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Regional lung aeration and ventilation during pressure support and biphasic positive airway pressure ventilation in experimental lung injury

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Abstract

Introduction: There is an increasing interest in biphasic positive airway pressure with spontaneous breathing (BIPAP+SB_{mean}), which is a combination of time-cycled controlled breaths at two levels of continuous positive airway pressure (BIPAP+SB_{controlled}) and non-assisted spontaneous breathing (BIPAP+SB_{spont}), in the early phase of acute lung injury (ALI). However, pressure support ventilation (PSV) remains the most commonly used mode of assisted ventilation. To date, the effects of BIPAP+SB_{mean} and PSV on regional lung aeration and ventilation during ALI are only poorly defined.

Methods: In 10 anesthetized juvenile pigs, ALI was induced by surfactant depletion. BIPAP+SB_{mean} and PSV were performed in a random sequence (1 h each) at comparable mean airway pressures and minute volumes. Gas exchange, hemodynamics, and inspiratory effort were determined and dynamic computed tomography scans obtained. Aeration and ventilation were calculated in four zones along the ventral-dorsal axis at lung apex, hilum and base.

Results: Compared to PSV, BIPAP+SB_{mean} resulted in: 1) lower mean tidal volume, comparable oxygenation and hemodynamics, and increased PaCO₂ and inspiratory effort; 2) less nonaerated areas at end-expiration; 3) decreased tidal hyperaeration and re-aeration; 4) similar distributions of ventilation. During BIPAP+SB_{mean}: i) BIPAP+SB_{spont} had lower tidal volumes and higher rates than BIPAP+SB_{controlled}; ii) BIPAP+SB_{spont} and BIPAP+SB_{controlled} had similar distributions of ventilation and aeration; iii) BIPAP+SB_{controlled} resulted in increased tidal re-aeration and hyperaeration, compared to PSV. BIPAP+SB_{spont} showed an opposite pattern.

Conclusions: In this model of ALI, the reduction of tidal re-aeration and hyperaeration during BIPAP+SB_{mean} compared to PSV is not due to decreased nonaerated areas at end-expiration or different distribution of ventilation, but to lower tidal volumes during BIPAP+SB_{spont}. The ratio between spontaneous to controlled breaths seems to play a pivotal role in reducing tidal re-aeration and hyperaeration during BIPAP+SB_{mean}.

Introduction

Maintenance of spontaneous breathing activity during ventilatory support in acute lung injury (ALI) may improve pulmonary gas exchange, systemic blood flow, and oxygen

supply to the tissues [1]. Most importantly, spontaneous breathing activity may contribute to decrease the time of ventilatory support and the length of stay in the intensive care unit [2]. Although pressure support ventilation (PSV) is the most frequently used form of assisted mechanical ventilation [3], there is increasing interest in biphasic positive airway pressure with superposed spontaneous breathing (BIPAP+SB_{mean}) [4]. PSV is a pressure-limited, flow-cycled mode in which every breath is supported by a con-

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stant level of pressure at the airways, thus the tidal volume (V_T) and inspiratory flow may adapt to the demands of the patient [5]. In contrast, BIPAP+SB_{mean} is a combination of time-cycled controlled breaths at two levels of continuous positive airway pressure (BIPAP+SB_{controlled}) and non-assisted spontaneous breathing (BIPAP+SB_{spont}) [4]. Compared with controlled mechanical ventilation and PSV, a possible advantage of non-assisted spontaneous breath during BIPAP+SB_{mean} is that they may generate higher transpulmonary pressures in dependent lung areas, contributing to lung recruitment, reduction of cyclic collapse/reopening and improvement of ventilation/perfusion matching [6-8].

Previous studies comparing PSV with BIPAP+SB_{mean} have not assessed the distribution of both aeration and ventilation [6,9,10]. In experimental ALI, we observed that aeration compartments of the whole lungs did not differ between BIPAP+SB_{mean} or PSV and controlled mechanical ventilation [11]. In contrast, Yoshida and colleagues [10] suggested that, in patients with ALI, improvement of lung aeration is more pronounced during BIPAP+SB_{mean} than PSV. However, both in an animal [11] and patient study [10], aeration was assessed at end-expiration with static computed tomography (CT) during breath holding, possibly introducing artifacts. As dynamic CT (CT_{dyn}) does not require breath holding, it may be considered a suitable technique for assessing lung aeration and ventilation during BIPAP+SB_{mean} and PSV.

In the current study, we investigated the distributions of regional aeration and ventilation at the lungs' apex, hilum and base during PSV and BIPAP+SB_{mean} using CT_{dyn} in experimental ALI. We hypothesized that BIPAP+SB_{mean}, compared with PSV: is associated with decreased amounts of nonaerated lung tissue and increased relative ventilation in dorsal lung zones due to increased inspiratory effort; and decreases tidal reaeration and hyperaeration through reduction of nonaerated lung tissue and different distribution of ventilation.

Materials and methods

The protocol of this study has been approved by the local animal care committee and the Government of the State Saxony, Germany. Ten pigs (weighing 25.0 to 36.5 kg) were pre-medicated and anesthetized with intravenous midazolam, ketamine, and remifentanyl. The trachea was intubated and lungs were ventilated with an EVITA XL 4 Lab (Dräger Medical AG, Lübeck, Germany) in the volume-controlled mode using a V_T of 12 ml/kg, inspiratory: expiratory ratio (I:E) of 1:1, fraction of inspired oxygen (FiO₂) of 0.5, positive end-expiratory pressure (PEEP) of 5 cmH₂O, and respiratory rate (RR) set to achieve normocapnia. We decided to use a PEEP of 5 cmH₂O to allow a better differentiation of tidal recruitment/reaeration and tidal

hyperaeration between the modes investigated. Previous data from our group [12] suggest that such phenomena occur simultaneously but in different proportions depending on the level of PEEP. A FiO₂ of 0.5 was chosen to allow adequate oxygenation without increasing atelectasis. FiO₂ and PEEP were not changed during the experiments. An esophageal catheter (Erich Jaeger GmbH, Höchberg, Germany) was advanced through the mouth into the mid chest. A crystalloid solution (E153, Serumwerk Bernburg AG, Bernburg, Germany) at a rate of 10 to 20 mL.kg⁻¹.h⁻¹ was used to maintain volemia.

