Higher Levels of Spontaneous Breathing Induce Lung Recruitment and Reduce Global Stress/Strain in Experimental Lung Injury

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ABSTRACT

Background: Spontaneous breathing (SB) in the early phase of the acute respiratory distress syndrome is controversial. Biphasic positive airway pressure/airway pressure release ventilation (BIPAP/APRV) is commonly used, but the level of SB necessary to maximize potential beneficial effects is unknown.

Methods: Experimental acute respiratory distress syndrome was induced by saline lung lavage in anesthetized and mechanically ventilated pigs (n = 12). By using a Latin square and crossover design, animals were ventilated with BIPAP/APRV at four different levels of SB in total minute ventilation (60 min each): (1) 0% (BIPAP/APRV$_{0\%}$); (2) greater than 0 to 30% (BIPAP/APRV$_{>0-30\%}$); (3) greater than 30 to 60% (BIPAP/APRV$_{>30-60\%}$); and (4) greater than 60% (BIPAP/APRV$_{>60\%}$). Gas exchange, hemodynamics, and respiratory variables were measured. Lung aeration was assessed by high-resolution computed tomography. The distribution of perfusion was marked with ^{68}Ga-labeled microspheres and evaluated by positron emission tomography.

Results: The authors found that higher levels of SB during BIPAP/APRV (1) improved oxygenation; (2) decreased mean transpulmonary pressure (stress) despite increased inspiratory effort; (3) reduced nonaerated lung tissue, with minimal changes in the distribution of perfusion, resulting in decreased low aeration/perfusion zones; and (4) decreased global strain (mean ± SD) (BIPAP/APRV$_{0\%}$: 1.39 ± 0.08; BIPAP/APRV$_{0-30\%}$: 1.33 ± 0.03; BIPAP/APRV$_{30-60\%}$: 1.27 ± 0.06; BIPAP/APRV$_{>60\%}$: 1.25 ± 0.04, $P < 0.05$ all *vs.* BIPAP/APRV$_{0\%}$, and BIPAP/APRV$_{>60\%}$ *vs.* BIPAP/APRV$_{0-30\%}$).

Conclusions: In a saline lung lavage model of experimental acute respiratory distress syndrome in pigs, levels of SB during BIPAP/APRV higher than currently recommended for clinical practice, that is, 10 to 30%, improve oxygenation by increasing aeration in dependent lung zones without relevant redistribution of perfusion. In presence of lung recruitment, higher levels of SB reduce global stress and strain despite an increase in inspiratory effort. (**ANESTHESIOLOGY** 2014; 120:673-82)

THE acute respiratory distress syndrome (ARDS) is characterized by major loss of aerated lung tissue.[1] Depending on the capability of lungs to redistribute pulmonary blood flow toward better-aerated lung zones, ventilation/perfusion ($\dot{V}_A / \dot{Q}$) mismatch may result, impairing gas exchange. To improve oxygenation and carbon dioxide elimination and alleviate the work of breathing in such patients, mechanical ventilation (MV) is often required. Typically, MV in patients with ARDS is delivered with lower tidal volumes (V_T) in controlled or assist-controlled modes, allowing only minimal or no inspiratory effort. As a result, collapse of dependent lung zones and a further deterioration of gas exchange may occur.[2]

What We Already Know about This Topic

- It is not clear which level of spontaneous breathing is helpful during mechanical ventilation in patients with acute respiratory distress syndrome

What This Article Tells Us That Is New

- In anesthetized pigs with moderate acute respiratory distress syndrome induced by saline lavage, higher levels of spontaneous breathing with controlled ventilation decreased the mechanical stress in lungs compared with ventilation without spontaneous breathing

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When spontaneous breathing (SB) activity is allowed during MV, the transpulmonary pressure in dependent

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lung zones may increase and recruit atelectatic lung tissue, contributing to increased aeration and perfusion in those zones.[3–5] Such effects are more likely to be achieved if SB is not supported by positive airway pressure, as for example during biphasic positive airway pressure/airway pressure release ventilation (BIPAP/APRV).[6] It has been recommended that 10 to 30% of total minute ventilation should originate from SB in patients during BIPAP/APRV to improve lung function.[7] However, the level of SB and the associated inspiratory effort needed to optimize lung tissue recruitment during BIPAP/APRV have not yet been determined. Theoretically, an inspiratory effort too low to generate sufficient transpulmonary pressure may not efficiently recruit and shift pulmonary perfusion to most dependent lung zones. However, too high levels of SB require longer times at lower airway pressures, possibly compromising the stability of lung units.

In the current work, we investigated the effects of different levels of SB during BIPAP/APRV on the regional distribution of lung perfusion and aeration using combined positron emission tomography/computed tomography (PET/CT) in a model of mild to moderate experimental ARDS in pigs. We hypothesized that during BIPAP/APRV, an increased contribution of SB to minute ventilation to levels higher than currently recommended for clinical practice (*i.e.*, >30% of total minute ventilation) could be necessary to improve oxygenation (primary endpoint), maximize lung recruitment, and effectively redistribute perfusion toward dependent lung zones.

Materials and Methods

Anesthesia and Initial Ventilator Settings

After obtaining approval from the local animal care committee (Landesdirektion Dresden, Dresden, Germany), 12 pigs weighing 26 to 40 kg were intramuscularly premedicated with midazolam (1 mg/kg) and ketamine (10 mg/kg). An ear vein was punctured and intravenous anesthesia was induced in supine position and maintained with midazolam (bolus = 0.5 to 1 mg/kg, followed by 1 to 2 mg kg^{-1} h^{-1}) and ketamine (bolus = 3 to 4 mg/kg, followed by 10 to 18 mg kg^{-1} h^{-1}), whereas paralysis was achieved with atracurium (bolus = 3 to 4 mg/kg, followed by 1 to 2 mg kg^{-1} h^{-1}). The animals were intubated orotracheally with a cuffed endotracheal tube (8.0-mm internal diameter) and ventilated with a mechanical ventilator EVITA XL (Dräger Medical AG, Lübeck, Germany) in volume-controlled mode with the following settings: fraction of inspired oxygen of 1.0, tidal volume (V_T) of 10 ml/kg, positive end-expiratory pressure of 5 cm H$_2$0, inspiratory:expiratory (I:E) ratio of 1:1, and inspiratory airway flow (F) of 35 l/min. Respiratory rate was titrated to achieve Paco$_2$ of 35 to 45 mmHg. Intravascular volume was maintained with a crystalloid solution (E153; Serumwerk Bernburg AG, Bernburg, Germany) at a rate of 10 to 15 mg kg^{-1} h^{-1}.

