Barcelona, Spain. The protocol was approved by the Institutional Review Board and Ethics Committee. Animals were managed according to the National Institutes of Health guidelines for the Use and Care of Animals (8).

Animal Preparation and Handling. A detailed description of methods regarding animal preparation and handling are provided in the supplemental data (Supplemental Digital Content 2, http://links.lww.com/CCM/A351). Eight female Large White-Landrace pigs (weight, 31.5 ± 3.2 kg; range, 27–37 kg) were anesthetized, orotracheally intubated, and connected to a SERVO-i mechanical ventilator (Maquet, Wayne, NJ). Pigs were mechanically ventilated in volume-control square-wave inspiratory flow, without inspiratory pause, with tidal volume (V_T) 10 mL/kg, PEEP of 2 cm H_2O, and respiratory rate adjusted to maintain $Paco_2$ between 40 and 45 mm Hg. Inspiratory gases were conditioned to 37°C through a heated humidifier. The femoral artery was surgically cannulated and a pulmonary artery catheter was introduced through the internal jugular vein. Finally, an orogastric tube,

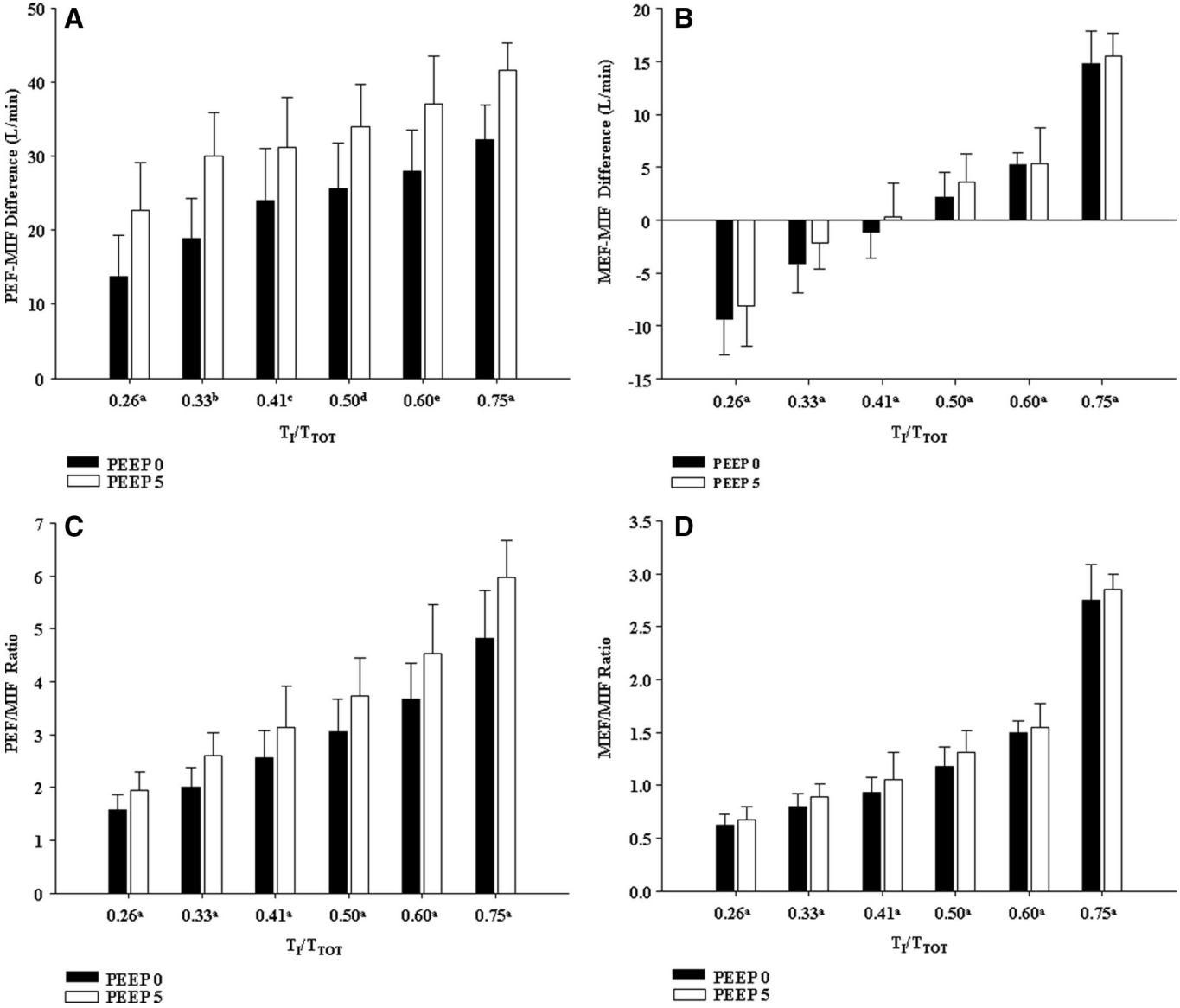

Figure 1. Expiratory–inspiratory flow bias by duty cycle (T_I/T_{TOT}) and positive end-expiratory pressure (*PEEP*). *A*, T_ITT_{TOT} ($p < .0001$) and PEEP ($p < .0001$) increased differences between peak expiratory flow (*PEF*) and mean inspiratory flow (*MIF*). *B*, T_ITT_{TOT} ($p < .0001$) and PEEP ($p < .0001$) increased differences between mean expiratory flow (*MEF*) and mean inspiratory flow (*MIF*). *C*, T_ITT_{TOT} ($p < .0001$) and PEEP ($p < .0001$) increased ratios between PEF and MIF. *D*, T_ITT_{TOT} ($p < .0001$) and PEEP ($p < .0001$) increased ratios between MEF and MIF. N = 348. [a]$p < .05$ vs. all T_ITT_{TOT}; [b]$p < .05$ vs. T_ITT_{TOT} 0.26, 0.50, 0.60, and 0.75; [c]$p < .05$ vs. T_ITT_{TOT} 0.26, 0.60, and 0.75; [d]$p < .05$ vs. T_ITT_{TOT} 0.26, 0.33, and 0.75; [e]$p < .05$ vs. T_ITT_{TOT} 0.26, 0.33, 0.41, and 0.75.

which comprises a polyurethane esophageal balloon, was introduced through the mouth of the pig. After surgical preparation, pigs were placed in the prone position, and the surgical bed was oriented approximately 30 degrees in the reverse Trendelenburg position.

Experimental Protocol. After 4, 24, 48, and 72 hrs of mechanical ventilation, pigs were paralyzed and six levels of T_IT_{TOT} of 0.26, 0.33, 0.41, 0.50, 0.60, and 0.75 (inspiratory: expiratory ratios: 1:2.9, 1:2, 1:1.4, 1:1, 1.5:1, and 3:1, respectively) with either no PEEP or 5 cm of H_2O of PEEP were randomly applied. Each ventilation period, with a given T_IT_{TOT}–PEEP, lasted approximately 30 mins. Throughout the protocol, endotracheal suctioning was performed when considered clinically indicated by audible retention of secretions or after visible translocation toward the lungs of a large accrual of mucus.