Hemodynamics was monitored with catheters placed in right external carotid and pulmonary arteries. Arterial and mixed venous blood samples were analyzed.

Airway flow, airway pressure (P_{aw}) and esophageal pressure were measured using calibrated flow and pressure sensors placed at the endotracheal tube, and respiratory parameters calculated. The ratio of inspiratory to total respiratory cycle (Ti/Ttot) was also determined. The product of inspiratory esophageal pressure vs. time (PTP), the difference between P_{aw} at the beginning of inspiration and 100 ms thereafter ($P_{0.1}$), and the dynamic intrinsic PEEP (PEEP_{i,dyn}) were determined. Values of PTP, $P_{0.1}$ and PEEP_{i,dyn} were taken from two minute and four minute recordings during controlled and assisted mechanical ventilation, respectively.

Respiratory parameters were computed from controlled (BIPAP+SB_{controlled}) and spontaneous (BIPAP+SB_{spont}) breath cycles. The contributions of spontaneous and controlled breaths to BIPAP+SB_{mean} were weighted by their respective rates (weighted mean BIPAP+SB_{mean}). Mean airway and transpulmonary pressures were weighted also by time, that is as the integral of the area under the flow curve divided by time, as shown in detail in Additional file 1.

Dynamic computed tomography

CT_{dyn} measurements were performed with a Somatom Sensation 16 (Siemens, Erlangen, Germany) at three different lung levels: apex (about 3 cm cranial to the carina); hilum (at carina level); base (about 2 to 3 cm caudal to the carina). Scans were obtained every 120 ms during a period of 60 seconds, resulting in approximately 500 images per level. Each image obtained corresponded to a matrix with 512 × 512 voxels of 0.443 × 0.443 × 1 mm³. Segmentation of the region of interest contained between the boundaries defined by the rib cage and mediastinal organs was performed semi-automatically, with software (CHRISTIAN II, Technical University Dresden, Germany) developed by one of the authors (MC). Each level was further divided into four zones of equal heights from ventral to dorsal (1 = ventral, 2 = mid-ventral, 3 = mid-dorsal, and 4 = dorsal). The four zones had equal height at each different level (apex, hilum, and base).

Aeration compartments at end-expiration and end-inspiration were computed based on an arbitrary scale for attenuation described elsewhere [13]. Accordingly, ranges of -1000 to -900 Hounsfield units (HU), -900 to -500 HU, -500 to -100 HU, and -100 to +100 HU were used to define the hyperaerated, normally aerated, poorly aerated, and nonaerated compartments, respectively.

Tidal re-aeration was calculated as the decrease in the percentage of nonaerated and poorly aerated compartments from end-expiration to end-inspiration [14]. Tidal hyperaeration was calculated as the increase in the percentage of hyperaeration from end-expiration to end-inspiration [14].

Ventilation in one zone of a given level was computed as the variation of gas content between end-inspiration and end-expiration of that zone divided by the total variation of gas content in the respective level.

For BIPAP+SB_{mean}, CT variables were computed in the same way as for respiratory parameters, that is weighted means of spontaneous and controlled breaths.

Protocol for measurements

After preparation, animals were allowed to stabilize for 15 minutes (baseline, volume-controlled mode). ALI was induced by means of surfactant depletion [15] and considered stable if partial pressure of oxygen (PaO₂)/FiO₂ was 200 mmHg or less for at least 30 minutes (injury, volume-controlled mode). After obtaining the measurements at injury, BIPAP+SB_{controlled} was initiated as follows: the driving pressure, which corresponded to the difference between the higher and the lower continuous positive P_{aw} level of 5 cmH₂O, was set to obtain V_T of 7 to 8 ml/kg and mechanical RR was set to reach partial pressure of carbon dioxide (PaCO₂) in the range of 50 to 60 mmHg, without spontaneous breathing. The I:E ratio was set to achieve mean P_{aw} in the range of 8 to 10 cmH₂O, as expected in PSV. At the same time, depth of anesthesia was reduced, remaining constant thereafter. Lower mechanical RR combined with reduced depth of anesthesia enabled spontaneous breathing (unsynchronized and superimposed to BIPAP+SB_{controlled}). When spontaneous breathing represented 20% or more of total minute ventilation, all animals were subjected to BIPAP+SB_{mean} and PSV in randomized sequence for 60 minutes. During BIPAP+SB_{mean}, the initial ventilatory settings of BIPAP+SB_{controlled} were kept unchanged and spontaneous breathing efforts and rate increased according to the respiratory drive of the animals, without pressure support. During PSV, the target pressure support was set to achieve V_T of 7 to 8 ml/kg, the inspiratory flow trigger was fixed at 2.0 L/min and the ventilator cycled-off at 25% of peak flow. Each assisted mechanical ventilation mode lasted 60 minutes. Measurements were performed at the following steps: baseline, injury and at the end of each

assisted mechanical ventilation mode. The time elapsed between stabilization of injury, and first and second assisted mechanical ventilation mode corresponded to 60 and 120 minutes, respectively.

Statistics

Data are given as mean ± standard deviation. Changes in functional variables were tested with two-tailed student's paired t-tests. Variables derived from CT_{dyn} measurements were evaluated with mixed linear models using the following factors: level (apex, hilum, and base), zone (1 to 4) and type of mechanical ventilation (PSV, BIPAP+SB_{mean}, BIPAP+SB_{controlled} and BIPAP+SB_{spont}). Compound symmetry for the measures on the same animal was assumed. Identical correlations were also assumed and their strength was estimated by components of variance. Residuals were checked for normal distribution, as suggested by their plots. Final mixed linear models resulted from stepwise model choices and included only statistical significant effects. Multiple comparisons were adjusted by the Bonferroni procedure. Univariate and multivariate analysis were performed with the software SPSS (Version 15.0, Chicago, IL, USA) and SAS (Procedure Mixed, Version 8, SAS Institute Inc, Cary, NC, USA), respectively. Statistical significance was accepted at $P < 0.05$ in all tests.