Instrumentation and Measurement Devices

An indwelling catheter was inserted into the external carotid artery and the mean arterial pressure was continuously monitored with a CMS Monitor (IntelliVue Patient Monitor MP 50 Philips, Böblingen, Germany). In addition, a pulmonary artery catheter (Opticath; Abbott, Abbott Park, IL) was advanced through an introducer set placed in the external jugular vein, and the mean pulmonary artery pressure was measured with the CMS Monitor. Urine was collected with a catheter inserted into the bladder during a mini-laparotomy.

Airflow was measured using the internal sensors of the mechanical ventilator. Airway pressure (P_{aw}) was monitored using a pressure transducer (163PC01D48-PCB; Sensortechnics GmbH, Puchberg, Germany) at the endotracheal tube. An esophageal balloon catheter (Erich Jaeger, Höchberg, Germany) was connected to a pressure transducer (163PC01D48-PCB; Sensortechnics GmbH) to measure the esophageal pressure (P_{es}) and positioned as described elsewhere.[8] In brief, positive swings in both P_{es} and P_{aw} were generated applying gentle pressure to the abdomen or rib cage. The position was considered adequate if delta P_{es}/delta P_{aw} was within 10% of unity. The transpulmonary pressure (P_L) was calculated as $P_{aw} – P_{es}$. Peak and mean P_{aw}, as well as P_L, were computed ($P_{aw,peak}$, $P_{aw,mean}$, $P_{L,peak}$, and $P_{L, mean}$, respectively).

A 16-electrode belt for electrical impedance tomography (Evaluation Kit 2; Dräger Medical AG) was placed around the chest below the upper limbs.

Blood Gases and Hemodynamics

Arterial and mixed venous blood samples were analyzed using the ABL 505 (Radiometer, Copenhagen, Denmark). Oxygen saturation and hemoglobin concentration were assessed using an OSM 3 Hemoximeter (Radiometer) calibrated for porcine blood, and venous admixture $\dot{Q}_{VA} / \dot{Q}_t$ was calculated using standard formulae. Thermodilution cardiac output, mean arterial, mean pulmonary arterial, central venous, and pulmonary artery occlusion pressures were measured using the CMS Monitor.

Inspiratory Esophageal Pressure Time Product

Respiratory signals were acquired at a sample frequency of 200 Hz, using an A/D-card (NI USB-6210; National Instruments, Austin, TX) connected to a laptop. Extraction of respiratory parameters was performed off-line from 10-min recordings of airflow, P_{aw}, and P_{es}. The product of esophageal pressure *versus* time (pressure time product [PTP]) was calculated during inspiration, using the first value at the beginning of the respiratory cycle as offset. PTP was averaged throughout acquisition periods.

Distribution of Aeration

The distribution of aeration was determined with helical CT scans of the chest during end-expiratory occlusions (Biograph16 Hirez PET/CT; Siemens, Knoxville, TN). The

CT scanner was set as follows: collimation, 16×0.75 mm; pitch, 1.35; bed speed, 38.6 mm/s; voltage, 120 kV; and tube current–time product, 120 mAs. Images were reconstructed with slices of 1.0-mm thickness, yielding matrices with 512×512 pixels with a surface of 0.426×0.426 mm^2.

The region of interest was manually defined, and the trachea, main bronchi, and associated blood vessels were excluded. Regions of interest were analyzed for hyperaerated, normally aerated, poorly aerated, and nonaerated lung compartments based on a scale for attenuation described elsewhere.[9] The density of the resulting voxels, as well as total lung volume, total lung tissue mass, and total lung gas volume (TLGV), was also calculated.[9]

Distribution of Perfusion

The distribution of relative perfusion ($\dot{Q}_{rel}$) was determined using a ^{68}Ga-labeled tracer and PET scanning[10] (Biograph16 Hirez) and normalized to voxel tissue mass measured by CT (see text, Supplemental Digital Content 1, http://links.lww.com/ALN/B30).

Distribution of Normalized Aeration/Perfusion

For each voxel of the PET scan, we also calculated the ratio between aeration and $\dot{Q}_{rel}$ ($A_e / \dot{Q}_{rel}$), both normalized by their respective mean values. Aeration-dominated, perfusion-dominated, and $A_e / \dot{Q}_{rel}$-balanced compartments were arbitrarily defined as $A_e / \dot{Q}_{rel} > 5$, $A_e / \dot{Q}_{rel} < 1/5$, and $1/5 \le A_e / \dot{Q}_{rel} \le 5$, respectively.

Mean Lung Strain

Because the end-inspiratory lung gas volumes may vary cycle-by-cycle in presence of SB, the mean lung strain ($Strain_{L,mean}$) was estimated from the mean V_T, determined from the flow signal, and TLGV, measured with CT at end-expiration, as $Strain_{L,mean} = 1 + mean\ V_T/TLGV$.

Protocol for Measurements

After instrumentation, the lungs were recruited with an inspiratory pressure of 30 cm H_2O for 30 s to reset the lung history and the animals allowed to stabilize for 15 min. Then, baseline measurements were taken under volume-controlled MV (baseline 1).

Lung injury mimicking ARDS was induced by repetitive lung lavage with warm (38°C) 0.9% saline solution.[11] Lung injury was considered stable if the ratio of partial pressure of arterial oxygen to fraction of inspired oxygen remained less than 200 mmHg for at least 30 min, whereupon measurements were performed (injury).

After these measurements, the MV mode was switched to BIPAP/APRV with the following settings: fraction of inspired oxygen, 0.5; positive end-expiratory pressure, 10 cm H_2O; a driving pressure gradient amounting to $V_T \approx 6$ ml/kg; inspiratory and expiratory times to achieve I:E, 1:1; and an respiratory rate resulting in a pH range of 7.30 to 7.45. After 30 min, further measurements were performed (baseline 2).

After baseline 2, muscle paralysis was ended to resume SB. Animals were then ventilated with BIPAP/APRV at four different levels of contribution of SB to minute ventilation (60 min each, crossover design): (1) 0% (BIPAP/APRV$_{0\%}$); (2) greater than 0 to 30% (BIPAP/APRV$_{>0-30\%}$); (3) greater than 30 to 60% (BIPAP/APRV$_{>30-60\%}$); and (4) greater than 60% (BIPAP/APRV$_{>60\%}$). In each phase, the mandatory rate of BIPAP/APRV was adjusted by changing the inspiratory and the expiratory times in the same proportion, while keeping the other mechanical ventilator settings, including I:E = 1:1, constant, to minimize changes in $P_{aw,mean}$. To avoid predominance of any particular level of contribution of SB to minute ventilation, the sequences of SB levels were defined according to a specific 4×4 (therapies × animals) Latin square, as follows: sequence 1—A B C D; sequence 2—B A D C; sequence 3—C D B A; sequence 4—D C A B; A, B, C, and D, letters representing the levels of SB. Each animal was randomly assigned to one of these sequences using sealed envelopes, allowing each sequence to be selected three times.