Respiratory Measurements. Airway pressure, esophageal pressure, and respiratory flow rate ($\dot{V}$) were assessed and recorded on a personal computer for subsequent analysis as previously reported (9). We calculated the difference and the ratio between peak expiratory flow and mean inspiratory flow (MIF) and between mean expiratory flow, from beginning of expiration until expiratory flow reached zero, and MIF. The static elastance of the respiratory system, static elastance of the chest wall, and static elastance of the lung, total inspiratory resistance of the respiratory system, the inspiratory air flow-resistive component, and inspiratory tissue resistances were calculated using standard formulae (9).

Hemodynamic Measurements. After assessment of pulmonary variables, gas exchange (arterial and mixed venous blood), mean arterial pressure, central venous pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure, and cardiac output were measured. Stroke volume, systemic vascular resistance, pulmonary vascular resistance, and venous admixture were computed.

Tracheal Mucus Velocity. Tracheal mucus movement was measured during each 30-min ventilation period of the daily protocol as previously reported (4, 10). Briefly, radio-opaque tantalum disks were endoscopically insufflated into the trachea. Timed serial lateral fluoroscopic images (Supplemental Fig. 1 [Supplemental Digital Content 1, http://links.lww.com/CCM/A350]) were taken to compute tracheal mucus velocity through movement of the markers. Mucus velocity per each ventilation period was averaged from velocities of all tracked markers. Disks were tracked as long as they remained in the visual field of the fluoroscope or until they consistently presented a velocity between −0.09 and 0.09 mm/min. The direction of the movement of each marker was described by a positive vector (toward the glottis) or negative vector (toward the lungs). Additionally, a number from zero (most dependent part of the trachea, i.e., ventral tracheal surface) to six (most nondependent, i.e., dorsal tracheal surface) was assigned to each tantalum disk to describe its punctual vertical position within the trachea. Analysis of effects of duty cycle and PEEP was restricted on retained mucus at the dependent parts of the trachea, because we previously demonstrated (4) that mucus lining the nondependent tracheal regions is primarily transported by cilia. During the analysis of the tracheal mucus velocities, the observers were blinded to the T_IT_{TOT}–PEEP association applied.

Statistical Analysis. Continuous variables were analyzed using a restricted maximum likelihood analysis, based on repeated measures approach, including T_IT_{TOT}, PEEP, and their interaction as factors. Each pair-wise comparison was corrected using Bonferroni's method. After duty cycle dichotomization, continuous variables were compared through either paired Student *t* test or the Wilcoxon signed rank sum test in the case of variables that were normally or not normally distributed,