Results

Induction of acute lung injury

ALI was achieved with one to five lavages (median = 2.5), resulting in increased peak and mean P_{aw} and mean transpulmonary pressure (P_{peak}, P_{mean}, and P_{pl} mean, respectively; Table 1), as well as reduced oxygenation and increased mean pulmonary artery pressure (Table 2).

Assisted mechanical ventilation

During BIPAP+SB_{mean} we detected spontaneous breathing only on low but not on high continuous positive P_{aw} levels. Minute ventilation did not differ between PSV and BIPAP+SB_{mean} (Table 1). However, mean V_T was higher, whereas mean RR was lower during PSV. P_{peak} during BIPAP+SB_{controlled} and PSV were comparable. The time spent during inspiration was proportionally shorter in BIPAP+SB_{mean} than PSV, as reflected by Ti/Tot. P_{mean} during BIPAP+SB_{mean} did not differ from PSV. However, P_{mean} and P_{pl} mean were higher during BIPAP+SB_{controlled} and lower during BIPAP+SB_{spont} as compared with PSV. PEEP_{i,dyn} values did not differ between assisted mechanical ventilation modes, but values of P_{0,1} and PTP were higher during BIPAP+SB_{mean} compared with PSV.

Arterial oxygenation and hemodynamic variables did not differ between the assisted mechanical ventilation modes,

Table 1: Respiratory parameters

	Baseline	Injury	PSV	BIPAP+SB _{mean}	BIPAP+SB _{controlled}	BIPAP+SB _{spont}
MV (L/min)	5.1 ± 1.7	4.1 ± 1.7	6.6 ± 1.9	6.2 ± 2.1	2.3 ± 0.9 †,‡	4.0 ± 2.2 †,‡,§
V _T (mL)	347 ± 58	349 ± 61	202 ± 48	129 ± 40 †	255 ± 103	97 ± 34 †,‡,§
RR (/min)	15 ± 4	14 ± 4	34 ± 11	51 ± 17 †	9 ± 3 †,‡	43 ± 17 †,‡,§
Ti/Ttot	0.49 ± 0.01	0.49 ± 0.01	0.33 ± 0.05	--	0.24 ± 0.08 †	0.26 ± 0.06 †,‡
P _{peak} (cmH ₂ O)	20 ± 2	34 ± 3 *	23 ± 2	--	24 ± 3	--
P _{aw} mean (cmH ₂ O)	11 ± 1	15 ± 1 *	9 ± 1	9 ± 1	14 ± 2 †,‡	5 ± 1 †,‡,§
P _{pl} mean (cmH ₂ O)	3 ± 2	7 ± 2 *	2 ± 1	2 ± 1	6 ± 3 †,‡	1 ± 1 †,‡,§
PEEP _{i,dyn} (cmH ₂ O)	--	--	1 ± 1	1 ± 1	--	--
PTP (cmH ₂ O.s.min ⁻¹)	--	--	7 ± 5	91 ± 54 †	--	--
P0.1 (cmH ₂ O)	--	--	1 ± 1	3 ± 1 †	--	--

Values are given as mean ± standard deviation; baseline, before induction of acute lung injury; injury, after induction of acute lung injury. The contributions of spontaneous and controlled breaths to BIPAP+SB_{mean} were weighted by their respective rates (weighted mean). * $P < 0.05$ vs. Baseline; † $P < 0.05$ vs. PSV; ‡ $P < 0.05$ vs. BIPAP+SB_{mean}; § $P < 0.05$ vs. BIPAP+SB_{controlled}. BIPAP+SB_{controlled}, controlled breath cycles during BIPAP+SB_{mean}; BIPAP+SB_{mean}, biphasic positive airway pressure + spontaneous breathing; BIPAP+SB_{spont}, spontaneous breath cycles during BIPAP+SB_{spont}; MV, minute volume; P_{0.1}, airway pressure generated 100 ms after onset of an occluded inspiratory effort; P_{aw} mean, mean airway pressure; PEEP_{i,dyn}, dynamic intrinsic end-expiratory pressure; P_{peak}, peak airway pressure; P_{pl} mean, mean transpulmonary pressure; PSV, pressure support ventilation; PTP, inspiratory esophageal pressure time product; RR, respiratory rate; Ti/Ttot, inspiratory to total respiratory time; V_T, tidal volume.

Table 2: Gas exchange and hemodynamic variables

	Baseline	Injury	PSV	BIPAP+SB _{mean}
Gas exchange				
PaO ₂ /FIO ₂ (mmHg)	513 ± 62 (489.6-547.2)	119 ± 30* (92.0-143.1)	264 ± 127 (136.0-378.7)	246 ± 112 (143.1-332.5)
\dot{Q}_{VA} / \dot{Q}_T (%)	5.5 ± 1.4 (4.4-6.5)	33.9 ± 12.8* (24.7-39.7)	16.9 ± 10.4 (6.7-24.3)	19.8 ± 12.1 (11.6-28.7)
PaCO ₂ (mmHg)	34 ± 6 (29.4-39.7)	39 ± 8* (30.1-46.5)	48 ± 6 (44.2-55.2)	59 ± 13 [†] (46.9-66.2)
Hemodynamics				
CO (L/min)	3.2 ± 0.8 (2.4-3.8)	3 ± 0.8 (2.3-3.8)	4.3 ± 1.4 (2.8-5.3)	4.2 ± 1.2 (3.2-5.2)
HR (/min)	77 ± 13 (69-83)	75 ± 12 (65-86)	91 ± 18 (83-100)	91 ± 19 (77-110)
MAP (mmHg)	73 ± 9 (67-79)	69 ± 12 (62-75)	75 ± 8 (71-77)	79 ± 14 (68-98)
MPAP (mmHg)	22 ± 4 (20-24)	30 ± 5* (27-32)	31 ± 5 (26-35)	33 ± 6 (30-36)
CVP (mmHg)	10 ± 3 (8-12)	11 ± 2 (10-11)	9 ± 2 (8-10)	9 ± 2 (7-11)
PCWP (mmHg)	13 ± 2 (12-14)	14 ± 2 (12-15)	13 ± 4 (11-14)	12 ± 2 (11-15)

Values are given as mean ± standard deviation. Baseline, before induction of acute lung injury; injury, after induction of acute lung injury. * $P < 0.05$ vs. baseline; [†] $P < 0.05$ vs. PSV.