Measurements were taken at the end of each level of contribution of SB to minute ventilation (times 1 to 4). To minimize carryover effects, a derecruitment maneuver consisting of 15 s of disconnection from the ventilator was performed before each level of SB. An intravenous bolus of 0.3 mg/kg of atracurium was given before this to suppress SB during the disconnection. The derecruitment maneuver was considered stable if the global impedance measured by electrical impedance tomography varied less than 5% during the last 5 s. After that, the electrical impedance tomography belt was removed to avoid interference with CT measurements. If level B, C, or D followed in the randomized sequence, SB was resumed within 15 min after reconnection to the ventilator. During BIPAP/APRV$_{0\%}$ (level A), atracurium was infused at 1 to 2 mg kg^{-1} h^{-1} to suppress SB. Infusion rates of midazolam and ketamine remained unchanged. In addition, a period of 15 min of ventilation was allowed to match the time needed for resuming SB in levels B, C, and D. At the end of the experiments, the animals were killed with intravenous injections of thiopental (2 g) and KCl 1 M (50 ml).

Classification of Respiratory Cycles

During BIPAP/APRV, two basic types of respiratory cycles can occur, namely controlled and spontaneous cycles. A third type of respiratory cycle, the so-called "mixed cycle," may also exist if the inspiratory effort, detected as negative swings in P_{es}, occurs simultaneously with ventilator cycling from lower to higher P_{aw}. The classification of respiratory cycles was performed automatically, but checked visually by one of the investigators (N.C.).

Statistical Analyses

The sample size calculation for testing the primary hypothesis (SB during BIPAP/APRV increases the arterial partial pressure of oxygen) was based on effect estimates obtained from pilot studies, as well as our own previous data.[12] Accordingly, we

expected a sample size of 12 animals to provide the appropriate power (1-β = 0.8) to identify significant (α = 0.05) differences in oxygenation with different levels of SB, taking a mean difference of 85 ± 70 mmHg, two-tailed test and multiple comparisons (n = 6) into account (α* = 0.0083, α* Bonferroni adjusted).

Data are presented as mean ± SD, unless stated otherwise. For statistical analysis, general linear model statistics with Sidak adjustment (two-tailed; model: variable [group]; repeated measures: therapy). Correlation analysis was conducted to assess associations between variables of interest (Pearson correlation coefficient). The statistical analysis was performed with SPSS (version 15.0; SPSS Inc., Chicago, IL). Statistical significance was accepted at P value less than 0.05.

Results

Figure 1 shows tracing records of airflow, P_{aw}, and P_{es} for different levels of SB in a representative animal. There were no missing data for any of the variables investigated.

As shown in table 1, minute ventilation, mean V_T, and respiratory rate did not differ among levels of SB. However, V_T from mixed as well as spontaneous cycles increased with the level of SB. During BIPAP/APRV$_{>0–30\%}$, minute ventilation resulted mainly from mixed cycles. BIPAP/APRV with SB reduced $P_{aw,peak}$, $P_{aw,mean}$, and $P_{L,peak}$ compared with BIPAP/APRV$_{0\%}$. Furthermore, BIPAP/APRV$_{30–60\%}$ and BIPAP/APRV$_{>60\%}$ reduced $P_{aw,peak}$ and $P_{aw,mean}$ compared with BIPAP/APRV$_{>0–30\%}$, as well as $P_{L,mean}$ compared with BIPAP/APRV$_{0\%}$. In addition, PTP increased significantly with the level of SB.

As depicted in table 2, BIPAP/APRV$_{>60\%}$ yielded higher arterial partial pressure of oxygen to fraction of inspired oxygen ratio than BIPAP/APRV$_{0\%}$, whereas $\dot{Q}_{VA}/\dot{Q}_t$ and arterial partial pressure of carbon dioxide did not differ significantly among levels of SB. Mean pulmonary arterial pressure decreased during BIPAP/APRV$_{>0–30\%}$, BIPAP/APRV$_{30–60\%}$, and BIPAP/APRV$_{>60\%}$ compared with BIPAP/APRV$_{0\%}$. Other hemodynamic variables were comparable among levels of SB.

Figure 2 shows maps of aeration, aeration compartments, $\dot{Q}_{rel}$, and $A_e/\dot{Q}_{rel}$ in a representative animal.

As shown in table 3, all levels of SB increased total lung volume and TLGV compared with BIPAP/APRV$_{0\%}$, but total lung tissue mass did not differ significantly. During BIPAP/APRV$_{>60\%}$, TLGV was even higher than at other levels of SB. The analysis of aeration shown in figure 3 revealed that BIPAP/APRV$_{30–60\%}$ and BIPAP/APRV$_{>60\%}$ increased the number of normally aerated and decreased nonaerated compartments, as compared with BIPAP/APRV$_{0\%}$. Furthermore, the reduction in nonaerated compartments during BIPAP/APRV$_{>60\%}$ was more pronounced than during BIPAP/APRV$_{0–30\%}$. Strain$_{L,mean}$ progressively decreased from BIPAP/APRV$_{0\%}$ (1.39 ± 0.08) to BIPAP/APRV$_{>60\%}$ (1.25 ± 0.04; BIPAP/APRV$_{0–30\%}$: 1.33 ± 0.03 and BIPAP/APRV$_{30–60\%}$: 1.27 ± 0.06, respectively).

As shown in figure 4, higher levels of SB were associated with a significant shift of aeration toward the more dependent zones, mainly in the dorsal parts of the lungs.
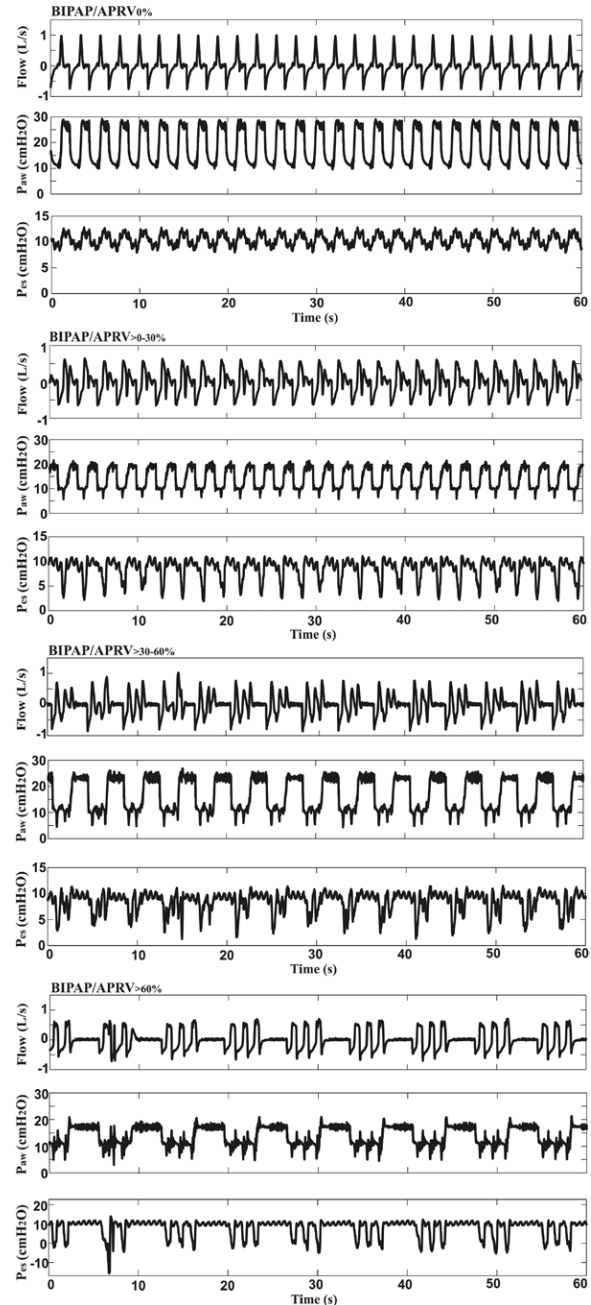