Table 1. Mucus clearance analysis

	0.25–0.41 Duty Cycle	0.50–0.75 Duty Cycle	*p*
Mucus clearance analysis			
Mucus velocity (mm/min)[a]	−0.22 ± 1.71 (−5.78–2.42)	0.53 ± 1.06 (−1.91–3.88)	.0048
Incidence of mucus moving toward glottis[b] ≤48 hrs of mechanical ventilation	19/66 (28.79)	28/74 (37.84)	.2858
Incidence of mucus moving toward lungs[b] ≥48 hrs of mechanical ventilation	38/68 (55.88)	27/71 (38.03)	.0420
Respiratory air flow analysis[c]			
Inspiratory flow (L/min)	19.8 ± 4.4	10.8 ± 2.6	<.0001
PEF (L/min)	43.3 ± 7.1	43.8 ± 6.7	.2887
MEF (L/min)	15.7 ± 2.2	18.6 ± 4.4	<.0001
PEF-MIF difference (L/min)	23.5 ± 8.6	33.0 ± 7.6	<.0001
MEF-MIF difference (L/min)	−4.1 ± 4.6	7.9 ± 5.9	<.0001
PEF-MIF ratio	2.3 ± 0.7	4.3 ± 1.2	<.0001
MEF-MIF ratio	0.8 ± 0.2	1.8 ± 0.7	<.0001

MEF, mean expiratory flow; MIF, mean inspiratory flow; PEF, peak expiratory flow.

[a]Ninety-four observations (tracked disks velocity means of the 4-day study for each animal and condition) were analyzed; [b]two hundred seventy-nine categorical observations (vectors of mucus velocities toward either the glottis or the lungs for each day, animal, and condition) were analyzed. Only occurrence of mucus moving toward the lungs is reported; [c]three hundred forty-eight observations (respiratory parameters for each day, animal, and condition) were analyzed. Overall, results are means ± SD (range).

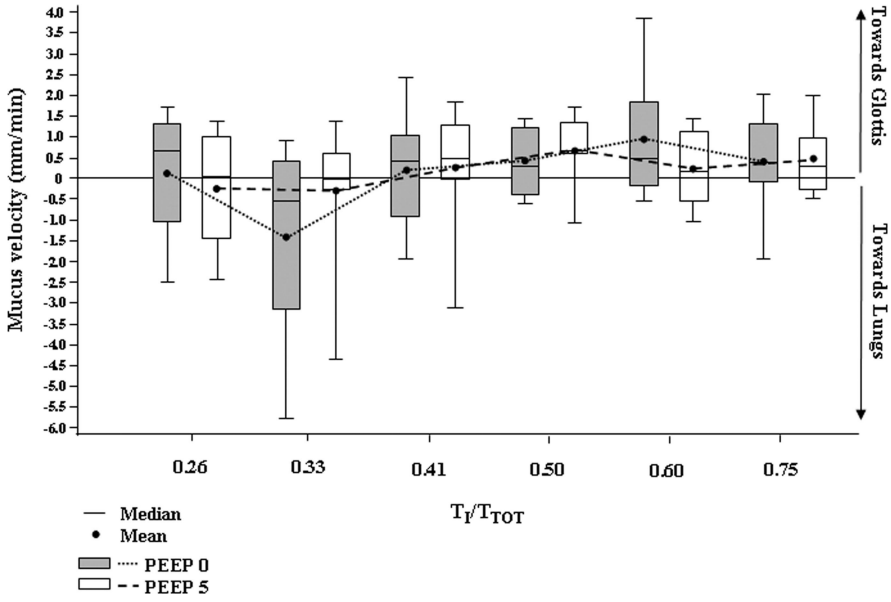

Figure 2. Tracheal mucus velocity by duty cycle (T_I/T_{TOT}) and positive end-expiratory pressure (*PEEP*). In each box plot, the median value is indicated by the center *horizontal line*, the mean is indicated by the *black dot*, and the 25th and 75th percentiles are indicated by the lower and upper box *horizontal lines*. *Whiskers* above and below the box indicate the 90th and 10th percentiles. No effect of PEEP was found ($p = .48$); however, as T_I/T_{TOT} was prolonged beyond 0.41, a trend toward improved mucus clearance was found ($p = .064$). N = 94.

respectively. Categorical variables were analyzed using Fisher exact test. Multivariate logistic regression analysis was performed to assess association between predefined variables with risks for mucus moving toward the lungs as a result of mucus hypersecretion and build-up at the proximal trachea. A two-sided $p < .05$ was considered statistically significant. All statistical analyses were performed using SAS software (version 9.2; SAS Institute, Cary, NC).

RESULTS

Six of the eight studied pigs completed the 84-hr study. Experiment using pig 1 was electively planned to last 60 hrs and pig 6 died at 64 hrs from accidental extubation. Pigs were placed on a surgical bed oriented 26.7 ± 0.8 degrees above horizontal, resulting in tracheal orientation of 19.3 ± 3.8 degrees.