BIPAP+SB_{mean}, biphasic positive airway pressure + spontaneous breathing; CO, cardiac output; CVP, central venous pressure; FIO₂, fraction of inspired oxygen; HR, heart rate; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; PaCO₂, partial pressure of arterial carbon dioxide; PaO₂, partial pressure of arterial oxygen; PCWP, pulmonary artery occlusion pressure; PSV, pressure support ventilation;

\dot{Q}_{VA} / \dot{Q}_T , mixed venous admixture.

but PaCO₂ was higher during BIPAP+SB_{mean} than PSV (Table 2).

The statistical analysis evidenced no effect of the sequence of ventilation modes on the hyperaerated, normally aerated, poorly aerated, and nonaerated compartments at end-expiration. The Additional files 2 and 3 show CT_{dyn} videos of lungs during BIPAP+SB_{mean} and PSV in one animal, respectively.

During BIPAP+SB_{mean} and PSV, we observed at end-expiration and end-inspiration (Figures 1 and 2, respectively) a gravity-dependent loss of lung aeration, characterized by increase of nonaerated and poorly aerated areas, as well as decrease in hyperaerated and normally aerated tissue in dorsal zones, as compared with ventral ones ($P < 0.0001$). Similarly, the percentages of nonaerated and poorly aerated areas increased, whereas those from nor-

mally aerated and hyperaerated areas decreased from lung apex to base following the gravitational gradient, independent from the assisted mechanical ventilation mode and lung zone ($P < 0.0001$).

Compared with PSV, BIPAP+SB_{controlled} and BIPAP+SB_{spont} resulted in a reduction of the percentage of nonaeration at end-expiration at the lung base (Figure 1, $P < 0.05$). At end-inspiration, BIPAP+SB_{mean} led to an increased percentage of normally aerated tissue at apex and hilum, as well as reduced poorly aerated and nonaerated tissue at apex and base, respectively, mainly during controlled breaths (Figure 2, $P < 0.05$). The distribution of aeration during BIPAP+SB_{controlled} and BIPAP+SB_{spont} was comparable at end-expiration, as well as end-inspiration (Figures 1 and 2, respectively).