Fig. 1. Respiratory tracings of airflow (Flow), airway pressure (P_{aw}), and esophageal pressure (P_{es}) during biphasic positive airway pressure/airway pressure release ventilation (BIPAP/APRV) at four different levels of spontaneous breathing in total minute ventilation (0%, >0 to 30%, >30 to 60%, and >60%) in a representative animal.

Figure 5 depicts the patterns of $A_e/\dot{Q}_{rel}$ compartments. BIPAP/APRV$_{0–30\%}$, BIPAP/APRV$_{30–60\%}$, and BIPAP/APRV$_{>60\%}$ reduced the amount of low $A_e/\dot{Q}_{rel}$ areas compared with BIPAP/APRV$_{0\%}$.

The association analysis revealed that PTP and $P_{L,mean}$ were negatively correlated (r^2 = 0.216, P = 0.004). In turn, $P_{L,mean}$ increased proportionally to the amount of nonaerated lung tissue (r^2 = 0.205, P = 0.001).

Table 1. Respiratory Variables

	BL	IN	BL2	BIPAP/ APRV$_{0\%}$	BIPAP/ APRV$_{>0-30\%}$	BIPAP/ APRV$_{>30-60\%}$	BIPAP/ APRV$_{>60\%}$
MV (l/min)	5.62 ± 0.80	5.42 ± 0.82	6.43 ± 1.57	5.73 ± 1.35	5.44 ± 1.53	5.64 ± 1.22	5.59 ± 1.12
MV$_{SB}$ (% of total MV)					21.8 ± 16.3	43.3 ± 9.5#	66.3 ± 8.9#†
MV$_{spont. cycles}$ (%)					5.6 ± 4.9	37.9 ± 7.9#	59.7 ± 6.9#†
MV$_{contr. cycles}$ (%)					25.0 ± 23.4	15.5 ± 14.3	12.4 ± 10.2
MV$_{mixed cycles}$ (%)					70.6 ± 25.5	47.9 ± 16.6#	28.9 ± 14.2#
V$_T$ (ml/kg)	10.5 ± 1.0	10.2 ± 0.6	6.0 ± 0.3	6.1 ± 0.3	6.0 ± 0.6	5.5 ± 1.0	5.4 ± 0.9
V$_{Tspont cycles}$ (ml/kg)					3.6 ± 1.3	4.3 ± 1.5#	4.9 ± 1.1#
V$_{Tcontr. cycles}$ (ml/kg)					5.1 ± 0.7	6.5 ± 0.4#	5.4 ± 1.1
V$_{Tmixed cycles}$ (ml/kg)					6.5 ± 0.3	7.4 ± 0.4#	8.1 ± 1.1#
RR (breaths/min)	15.3 ± 1.1	15.2 ± 1.2	30.1 ± 5.2	26.9 ± 5.8	26.0 ± 7.1	29.8 ± 5.1	30.2 ± 5.7
RR$_{spont cycles}$ (breaths/min)					2.9 ± 2.5	15.8 ± 3.1#	20.9 ± 4.8#†
RR$_{contr. cycles}$ (breaths/min)					5.7 ± 4.5	3.4 ± 3.0	3.2 ± 2.7
RR$_{mixed cycles}$ (breaths/min)					17.4 ± 8.9	10.7 ± 4.6	6.1 ± 3.4#†
P$_{aw,peak}$ (cm H$_2$O)	19.4 ± 1.3	34.3 ± 3.2	27.0 ± 2.9	23.6 ± 2.9	20.0 ± 3.3*	16.6 ± 1.9*#	15.8 ± 1.5*#
P$_{aw,peak; spont. cycles}$ (cm H$_2$O)					13.4 ± 1.2	12.8 ± 1.1	13.4 ± 1.1
P$_{aw,peak; contr. cycles}$ (cm H$_2$O)					19.6 ± 1.4	19.4 ± 2.5	20.1 ± 1.4
P$_{aw,peak; mixed cycles}$ (cm H$_2$O)					19.4 ± 2.8	19.8 ± 2.8	20.7 ± 1.9
P$_{aw,mean}$ (cm H$_2$O)	10.9 ± 0.7	16.8 ± 1.6	17.3 ± 1.3	16.2 ± 1.3	14.5 ± 1.4*	13.5 ± 1.1*#	12.6 ± 0.7*#†
P$_{aw,mean; spont cycles}$ (cm H$_2$O)					10.9 ± 0.9	10.9 ± 1.1	10.5 ± 0.2
P$_{aw,mean; contr. cycles}$ (cm H$_2$O)					14.8 ± 0.8	15.9 ± 1.4	17.1 ± 1.1#
P$_{aw,mean; mixed cycles}$ (cm H$_2$O)					14.2 ± 1.2	15.8 ± 1.6#	16.5 ± 1.3#†
P$_{L,peak}$ (cm H$_2$O)	9.9 ± 1.3	24.3 ± 3.9	16.0 ± 4.0	13.5 ± 3.1	11.1 ± 3.8*	8.7 ± 2.6*	8.9 ± 2.5*
P$_{L,peak; spont cycles}$ (cm H$_2$O)					5.3 ± 1.3	5.8 ± 2.5	6.8 ± 2.4
P$_{L,peak; contr. cycles}$ (cm H$_2$O)					9.2 ± 2.1	9.2 ± 2.1	10.3 ± 1.7
P$_{L,peak; mixed cycles}$ (cm H$_2$O)					10.1 ± 2.3	10.8 ± 2.6	13.0 ± 3.1
P$_{L,mean}$ (cm H$_2$O)	3.1 ± 0.8	9.1 ± 2.7	7.4 ± 2.4	6.7 ± 1.5	5.8 ± 2.1	4.7 ± 1.5*	4.8 ± 1.2*
P$_{L,mean; spont cycles}$ (cm H$_2$O)					3.1 ± 0.8	2.9 ± 1.4	3.4 ± 0.9
P$_{L,mean; contr. cycles}$ (cm H$_2$O)					4.9 ± 1.5	5.8 ± 1.5	7.4 ± 1.4#†
P$_{L,mean; mixed cycles}$ (cm H$_2$O)					5.2 ± 1.3	6.1 ± 1.7#	7.4 ± 1.9#†
PTP (cm H$_2$O × s/min)					28.6 ± 24.4	45.5 ± 31.0#	58.2 ± 39.6#
PTP$_{spont cycles}$ (cm H$_2$O × s/min)					2.7 ± 2.7	25.0 ± 15.8#	42.8 ± 24.9#†
PTP$_{mixed cycles}$ (cm H$_2$O × s/min)					25.9 ± 24.6	20.5 ± 15.8	15.4 ± 15.4
Relative change of PTP					1.0	2.1 ± 1.2	3.4 ± 2.5