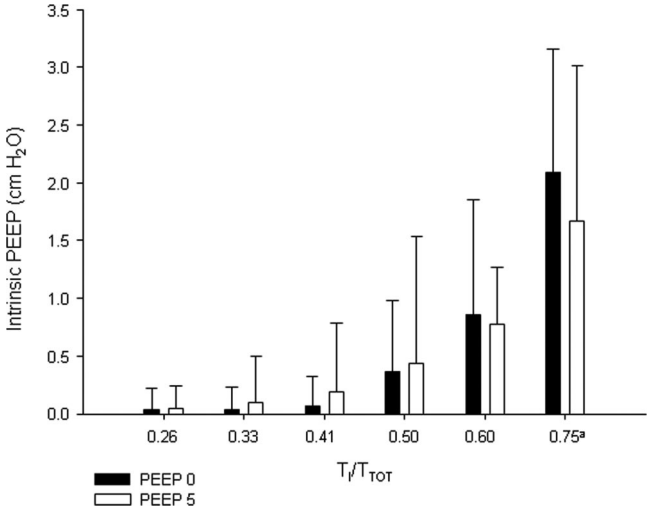

Figure 3. Effects of duty cycle (T_I/T_{TOT}) and positive end-expiratory pressure (*PEEP*) on development of intrinsic PEEP. T_IT_{TOT} progressively increased intrinsic PEEP ($p < .0001$). N = 348. [a]$p < .0001$ vs. T_IT_{TOT} 0.26–0.60.

Table 2. Multivariate analysis

	N	Odds Ratio	95% Confidence Interval	*p*
Hours of mechanical ventilation >48 hrs	252	1.910	1.156–3.192	.0192
Time since last tracheal aspiration >120 mins	252	3.886	1.986–5.691	<.0001

Efficacy Analysis: Effects of T_I/T_{TOT} and PEEP on Air Flows

The respiratory rate throughout the study was 19 ± 1 breaths per minute (range, 18–21 breaths per minute) and V_T was 322 ± 29 mL (range, 270–370 mL). The prolongation of T_I/T_{TOT} progressively decreased the inspiratory flow (Supplemental Fig. 2 [Supplemental Digital Content 3, http://links.lww.com/CCM/A352]). An increase in peak expiratory flow was found, as expected, when the expiratory lung volume increased, because to the extrinsic PEEP, or when T_I/T_{TOT} was increased to 0.75, resulting in intrinsic PEEP (Supplemental Fig. 3 [Supplemental Digital Content 4, http://links.lww.com/CCM/A353]). Similarly, a significant increase in mean expiratory flow was found when PEEP was applied and at T_I/T_{TOT} of 0.75, at which expiratory flow did not reach zero flow before the next inspiration (Supplemental Fig. 4 [Supplemental Digital Content 5, http://links.lww.com/CCM/A354] and Supplemental Fig. 5 [Supplemental Digital Content 6, http://links.lww.com/CCM/A355]). Consequently, prolongation of T_I/T_{TOT} and PEEP increased expiratory–inspiratory flow bias. Figure 1 and Table 1 depict effects of T_I/T_{TOT} and PEEP on peak expiratory flow–MIF difference (Fig. 1*A*), mean expiratory flow–MIF difference (Fig. 1*B*), peak expiratory flow-to-MIF ratio (Fig. 1*C*), and mean expiratory flow-to-MIF ratio (Fig. 1*D*).

Table 3. Effects of duty cycles and positive end-expiratory pressure on respiratory mechanics

	Duty Cycle 0.26		Duty Cycle 0.33		Duty Cycle 0.41	
	PEEP 0	PEEP 5	PEEP 0	PEEP 5	PEEP 0	PEEP 5
Respiratory rate, breaths/min	19.3 ± 0.8	19.3 ± 0.8	19.3 ± 0.8	19.3 ± 0.8	19.3 ± 0.8	19.3 ± 0.8
Esophageal pressure, cm H_2O	−0.7 ± 2.1	1.3 ± 1.6	−1.1 ± 2.1	1.1 ± 1.5	−0.4 ± 2.5	1.2 ± 1.4
Pa_{O_2}, mm Hg	175.5 ± 24.2	179.4 ± 25.0	178.0 ± 26.0	184.2 ± 15.5	173.0 ± 37.3	179.8 ± 26.1
Pa_{CO_2}, mm Hg	41.6 ± 8.6	43.3 ± 8.1	42.8 ± 9.5	44.3 ± 9.2	41.7 ± 9.2	41.9 ± 9.2
Static elastance of the respiratory system, cm H_2O/L	33.8 ± 7.2	33.3 ± 6.1	33.8 ± 7.6	33.8 ± 6.1	36.4 ± 10.0	33.8 ± 7.4
Static elastance of the lungs, cm H_2O/L	20.5 ± 7.7	20.2 ± 6.3	19.7 ± 8.7	19.5 ± 8.0	22.7 ± 10.5	21.0 ± 7.5
Static elastance of the chest wall, cm H_2O/L	12.9 ± 3.7	12.5 ± 3.3	13.6 ± 4.1	13.4 ± 4.7	13.7 ± 4.9	12.2 ± 5.0
Pulmonary shunt, %	3.4 ± 1.6	3.3 ± 2.0	3.7 ± 2.0	2.9 ± 1.5	3.2 ± 1.8	3.1 ± 1.7
Total inspiratory resistance of the respiratory system cm H_2O/L/sec	14.5 ± 5.0	13.6 ± 3.4	13.2 ± 4.1	13.2 ± 2.2	15.9 ± 9.5	15.6 ± 7.8
Inspiratory air-flow resistance, cm H_2O/L/sec	10.9 ± 3.3	10.2 ± 2.5	9.3 ± 2.5	9.0 ± 1.1	10.4 ± 6.6	10.6 ± 5.1
Inspiratory tissue resistance, cm H_2O/L/sec	3.6 ± 2.4	3.4 ± 1.8	3.9 ± 2.2	4.2 ± 1.9	5.5 ± 3.7	5.0 ± 3.4[c]

PEEP, positive end-expiratory pressure.