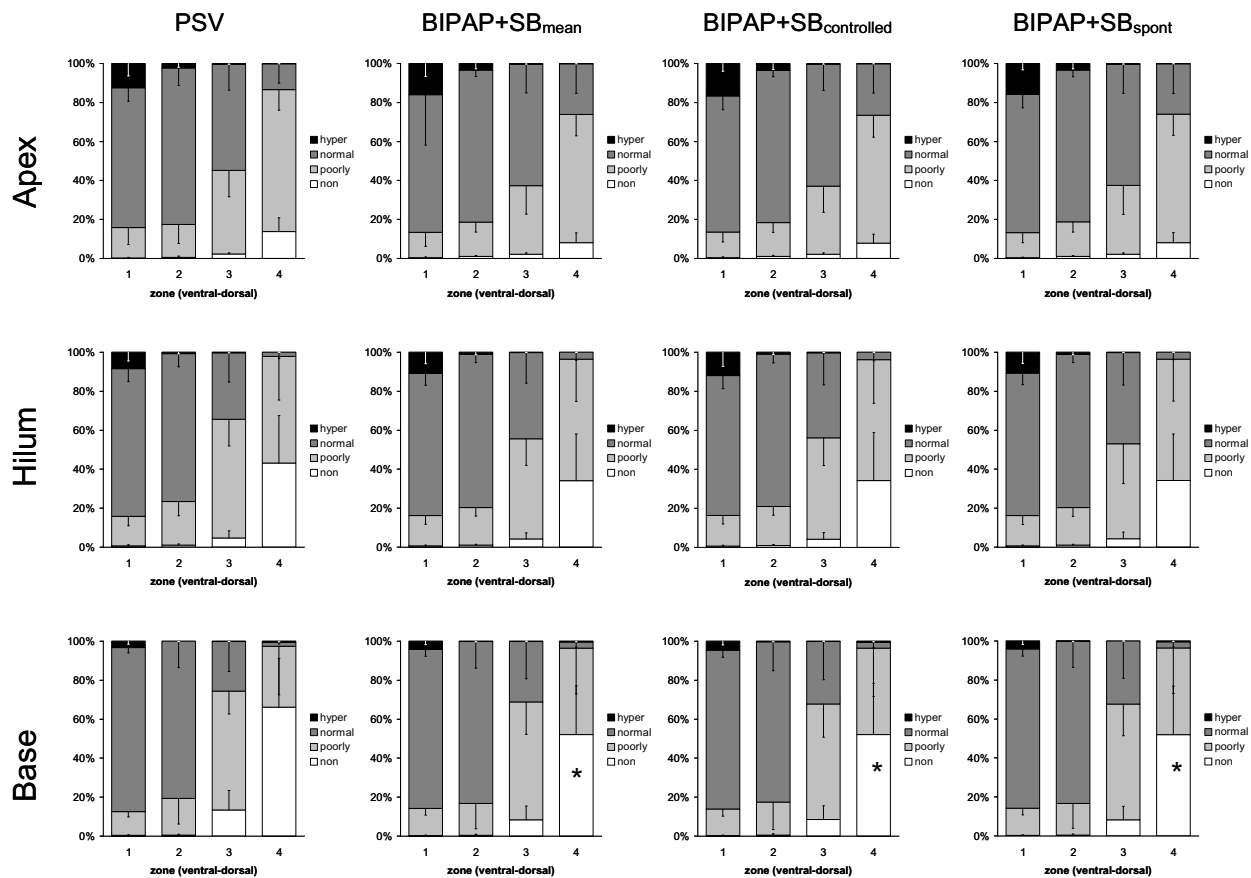


Figure 1 Distributions of hyperaerated (hyper), normally aerated (normal), poorly aerated (poorly) and nonaerated (non) compartments at end-expiration during pressure support ventilation (PSV), biphasic positive pressure ventilation + spontaneous breaths (BIPAP+SB_{mean}), controlled (BIPAP+SB_{controlled}) and spontaneous (BIPAP+SB_{spont}) breath cycles. Calculations were performed for different lung zones from ventral to dorsal (1 = ventral, 2 = mid-ventral, 3 = mid-dorsal, and 4 = dorsal) at lungs apex, hilum, and base using dynamic computed tomography. The contributions of BIPAP+SB_{spont} and BIPAP+SB_{controlled} to BIPAP+SB_{mean} were weighted by their respective rates (weighted mean). Bars and vertical lines represent means and standard deviations, respectively. * $P < 0.05$ vs. PSV; † $P < 0.05$ vs. BIPAP+SB_{controlled}.

As shown in Figure 3, tidal re-aeration had a gravity-dependent pattern ($P < 0.0001$), increasing from ventral to mid-dorsal ($P < 0.0001$), but decreasing from mid-dorsal to dorsal zones ($P < 0.0001$). Compared with PSV, BIPAP+SB_{mean} induced less tidal re-aeration in mid-dorsal zones, mainly due to spontaneous breaths. Also, in dorsal zones, tidal re-aeration was more pronounced during PSV than BIPAP+SB_{spont}. On the other hand, tidal re-aeration was less marked during PSV than controlled breaths of BIPAP+SB_{mean}.

Tidal hyperaeration increased from dorsal to ventral lung zones, as well as from apex to base (Figure 4, $P < 0.0001$ both). Tidal hyperaeration was decreased during BIPAP+SB_{mean} compared with PSV. In ventral zones of the lung apex and base, tidal hyperaeration increased during controlled but decreased during BIPAP+SB_{spont} compared with PSV.

Distribution of ventilation did not differ among the lung levels, but was lowest in ventral and highest in mid-ventral zones ($P < 0.0001$ both). No differences were observed among PSV, BIPAP+SB_{mean}, BIPAP+SB_{controlled} and BIPAP+SB_{spont} ($P = 1.0$).

Discussion

In a surfactant depletion model of ALI, we found that BIPAP+SB_{mean} compared with PSV resulted in: lower mean V_T , comparable oxygenation and hemodynamics, and increased $PaCO_2$ and inspiratory effort; less nonaerated areas at end-expiration; decreased tidal hyperaeration and re-aeration; and similar distributions of relative ventilation. During BIPAP+SB_{mean}: BIPAP+SB_{spont} had lower V_T and higher rate than BIPAP+SB_{controlled}; BIPAP+SB_{spont} and BIPAP+SB_{controlled} had similar distributions of ventilation and aeration; BIPAP+SB_{controlled} resulted in increased tidal