Data are shown as mean ± SD. Variables were measured during BIPAP/APRV with different levels of SB activity in total minute ventilation (0% [BIPAP/ APRV$_{0\%}$], >0 to 30% [BIPAP/APRV$_{>0-30\%}$], >30 to 60% [BIPAP/APRV$_{>30-60\%}$], and >60% [BIPAP/APRV$_{>60\%}$]). Differences among levels of inspiratory effort were tested with general linear model statistics and *post hoc* adjustment for multiple comparisons according to Sidak.

* $P < 0.05$ *vs.* BIPAP/APRV$_{0\%}$; # $P < 0.05$ *vs.* BIPAP/APRV$_{>0-30\%}$; † $P < 0.05$ *vs.* BIPAP/APRV$_{>30-60\%}$.

BIPAP/APRV = biphasic positive airway pressure/airway pressure release ventilation; BL = baseline; BL2 = baseline 2; IN = injury; MV = minute ventilation; MV$_{contr. cycles}$ = fraction of MV from controlled cycles; MV$_{mixed cycles}$ = fraction of MV from mixed cycles; MV$_{SB}$ = measured fraction of MV from spontaneous breathing activity; MV$_{spont. cycles}$ = fraction of MV from spontaneous cycles; RR = respiratory rate; RR$_{contr. cycles}$ = rate of controlled cycles; RR$_{mixed cycles}$ = rate of mixed cycles; RR$_{spont cycles}$ = rate of spontaneous cycles; P$_{aw,peak}$ = peak airway pressure; P$_{aw,peak; spont. cycles}$ = peak airway pressures of spontaneous cycles; P$_{aw,peak;contr. cycles}$ = peak airway pressures of controlled cycles; P$_{aw,peak; mixed cycles}$ = peak airway pressures of mixed cycles; P$_{aw,mean}$ = mean airway pressure; P$_{aw,mean; spont. cycles}$ = mean airway pressures of spontaneous cycles; P$_{aw,mean; contr. cycles}$ = mean airway pressures of controlled cycles; P$_{aw, mean; mixed cycles}$ = mean airway pressures of mixed cycles; P$_{L,peak}$ = peak transpulmonary pressure; P$_{L, peak; spont. cycles}$ = peak transpulmonary pressures of spontaneous cycles; P$_{L, peak; contr. cycles}$ = peak transpulmonary pressures of controlled cycles; P$_{L, peak; mixed cycles}$ = peak transpulmonary pressures of mixed cycles; P$_{L, mean}$ = mean transpulmonary pressure; P$_{L, mean; spont. cycles}$ = mean transpulmonary pressures of spontaneous cycles; P$_{L, mean; contr. cycles}$ = mean transpulmonary pressures of controlled cycles; P$_{L, mean; mixed cycles}$ = mean transpulmonary pressures of mixed cycles; PTP = pressure time product; PTP$_{spont cycles}$ = PTP of spontaneous cycles; PTP$_{mixed cycles}$ = PTP of mixed cycles; relative change of PTP = change of PTP related to BIPAP/APRV$_{>0-30\%}$; SB = spontaneous breathing; VT = mean tidal volume; VT$_{spont cycles}$ = VT of spontaneous cycles; VT$_{contr. cycles}$ = VT of controlled cycles; VT$_{mixed cycles}$ = VT of mixed cycles.

Discussion

The main findings of this study were that in a saline lung lavage model of experimental ARDS in pigs, higher levels of SB during BIPAP/APRV (1) improved oxygenation; (2) decreased mean transpulmonary pressure despite increased inspiratory effort; (3) reduced nonaerated lung tissue, with only minor changes in the distribution of perfusion, resulting in decreased low $A_e / \dot{Q}_{rel}$; and (4) reduced overall lung stress and strain.

To our knowledge, there were no previous studies addressing the effects of different levels of SB during BIPAP/APRV on lung aeration and perfusion. The saline lung lavage model of experimental ARDS was chosen because it reproduces many of functional features of

Table 2. Gas Exchange and Hemodynamic Variables

	BL	IN	BL2	BIPAP/ APRV$_{0\%}$	BIPAP/ APRV$_{>0-30\%}$	BIPAP/ APRV$_{>30-60\%}$	BIPAP/ APRV$_{>60\%}$
Pao$_2$/Fio$_2$	523.4 ± 41.8	72.5 ± 20.2	155.2 ± 26.5	278.9 ± 89.9	358.8 ± 94.7	381.7 ± 96.6	388.1 ± 57.7*
Paco$_2$ (mmHg)	39.8 ± 4.1	56.6 ± 10.2	61.5 ± 7.2	65.2 ± 6.9	61.9 ± 9.7	62.9 ± 11.9	66.2 ± 11.8
$\dot{Q}_{VA}/\dot{Q}_t$ (%)	11.6 ± 5.2	44.9 ± 11.9	41.8 ± 9.2	15.3 ± 7.8	11.4 ± 6.1	10.4 ± 7.4	10.2 ± 6.1
CO (l/min)	4.43 ± 0.86	4.11 ± 0.79	3.87 ± 0.71	4.53 ± 0.92	4.21 ± 0.84	4.23 ± 0.93	4.24 ± 0.80
HR (beats/min)	96.8 ± 10.5	95.0 ± 8.1	93.6 ± 13.0	92.4 ± 11.6	87.1 ± 13.3	87.3 ± 8.6	89.6 ± 12.3
MAP (mmHg)	79.0 ± 13.0	91.7 ± 11.4	94.3 ± 11.2	88.0 ± 10.1	86.6 ± 11.5	86.1 ± 10.5	89.0 ± 11.9
MPAP (mmHg)	22.1 ± 3.4	31.1 ± 5.9	34.1 ± 5.8	29.4 ± 5.1	25.3 ± 5.4*	25.2 ± 5.1*	25.7 ± 4.5*

Data are shown as mean ± SD. Variables were measured during BIPAP/APRV with different levels of spontaneous breathing activity in total minute ventilation (0% [BIPAP/APRV$_{0\%}$], >0 to 30% [BIPAP/APRV$_{>0-30\%}$], >30 to 60% [BIPAP/APRV$_{>30-60\%}$], and >60% [BIPAP/APRV$_{>60\%}$]). Differences among levels of inspiratory effort were tested with general linear model statistics, *post hoc* adjustment for multiple comparisons according to Sidak.