[a]$p < .05$ vs. duty cycle 0.26, 0.33, 0.5, and 0.6; [b]$p < .05$ vs. duty cycle 0.26, 0.4, and 0.5; [c]$p < .05$ vs. duty cycle 0.26; [d]$p < .05$ vs. duty cycle 0.26–0.41 and 0.75. Results are means ± SD.

Effects of T_I/T_{TOT} and PEEP on Mucus Transport

After insufflations, disks were placed 78.9 ± 32.0 mm distally from the tip of the tracheal tube (range, 11.4–159.6 mm). Overall, 5161 movements of 368 tantalum disks were averaged and 94 resulting mucus velocities were analyzed. Median number of disks tracked per ventilation period was 3 (range, 1–10). Mucus moved toward the glottis or the lungs or remained stationary in 55 of 94 (59%), 34 of 94 (36%), and 5 of 94 (5%) of the ventilation periods, respectively. Effects of T_I/T_{TOT} and PEEP on velocity of mucus are shown in Figure 2 (no effect of PEEP was found; $p = .48$); however, as T_I/T_{TOT} was prolonged from 0.26 to 0.75, a trend toward a reduction of velocity of mucus moving toward the lungs and an increased outward mucus velocity were found ($p = .06$). In Figure 2, two clusters of mucus velocities were identified, suggestive of a potential threshold effect on mucus clearance when T_I/T_{TOT} was prolonged beyond 0.41. Hence, as reported in Table 1, $T_I/T_{TOT} \geq 0.5$ in comparison to $T_I/T_{TOT} \leq 0.4$ generated higher expiratory flow bias, and mucus clearance was enhanced to 0.53 ± 1.06 mm/min (range, −1.91 to 3.88) from −0.21 ± 1.71 mm/min (range, −5.78 to 2.42; $p = .0048$), respectively.

The effect of duty cycles was particularly significant after prolonged mechanical ventilation. Analysis of the mucus movement direction per ventilation period after 3 days of mechanical ventilation showed a significant decrease in incidence of mucus moving toward the lungs as T_I/T_{TOT} was prolonged (Supplemental Fig. 6 [Supplemental Digital Content 7, http://links.lww.com/CCM/A356]).

Assessment of Variables Associated With Mucus Movement Toward the Lungs

As reported in Figure 3, Table 2, and Supplemental Figure 7 (Supplemental Digital Content 8, http://links.lww.com/CCM/A357), prolonged mechanical ventilation (longer than 48 hrs) and longer time since last tracheal aspiration (>120 mins) were associated with greater risk of mucus flowing toward the lungs. Overall, a tracheal aspiration was performed every 158 ± 89 mins. No differences in time from last tracheal aspiration was found for tested levels of T_I/T_{TOT} ($p = .85$) and PEEP ($p = .69$).

Safety Analysis: Effects of T_I/T_{TOT} and PEEP on Pulmonary Mechanics

Table 3 summarizes data on respiratory mechanics. Prolongation of T_I/T_{TOT} generated auto-PEEP, as reported in Figure 4. In particular, T_I/T_{TOT} of 0.75 caused the highest intrinsic PEEP (2.1 ± 1.1 cm H_2O [$p < .0001$] vs. T_I/T_{TOT} 0.26–0.5). Both intrinsic and extrinsic PEEP caused a significant increase in esophageal pressure. When PEEP was applied, static elastance of the respiratory system

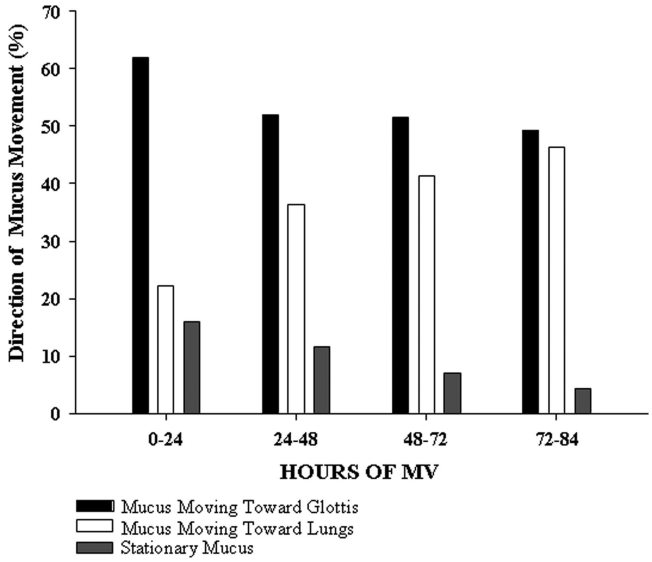

Figure 4. Distribution of frequency (%) of mucus movement measurements directed toward the glottis or the lungs or stationary by hours of mechanical ventilation (*MV*; 0–24, 24–48, 48–72, and 72–84 hrs). N = 279. $p = .0511$.