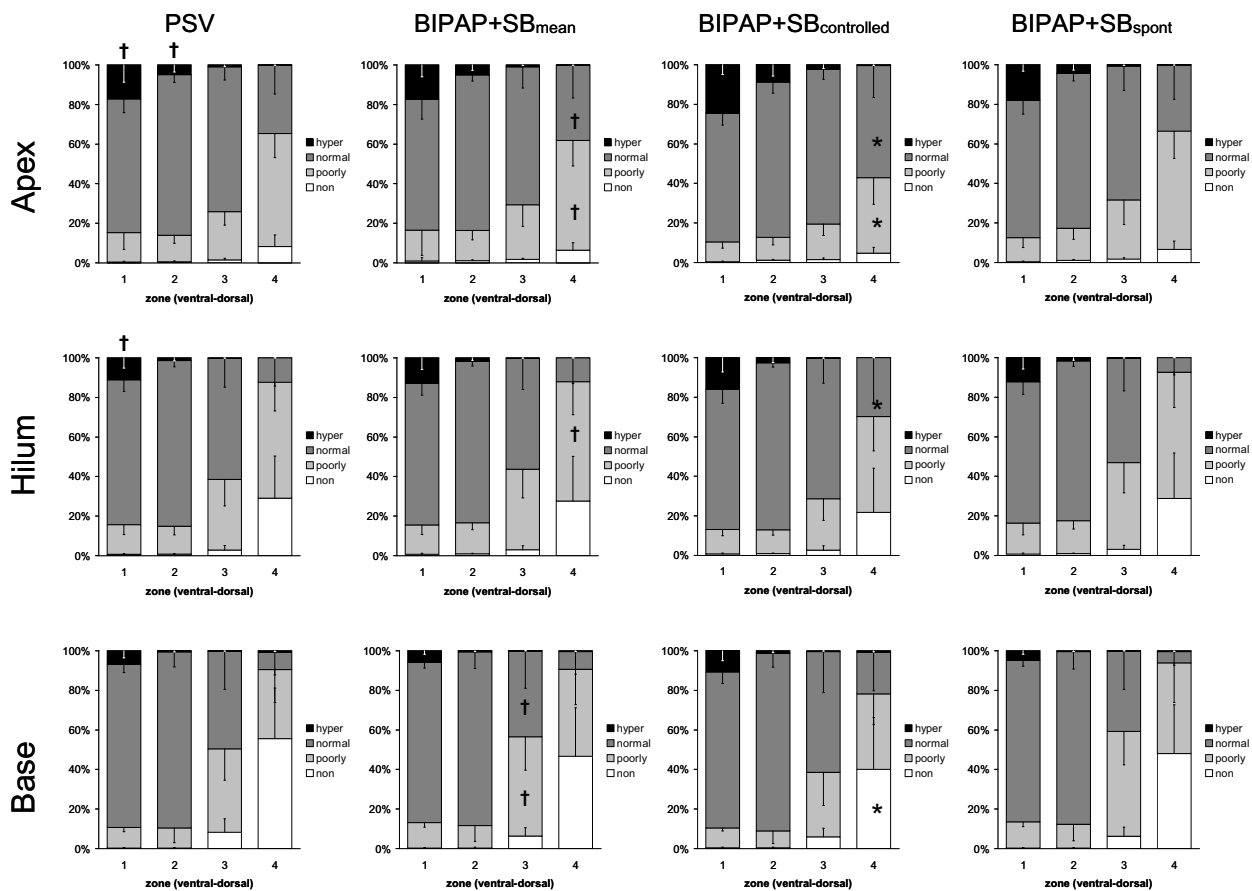


Figure 2 Distributions of hyperaerated (hyper), normally aerated (normal), poorly aerated (poorly) and nonaerated (non) compartments at end-inspiration during pressure support ventilation (PSV), biphasic positive pressure ventilation + spontaneous breaths (BIPAP+SB_{mean}), controlled (BIPAP+SB_{controlled}) and spontaneous (BIPAP+SB_{spont}) breath cycles. Calculations were performed for different lung zones from ventral to dorsal (1 = ventral, 2 = mid-ventral, 3 = mid-dorsal, and 4 = dorsal) at lungs apex, hilum, and base using dynamic computed tomography. The contributions of BIPAP+SB_{spont} and BIPAP+SB_{controlled} to BIPAP+SB_{mean} were weighted by their respective rates (weighted mean). Bars and vertical lines represent means and standard deviations, respectively. * $P < 0.05$ vs. PSV; † $P < 0.05$ vs. BIPAP+SB_{controlled}.

reaeration and hyperaeration, compared with PSV. BIPAP+SB_{spont} showed an opposite pattern.

To our knowledge, this is the first study showing that despite reduced nonaerated lung tissue during BIPAP+SB_{mean} compared with PSV, differences in tidal reaeration and hyperaeration seem to be due only to lower V_T of spontaneous breaths, because the distribution ventilation are comparable.

The present study differs from previous investigations on BIPAP+SB_{mean} and PSV [6,9-11] in that: CT_{dyn} was used to assess regional aeration during up to 60 seconds; no breath holds at end-expiration or end-inspiration were used; and both the mean P_{aw} and minute ventilation were comparable between BIPAP+SB_{mean} and PSV. Different investigators have used CT_{dyn} to quantify lung aeration, detect tidal recruitment and derecruitment, as well hyperaeration in ALI/acute respiratory distress syndrome (ARDS) [8,16,17].

When negative intrapleural pressures are generated, CT_{dyn} seems to be superior to static helical CT for quantifying lung aeration at mid-expiration and mid-inspiration [18]. Furthermore, as V_T during BIPAP+SB_{mean} and PSV are not constant [19], aeration measurements taken within a single breath may be less representative of longer periods of ventilation.

Aeration compartments

Compared with PSV, BIPAP+SB_{mean} reduced the percentage of nonaerated areas at end-expiration in dependent lung zones, both BIPAP+SB_{controlled} and BIPAP+SB_{spont}. At end-inspiration, the patterns of distribution of aeration were similar between BIPAP+SB_{mean} and PSV. Nonetheless, BIPAP+SB_{controlled} showed less poorly aerated and more normally aerated percentages of lung tissue than BIPAP+SB_{mean}. Two mechanisms can explain these obser-