* $P < 0.05$ *vs.* BIPAP/APRV$_{0\%}$.

BIPAP/APRV = biphasic positive airway pressure/airway pressure release ventilation; BL = baseline; BL2 = baseline 2; CO = cardiac output; HR = heart rate; IN = injury; MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; Paco$_2$ = arterial partial pressure of carbon dioxide; Pao$_2$/Fio$_2$ = ratio of arterial partial pressure of oxygen to the fraction of inspired oxygen; $\dot{Q}_{VA}/\dot{Q}_t$ = venous admixture.
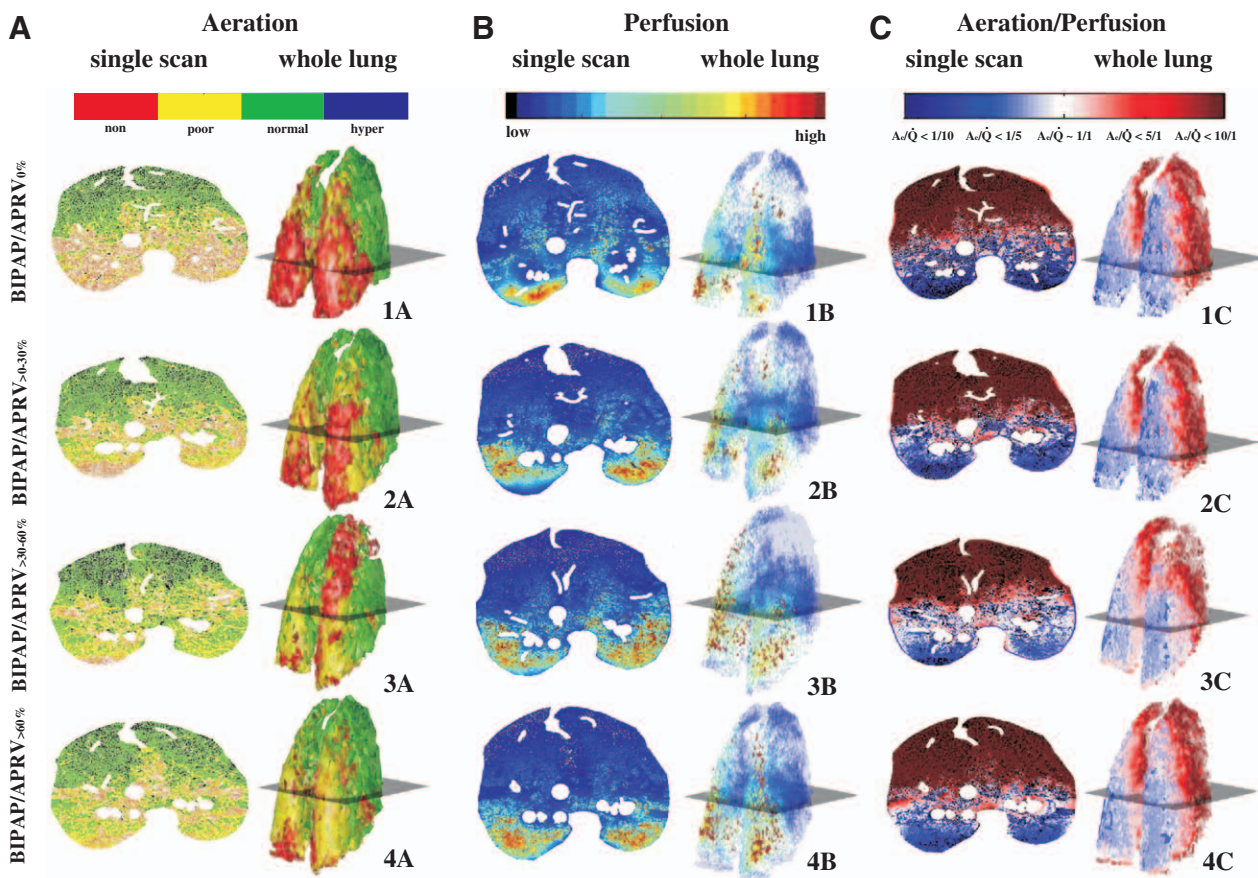

Fig. 2. Distributions of aeration (column *A*), perfusion (column *B*), and aeration/perfusion ($A_e/\dot{Q}$, column *C*) during biphasic positive airway pressure/airway pressure release ventilation (BIPAP/APRV) at four different levels of spontaneous breathing in total minute ventilation (0%, >0 to 30%, >30 to 60%, and >60%, rows 1–4, respectively) in a representative animal. Single scans represent the maximal cross-sectional areas of the respective whole lung images. Horizontal *color bars* denote the respective scales. Hyper = hyperaerated compartment; non = nonaerated compartment; normal = normally aerated compartment; poor = poorly aerated compartment.

ARDS.[13] In our experience, this model is suitable for a crossover study design because hemodynamics remains fairly stable, and the impairment of lung function can be maintained upon periodic derecruitment maneuvers. We opted for BIPAP/APRV because the desired level of SB is easily modulated by adjusting the time spent on lower and higher P$_{aw}$, and unsupported breaths are possible. CT and PET were considered well suited due to their relatively

Table 3. Computed Tomography Variables

	BL2	BIPAP/APRV$_{0\%}$	BIPAP/APRV$_{>0-30\%}$	BIPAP/APRV$_{>30-60\%}$	BIPAP/APRV$_{>60\%}$
Total lung volume (ml)	1,108.8±151.3	1,141.7±147.2	1,280.8±158.7*	1,321.7±191.3*	1,390.1±217.8*
Total lung tissue mass (g)	647.3±122.8	588.2±121.2	626.1±149.7	627.7±139.4	635.7±154.6
Total lung gas volume (ml)	461.4±58.4	553.4±92.1	654.7±59.3*	693.9±92.8*	754.3±118.9*#†

Data are shown as mean ± SD. Variables were measured during BIPAP/APRV with different levels of spontaneous breathing activity in total minute ventilation (0% [BIPAP/APRV$_{0\%}$], >0 to 30% [BIPAP/APRV$_{>0-30\%}$], >30 to 60% [BIPAP/APRV$_{>30-60\%}$], and >60% [BIPAP/APRV$_{>60\%}$]). Differences among levels of inspiratory effort were tested with general linear model statistics and *post hoc* adjustment for multiple comparison according to Sidak.