Table 3.—*Continued*

Duty Cycle 0.50		Duty Cycle 0.60		Duty Cycle 0.75		*p*		
PEEP 0	PEEP 5	PEEP 0	PEEP 5	PEEP 0	PEEP 5	Effect Duty Cycle	Effect PEEP	Effect Duty Cycle*PEEP
19.3 ± 0.8	19.3 ± 0.8	19.2 ± 0.9	19.3 ± 0.8	19.3 ± 0.8	19.3 ± 0.8	.3743	.2860	.3660
−0.3 ± 2.2	1.4 ± 1.9	−0.9 ± 1.8	1.1 ± 1.7	0.2 ± 2.2[a]	1.9 ± 1.8[a]	**.0033**	**<.0001**	.8140
174.9 ± 33.2	183.3 ± 21.2	177.8 ± 26.2	174.8 ± 29.5	181.9 ± 22.4	176.4 ± 35.7	.5567	.1087	**.0258**
41.5 ± 7.8	43.5 ± 10.0	42.4 ± 8.6	43.4 ± 10.0	42.2 ± 9.3	42.9 ± 9.1	.1129	**.0013**	.6354
36.5 ± 9.3	34.0 ± 7.4	34.2 ± 8.2	34.9 ± 7.4	33.2 ± 6.8	34.5 ± 6.7	.1313	**.0280**	**.0337**
22.4 ± 10.6	19.9 ± 7.5	19.6 ± 7.0	22.3 ± 7.4	19.3 ± 7.7	21.0 ± 5.9	.1682	.1332	.1133
13.8 ± 3.6	13.4 ± 3.8	14.3 ± 3.9	12.4 ± 4.4	13.2 ± 6.6	12.9 ± 3.6	.7646	**.0258**	.7670
3.8 ± 2.4	3.0 ± 1.7	3.2 ± 1.3	3.7 ± 2.9	3.2 ± 1.9	3.5 ± 3.9	.6726	.6557	.1197
17.7 ± 10.5	14.0 ± 3.2	14.9 ± 4.8	14.9 ± 4.4	15.4 ± 4.7	16.5 ± 4.6	**.0392**	.1094	.1725
11.9 ± 9.9	9.0 ± 2.6	8.4 ± 3.4	8.3 ± 2.3	7.8 ± 2.1[b]	8.2 ± 1.6[b]	**.0005**	.1359	.2988
5.8 ± 3.4[c]	5.0 ± 1.9[c]	6.3 ± 3.7[d]	6.6 ± 4.1[d]	8.0 ± 4.4[a]	8.3 ± 4.4[a]	**<.0001**	.4130	.8355

Table 4. Effects of duty cycles and positive end-expiratory pressure on hemodynamic data

	Duty Cycle 0.26		Duty Cycle 0.33		Duty Cycle 0.41	
	PEEP 0	PEEP 5	PEEP 0	PEEP 5	PEEP 0	PEEP 5
Heart rate, beats/min	74.3 ± 25.2	84.7 ± 39.2	87.7 ± 38.4	91.1 ± 38.6	75.8 ± 24.7	83.5 ± 37.3
Mean arterial pressure, mm Hg	88.7 ± 20.7	80.1 ± 21.8	84.5 ± 21.0	78.1 ± 17.0	80.7 ± 19.7	82.2 ± 19.3
Mean pulmonary arterial pressure, mm Hg	14.9 ± 4.4	17.5 ± 3.6	16.2 ± 5.4	17.9 ± 4.0	15.1 ± 4.3	17.6 ± 5.0
Central venous pressure, mm Hg	4.9 ± 4.4	4.9 ± 3.4	4.9 ± 4.2	4.8 ± 3.1	4.2 ± 3.4	5.4 ± 3.6
Pulmonary capillary wedge, mm Hg	6.0 ± 3.9	7.1 ± 3.8	5.8 ± 3.8	7.2 ± 3.5	5.9 ± 3.9	7.5 ± 3.7
Cardiac output, L/min	2.6 ± 1.1	2.7 ± 1.0	2.8 ± 1.0	3.0 ± 1.1	2.5 ± 0.8	2.7 ± 0.9
Stroke volume, mL	36.2 ± 11.6	34.8 ± 10.6	35.5 ± 11.3	34.3 ± 13.8	35.3 ± 9.9	36.1 ± 12.0
Systemic vascular resistance, dynes*sec/cm^5	2967.7 ± 1712.0	2614.7 ± 1506.5	2719.1 ± 1765.0	2166.6 ± 897.2	2712.8 ± 1250.4	2581.3 ± 1310.7
Pulmonary vascular resistance, dynes*sec/cm^5	307.38 ± 160.8	334.3 ± 108.9	312.9 ± 234.5	311.5 ± 83.9	313.9 ± 125.0	310.0 ± 91.0

PEEP, positive end-expiratory pressure.