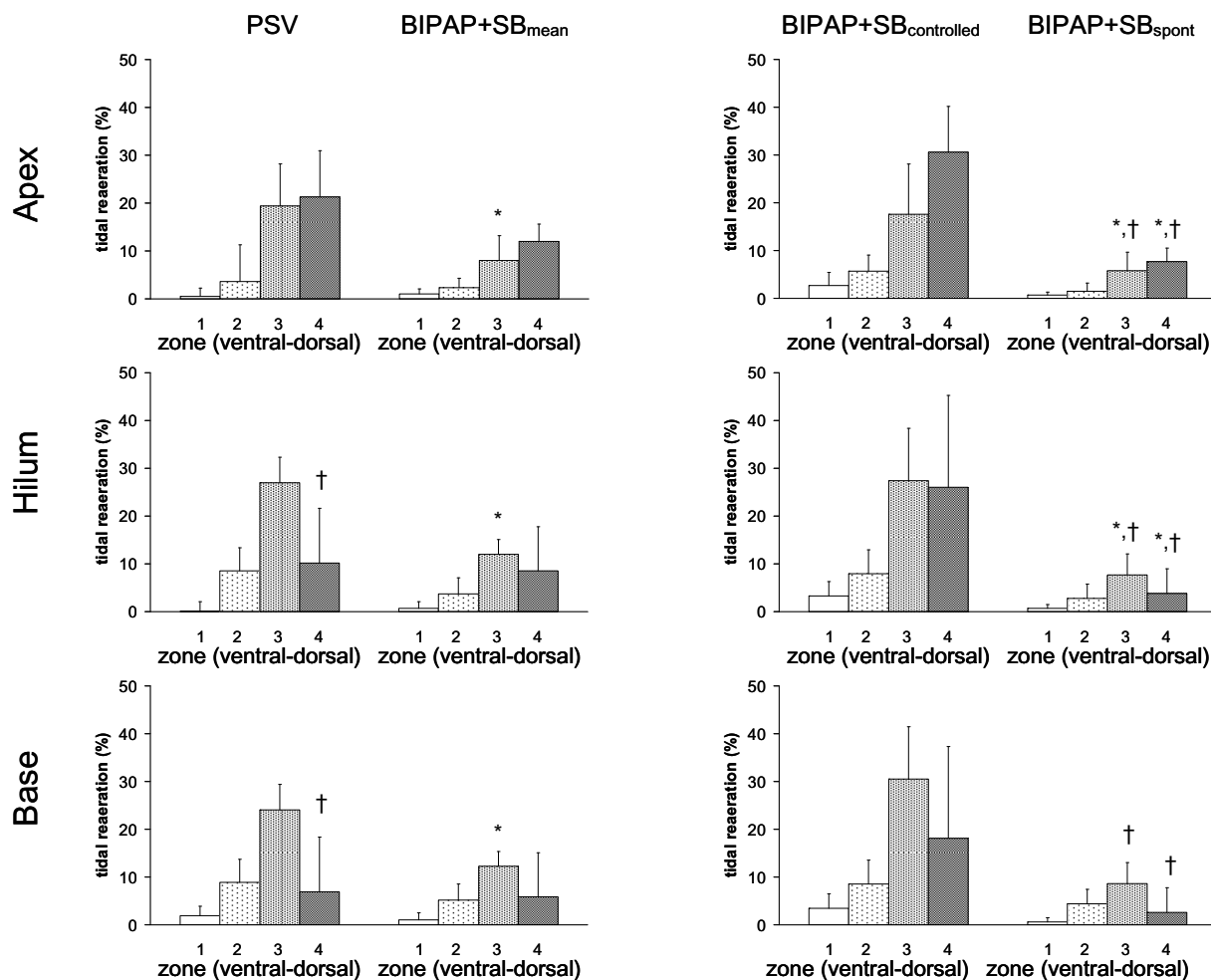


Figure 3 Tidal re-aeration during pressure support ventilation (PSV), biphasic positive pressure ventilation + spontaneous breaths (BIPAP+SB_{mean}), controlled (BIPAP+SB_{controlled}) and spontaneous (BIPAP+SB_{spont}) breath cycles. Calculations were performed for different lung zones from ventral to dorsal (1 = ventral, 2 = mid-ventral, 3 = mid-dorsal, and 4 = dorsal) at lungs apex, hilum, and base using dynamic computed tomography. The contributions of BIPAP+SB_{spont} and BIPAP+SB_{controlled} to BIPAP+SB_{mean} were weighted by their respective rates (weighted mean). Bars and vertical lines represent means and standard deviations, respectively. * $P < 0.05$ vs. PSV; † $P < 0.05$ vs. BIPAP+SB_{controlled}.

vations. First, spontaneous breathing may have favored recruitment of more dependent zones at end-expiration, with effects being preserved during controlled breaths. This hypothesis is supported by increased PTP and Ppl mean during BIPAP+SB_{mean} compared with PSV. Second, BIPAP+SB_{controlled} generated higher products of P_{aw} in time during inspiration, as shown by our data, thus promoting recruitment of lung zones with increased time constants, with effects being preserved during BIPAP+SB_{spont}. Indeed, it has been shown that in controlled ventilation the more tissue is recruited at end-inspiration, the more tissue remains recruited at end-expiration [20]. On the other hand, the amount of hyperaeration at end-inspiration was higher during BIPAP+SB_{controlled} than PSV, despite comparable Ppeak. The most probable explanation is that Pmean was higher

during BIPAP+SB_{controlled} than PSV. Another likely explanation is that the gas volume at end-expiration was higher, as suggested by lower percentages of nonaerated areas during BIPAP+SB_{mean}, generating an overall shift towards more aeration. Accordingly, hyperaeration was more localized in non-dependent lung zones. However, mean hyperaeration at end-inspiration was comparable between BIPAP+SB_{mean} and PSV, due to less hyperaeration during BIPAP+SB_{spont}.

Tidal re-aeration and hyperaeration

Tidal recruitment or re-aeration and tidal hyperaeration have been proposed to reflect the phenomena of cyclic collapse/reopening and overdistension of lung units in ALI/ARDS [14,21], which are important risk factors for ventilator-