* $P < 0.05$ *vs.* BIPAP/APRV$_{0\%}$; # $P < 0.05$ *vs.* BIPAP/APRV$_{>0-30\%}$; † $P < 0.05$ *vs.* BIPAP/APRV$_{>30-60\%}$.

BIPAP/APRV = biphasic positive airway pressure/airway pressure release ventilation; BL = baseline; BL2 = baseline 2; IN = injury.

high resolutions for assessing aeration and perfusion, respectively.

Although the total minute ventilation was comparable, the types of respiratory cycle differed importantly among the different levels of SB. It is worth noting that during BIPAP/APRV$_{>0-30\%}$, which corresponds to the level of SB suggested for clinical practice, most respiratory cycles were mixed, suggesting that the inspiratory efforts were synchronized with and supported by the ventilator. According to our data, nonsupported SB during BIPAP/APRV was first achieved when the level of SB exceeded 30% of total minute ventilation.

Our finding that SB during BIPAP/APRV improves oxygenation is in agreement with previous studies in the literature, both in experimental[14–16] and clinical[7,17] scenarios. However, our data suggest that levels of SB higher than those adopted in previous studies are necessary to maximize such an effect. Although the improvement of oxygenation at higher SB levels occurred at the

Fig. 3. Distributions of nonaerated (*red*), poorly aerated (*yellow*), normally aerated (*green*), and hyperaerated compartments (*black*). Values are given as mean (*bar*) and SD (*error bar*) and were calculated as percentage of mass of whole lungs during biphasic positive airway pressure/airway pressure release ventilation (BIPAP/APRV) at four different levels of spontaneous breathing in total minute ventilation (0%, >0 to 30%, >30 to 60%, and >60%). *$P < 0.05$ *versus* BIPAP/APRV$_{0\%}$ and #$P < 0.05$ *versus* BIPAP/APRV$_{>0-30\%}$.

cost of increased inspiratory effort, absolute PTP levels were within a physiological range,[18] indicating that muscle fatigue was unlikely to occur within the time frame of measurements. The increased PTP at higher levels of SB probably explains the reduction in nonaerated tissue and improved aeration, especially in the most dependent lung regions. However, the increased aeration was not accompanied by a redistribution of perfusion of similar magnitude, leading to a decrease of low $A_e/\dot{Q}_{rel}$ compartment and improvement in oxygenation.

We previously reported that BIPAP/APRV with approximately 60% of minute ventilation due to SB was not associated with lung recruitment and redistribution of perfusion.[12] Because PTP is comparable in both studies, a possible explanation is that, in the current study, positive end-expiratory pressure and the I:E ratio were higher (10 *vs.* 5 cm H$_2$O, and 1:1 *vs.* 1:2 to 1:4, respectively), which likely enhanced the recruiting effects of SB. In fact, in severe lung injury, SB may be associated with tidal reaeration, that is, cyclic collapse and reopening, of dependent zones when the positive end-expiratory pressure is not adequate.[19]

The lack of redistribution of perfusion toward dependent lung regions during BIPAP/APRV combined with SB can be explained by different mechanisms: (1) compression of lung capillaries in dependent zones due to superposed pressure caused by surrounding edema; or (2) obstruction of lung capillaries due to micro-thrombi. We cannot completely rule out that the hypoxic vasoconstriction effect was affected, but such a mechanism is unlikely, because increased inflammation is not a hallmark of the saline lung lavage model.[13]

The decrease in Strain$_{L,mean}$ at higher levels of SB is likely explained by lung recruitment and increased TLGV, at a comparable mean V$_T$ and total lung tissue mass. Taken together with the finding that P$_{L,mean}$ was decreased, our data suggest that higher levels of SB during BIPAP/APRV might reduce stress and strain and, therefore, reduce ventilator-associated lung injury. This hypothesis is in agreement with the findings of a recent investigation showing that in mild lung injury in rabbits, SB activity during assist-control pressure ventilation decreased histologic damage compared with controlled MV.[19] It is worth noting that, in contrast to BIPAP/APRV, pressure support ventilation does not increase
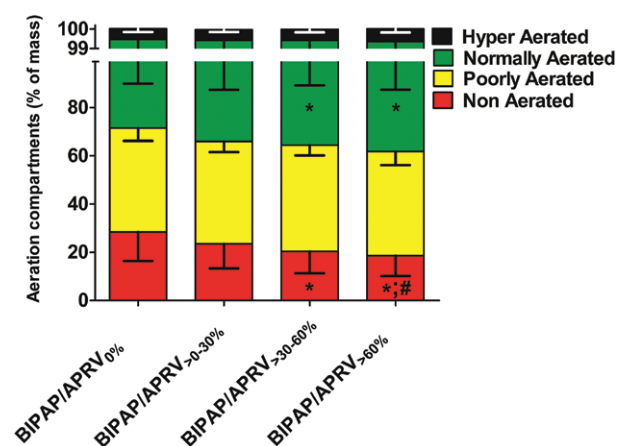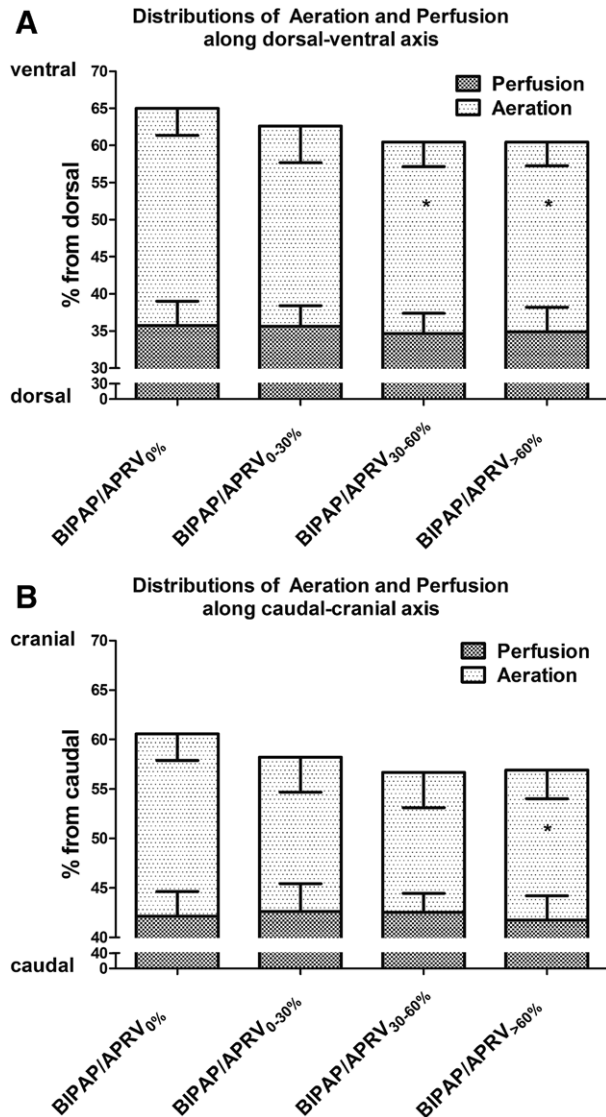
Fig. 4. Distributions of aeration and perfusion, along the dorsal-ventral axis (*A*) and the cranial-caudal axis (*B*) during biphasic positive airway pressure/airway pressure release ventilation (BIPAP/APRV) at four different levels of spontaneous breathing in total minute ventilation (0%, >0 to 30%, >30 to 60%, and >60%). Values are given as mean (*bar*) and SD (*error bar*). Lower values denote a shift toward dependent lung regions. *$P < 0.05$ *versus* BIPAP/APRV$_{0\%}$.