[a]$p < .05$ vs. duty cycle 0.26; [b]$p < .05$ vs. duty cycle 0.26–0.6; [c]$p < .05$ vs. duty cycle 0.26 and 0.33. Results are means ± SD. Italicized values indicate significance.

significantly decreased ($p = .028$ vs. PEEP 0), but mainly because of a decrease in static elastance of the chest wall. As T_IT_{TOT} was prolonged, we observed a significant decrease in inspiratory air-flow resistance ($p = .0005$); conversely, tissue resistance increased ($p < .0001$). This led to a resulting increase in total resistance of the respiratory system ($p = .0392$).

Effects of T_I/T_{TOT} and PEEP on Hemodynamic Measurements

Overall, four ventilation periods, in which T_IT_{TOT} was set at 0.26, 0.33, 0.41, and 0.50, could not be completed for severe hemodynamic instability when PEEP 5 was applied. Table 4 depicts effects of T_I/T_{TOT} and PEEP on hemodynamic data. Intrinsic PEEP caused by prolongation of the duty cycle did not cause hemodynamic compromise, but it progressively increased mean pulmonary artery pressure and pulmonary capillary wedge pressure. Conversely, extrinsic PEEP did cause a decrease in mean arterial pressure and increase in mean pulmonary artery pressure and pulmonary capillary wedge pressure.

DISCUSSION

The main finding of our study is the demonstration that after tracheal intubation and prolonged mechanical ventilation, mucus that accumulates at the proximal trachea is affected by inspiratory and expiratory air flows. To the best of our knowledge, the importance of achieving expiratory flow biases through adjustment of the ventilator settings has never been considered, particularly when trachea is oriented above horizontal, as in the semirecumbent position. Our findings suggest that during mechanical ventilation inspiratory flow plays a role in mucus retention, and setting the T_IT_{TOT} to achieve an expiratory flow bias can potentially prevent mucus retention.

Efficacy Analysis

In tracheally intubated patients, the mucociliary velocity is 80% slower than normal (1). Data from animal experimentation report similar results (3, 10). Additionally, when mucus reaches the proximal trachea, it cannot be cleared because of the mechanical blockage formed by the inflated endotracheal tube cuff. Previous *in vitro* studies (7, 11) and animal studies (5) have demonstrated that retained mucus can be transported by air flows via a two-phase gas–liquid flow. Such mechanism could be critical to counteract effects of gravity when the trachea is obliquely oriented, as in the semirecumbent position, and mucus transport depends on the balance between the gravitational force and airflow shear forces exerted against the mucus layer. *In vitro* studies (6, 12, 11) have shown that during the respiratory cycle, mucus velocity is associated with the gas density, air flow velocity, and mucus viscosity. Importantly, if the expiratory air velocity increases beyond the inspiratory air velocity, as when T_IT_{TOT} is prolonged, mucus moves outward.

In our current study, mucus was cleared through T_IT_{TOT} prolongation beyond 0.41, which generated, on average, peak and mean expiratory–inspiratory flow biases of 33.0 ± 7.6 L/min and 7.9 ± 5.9 L/min, respectively. Expiratory flow rate also increased when extrinsic PEEP was applied or when intrinsic PEEP developed. However, PEEP did not influence mucus transport. A few studies have assessed effects of PEEP as a strategy to promote movement of mucus, specifically in cystic fibrosis patients (13–15). Most likely, in our animal model, the minor PEEP-related increase of expiratory flow was not sufficient to affect tracheal mucus movement against gravity. However, these findings should not be extended to the smaller peripheral airways in which the velocity of air is drastically decreased and PEEP may exert additional benefits preventing premature airways closure and prolonging interaction between the air flow and the mucus layer. Importantly, higher levels of PEEP are often applied in critically ill patients; hence, further studies are warranted to assess whether PEEP higher than 5 cm H_2O may affect mucus clearance.

Interestingly, we did not find a clear linear relationship between air flows and resulting mucus velocities, because several confounding factors may have affected our results. First, mucus movement is governed by air flow and gravity forces only when a critical mucus thickness is achieved. In comparison to previous studies (5, 6, 11, 12) in which artificial mucus was provided, mucus production varies greatly *in vivo*. In our studies, during the first days of mechanical ventilation, when airways were not covered by thick mucus, speed of mucus likely depended on ciliary function. Conversely, in the last days of the study, the more mucus accumulated at the proximal trachea, without being aspirated the greater the effects of air flow and gravity on mucus movement. Importantly, we found higher risks for mucus moving to-