Fig. 5. Distributions of aeration/perfusion $\left(A_e/\dot{Q}\right)$ compartments in whole lungs during biphasic positive airway pressure/airway pressure release ventilation (BIPAP/APRV) at four different levels of spontaneous breathing in total minute ventilation (0%, >0 to 30%, >30 to 60%, and >60%). *$P < 0.05$ *versus* BIPAP/APRV$_{0\%}$.

end-expiratory volume and recruitment in experimental[12,20] or clinical[21] settings.

The finding that PTP was negatively correlated with $P_{L,mean}$ is somewhat surprising. When interpreting these results, it is important to keep in mind that this apparent paradox was detected after a period of SB of 60 min, representing rather a phenomenological than a cause–effect relationship. It has been shown that in experimental acute lung injury, the regional P_L decreases from nondependent to dependent regions. Because the elastance of the respiratory system is increased in lung injury, we would expect an increase in $P_{L,mean}$ during controlled MV. In
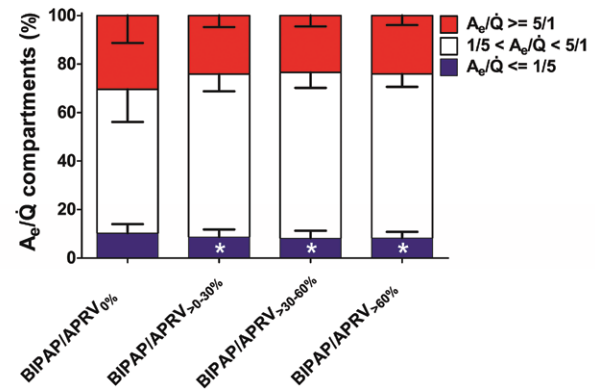
fact, when SB occurs simultaneously with ventilator cycling, the $P_{L,mean}$ should increase even more. However, when inspiratory efforts result in better aeration and lung elastance, the same V_T can be achieved with lower driving pressures, resulting in less $P_{L,mean}$. Thus, it is conceivable that increased inspiratory effort reduces lung stress in the presence of recruitment. Because we assessed respiratory variables at the end of each level of SB only, we cannot rule out the possibility that P_L first increased at the beginning of each level of SB. In fact, although high P_L is necessary to recruit lung units, once this has occurred, a much lower P_L is likely sufficient to keep those units open during the breathing cycle. This is similar to what can be observed during lung recruitment maneuvers in controlled ventilation, where P_L is first increased and, if recruitment occurs, a higher lung volume is reached at lower P_L due to decreased lung elastance (hysteresis phenomenon).[22] In addition, we cannot exclude the possibility that regional P_L, mainly in juxta-diaphragmatic areas, may have been higher than the mean value.

Possible Clinical Implications of the Findings

Our findings may have implications for MV in ARDS and the settings of BIPAP/APRV. First, our results suggest that in mild to moderate ARDS, muscle paralysis should not be used, and SB higher than currently recommended for clinical practice, that is, yielding more than 30% of total minute volume, maximizes lung recruitment, improves lung function, and minimizes global stress and strain. Such findings cannot be extrapolated to severe ARDS, where muscle paralysis in the first 48 h has been associated with an improved outcome.[23] Second, minute ventilation values from SB during BIPAP/APRV can be easily read from the display of most commercially available ventilators. Third, even if $P_{L,mean}$ is a crude estimate of global lung stress and does not allow regional assessment of P_L, it could prove useful to infer the

potential of BIPAP/APRV settings to reduce/increase ventilator-associated lung injury.

Limitations

This study has several limitations. First, because the saline lung lavage model is highly recruitable and causes only mild to moderate lung injury, our findings cannot be extrapolated to other models or clinical conditions where lung recruitability is limited and/or lung injury severe. Second, we used a crossover design, which does not assess the effects of different levels of SB on lung injury and inflammation. Third, although we used a Latin square design for sequences of SB levels, a time effect cannot be completely ruled out. Fourth, the possibility of carryover effects cannot be excluded, despite the use of derecruitment maneuvers preceding each level of SB. Fifth, we were not able to compute the relative contributions of SB activity and ventilator cycling on total V_T in mixed cycles. Sixth, CT data were obtained at end-expiration, whereas PET data were acquired during a period of approximately 6 min, thus corresponding more closely to the mean lung volume. However, the minor differences in lung volume between both situations are practically negligible when considering the total lung volume, even with regard to scattering effects. In fact, we could show that ^{68}Ga-labeled and fluorescent-labeled microspheres deliver similar information in terms of redistribution of pulmonary perfusion along the cranial-caudal and ventral-dorsal axes although PET has higher spatial resolution.[24] Seventh, it must be kept in mind that $A_e/\dot{Q}_{rel}$ does not represent $\dot{V}_A/\dot{Q}$. Accordingly, areas with apparently normal $A_e/\dot{Q}_{rel}$ may still be proportionally low ventilated. Eighth, our results were obtained with BIPAP/APRV and should not be directly extrapolated to other forms of assisted MV.

Conclusions

In a saline lung lavage model of experimental ARDS in pigs, levels of contribution of SB to minute ventilation during BIPAP/APRV higher than currently recommended for clinical practice, that is, more than 30%, improve oxygenation by increasing aeration in dependent lung zones without relevant redistribution of perfusion. In presence of recruitment, higher levels of SB reduce global lung stress and strain, despite increased inspiratory effort.

Acknowledgments

Competing Interests

The authors declare no competing interests.

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