Table 4.—*Continued*

Duty Cycle 0.50		Duty Cycle 0.60		Duty Cycle 0.75		*p*		
PEEP 0	PEEP 5	PEEP 0	PEEP 5	PEEP 0	PEEP 5	Effect Duty Cycle	Effect PEEP	Effect Duty Cycle*PEEP
81.0 ± 29.3	88.6 ± 42.7	79.1 ± 26.7	86.3 ± 32.7	87.6 ± 45.1	94.4 ± 35.8	.0700	*.0022*	.8929
85.5 ± 25.5	84.6 ± 21.5	85.9 ± 22.0	82.2 ± 21.9	80.5 ± 17.8	78.4 ± 21.4	.1570	*.0050*	.5092
17.0 ± 4.9	18.1 ± 4.4	16.5 ± 4.4[a]	19.1 ± 4.0[a]	18.0 ± 4.9[b]	19.5 ± 4.3[b]	*<.0001*	*<.0001*	.4260
5.2 ± 4.4	6.0 ± 3.5	5.0 ± 3.5	5.4 ± 3.2	4.9 ± 3.6	5.5 ± 3.1	.1155	.0545	.2501
6.5 ± 3.6	7.4 ± 3.4	7.0 ± 4.3	7.8 ± 3.7	6.8 ± 3.9[c]	7.9 ± 3.4[c]	*.0006*	*<.0001*	.9032
2.5 ± 0.7	2.7 ± 1.0	2.6 ± 0.8	2.7 ± 0.9	2.9 ± 1.7	2.9 ± 1.5	.0585	.0364	.7576
34.6 ± 11.3	35.1 ± 11.3	35.4 ± 10.7	32.9 ± 10.2	36.0 ± 13.3	33.4 ± 15.4	.6004	.2090	.7012
2722.6 ± 1170.3	2695.2 ± 1471.5	2597.1 ± 1081.2	2529.3 ± 1323.6	2466.9 ± 1348.5	2355.6 ± 1213.4	.2551	*.0039*	.3103
326.9 ± 108.0	330.1 ± 95.4	311.7 ± 96.6	351.8 ± 85.7	322.8 ± 125.0	350.9 ± 100.5	.8437	.2983	.8862

ward the lungs when tracheal aspiration was delayed beyond 2 hrs. These findings highlight potential risks for intubated patients who are not routinely tracheally aspirated, as recommended by international guidelines (16). Second, although in our study gases were optimally conditioned, viscosity may have changed throughout the 84-hr study, ultimately affecting mucus transport by two-phase gas–liquid flow.

To put these findings in perspective for the practicing physician, several important points should be addressed. First, in clinical practice, the same range of expiratory–inspiratory flow biases could be reproduced through modulation of V_T, respiratory rate, inspiratory rise time, and inspiratory pause time. To date, studies *in vitro* (7, 11) of volume-control ventilation have not found significant effects of inspiratory rise time, V_T, and respiratory rate on mucus clearance; however, these findings need further *in vivo* evidence. Also, heating and humidification of inspired gases play a primary role in mucus clearance via air flows. In our studies, we used a heated humidifier set at 37°C and a thermally insulated inspiratory circuit. Nevertheless, in clinical settings heat and moisture exchangers are often applied. To the best of our knowledge, only one study (17) of mechanically ventilated patients compared the effects of these devices on mucus transportability by cough; using a heat and moisture exchanger, after 72 hrs of mechanical ventilation less cough transportability was found. Our studies were conducted in healthy pigs, and this influenced mucus production and expiratory flow rates. In patients with acute lung injury, mucus production is drastically increased; thus, air flow could potentially affect movement of retained mucus from the very beginning of mechanical ventilation. Additionally, because passive expiratory flow rate depends on the elastic recoil and resistances of the respiratory system, in acute lung injury patients comparable effects on mucus movement could be generated at much lower T_IT_{TOT} or V_T because increased lung elastance is a distinctive feature of acute lung injury. Finally, our studies were conducted in sedated and paralyzed animals; therefore, our findings could not entirely apply to patients able to modulate the expiratory flow.

The outcomes of backward flow of mucus toward the lungs are yet to be assessed in intubated patients. Nevertheless, in previous animal studies (4) we found a significant association between mucus movement toward the lungs and pneumonia.

Safety Analysis

The prolongation of T_IT_{TOT} up to 0.75 induced intrinsic PEEP and a consequent slight increase in the esophageal pressure. However, similar to previous studies (5), the pressure transmitted by the intrinsic PEEP to the juxtacardiac space caused an increase in mean pulmonary artery pressure and pulmonary capillary wedge pressure but did not cause hemodynamic instability. The decrease in inspiratory flow rate was associated with a reduction of the inspiratory air flow resistances. However, the total inspiratory resistances of the respiratory system increased because of a sharp increase of the visco-elastic resistances, as expected (18, 19).

Similar to the effects of intrinsic PEEP, when PEEP was applied esophageal pressure increased significantly, but with a resulting significant reduction in mean arterial pressure. Nevertheless, cardiac output was ultimately maintained via a homeostatic response, characterized by the increase of heart rate and decrease of systemic vascular resistance. Importantly, throughout the study only four steps could not be completed for hemodynamic instability when PEEP was applied.

CONCLUSIONS

In conclusion, our results provide proof of a principle that after tracheal intubation, adjusting the T_IT_{TOT} to increase expiratory–inspiratory flow bias can improve mucus clearance and partially counteract effects of gravitational force on the accrued mucus. In particular, duty cycle <0.5 increases risk of mucus retention and abnormal flow of mucus toward the lungs. Mucus clearance through air flow is particularly effective during prolonged mechanical ventilation and when mucus is retained because of delayed tracheal aspiration. Importantly, no effects of PEEP on mucus clearance are evident; however, in healthy pigs, PEEP of 5 cm H_2O significantly impairs the hemodynamic status.

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