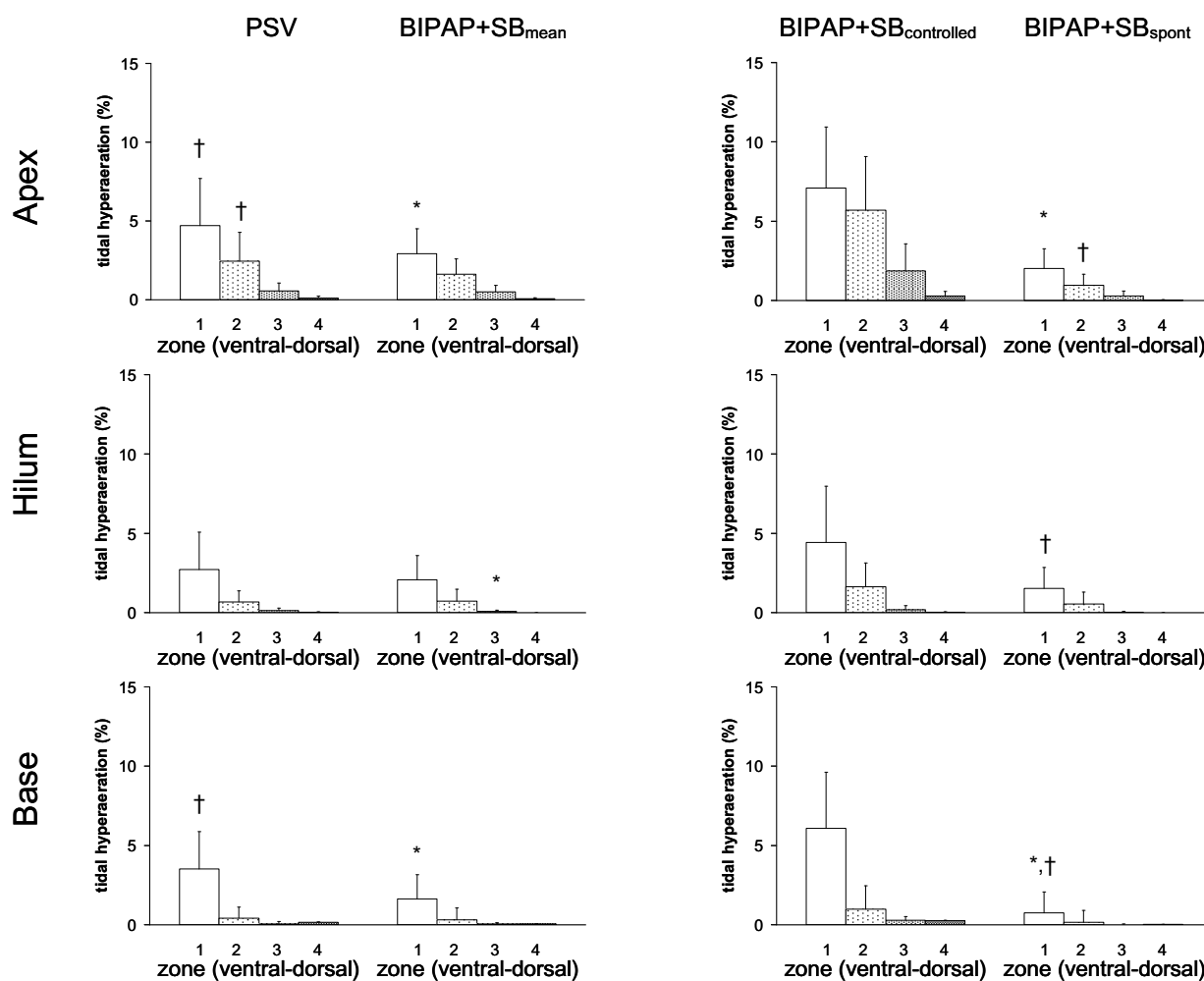


Figure 4 Tidal hyperaeration during pressure support ventilation (PSV), biphasic positive pressure ventilation + spontaneous breaths (BIPAP+SB_{mean}), controlled (BIPAP+SB_{controlled}) and spontaneous (BIPAP+SB_{spont}) breath cycles. Calculations were performed for different lung zones from ventral to dorsal (1 = ventral, 2 = mid-ventral, 3 = mid-dorsal, and 4 = dorsal) at lungs apex, hilum, and base using dynamic computed tomography. The contributions of BIPAP+SB_{spont} and BIPAP+SB_{controlled} to BIPAP+SB_{mean} were weighted by their respective rates (weighted mean). Bars and vertical lines represent means and standard deviations, respectively. * $P < 0.05$ vs. PSV; † $P < 0.05$ vs. BIPAP+SB_{controlled}.

associated lung injury [22]. Recruitment occurs mainly in nonaerated tissue [21], but seems to also take place in the poorly aerated tissue [14]. Tidal reaeration and hyperaeration have been described during studies on controlled mechanical ventilation [14,21,23,24], but data during assisted mechanical ventilation are scarce. Wrigge and colleagues [8] reported in an oleic acid model of ALI, more aeration and less tidal recruitment in dependent lung zones during BIPAP+SB_{mean} compared with pressure-controlled ventilation. However, other forms of assisted mechanical ventilation were not addressed. We found that mean tidal hyperaeration and reaeration were less pronounced during BIPAP+SB than PSV. However, when analyzed separately, we found that BIPAP+SB_{controlled} were associated with increased tidal hyperaeration and reaeration compared with

PSV, whereas BIPAP+SB_{spont} showed the opposite pattern. As mean V_T and Ppl were lower during BIPAP+SB_{spont} than BIPAP+SB_{controlled}, BIPAP+SB_{mean} could be claimed to be more lung protective than PSV due to lower mean distending volumes/pressures during spontaneous breathing. On the other hand, Ppl, tidal hyperaeration and reaeration were more pronounced during BIPAP+SB_{controlled} than PSV. Thus, the phenomena of cyclic collapse-reopening and overdistension may be more significant if the proportion of controlled to spontaneous breaths during BIPAP+SB_{mean} is high. Furthermore, RR was higher during BIPAP+SB_{mean} compared with PSV, which may favor lung injury [25]. Our findings raise the question on how much spontaneous breathing should be allowed or used during BIPAP+SB_{mean} to improve respiratory function and reduce ventilator-asso-

ciated lung injury. However, it was beyond the scope of this work to determine the impact of BIPAP+SB_{mean} and PSV on lung injury.

Distribution of ventilation and gas exchange

As BIPAP+SB_{mean} was associated with increased inspiratory effort, we expected the relative ventilation to be higher with that mode in the most dependent lung zones compared with PSV [26]. However, the distribution of ventilation was similar during BIPAP+SB_{mean} and PSV, both during spontaneous and controlled breaths. The most likely explanation is that although the inspiratory transpulmonary pressures in dependent zones increased aeration during BIPAP+SB_{mean} compared with PSV, the impedance to ventilation was likely to not be changed and shift of relative ventilation did not occur.

As the percentage of nonaerated areas was decreased during BIPAP+SB_{mean} compared with PSV, we expected an improvement in oxygenation. However PaO₂/FIO₂ and venous admixture were comparable between modes, suggesting that hypoxic vasoconstriction most likely played a role. BIPAP+SB_{mean} results in increased redistribution of pulmonary blood flow from dorsal to ventral zones [11]. Two possible mechanisms may explain limited carbon dioxide exchange during BIPAP+SB_{mean} compared with PSV, despite similar minute ventilation. First, total alveolar ventilation was reduced due low V_T in spontaneous breaths. Second, during controlled breaths, higher dead space due to increased hyperaerated areas may have occurred.

Limitations

This study has several limitations. First, the surfactant depletion model does not reproduce all features of clinical ALI and extrapolation of our results to the clinical scenario is limited. Second, artifacts introduced by the cranial-caudal movement of lungs were not compensated during calculations of aeration by CT_{dyn}, and levels chosen for the slices may have slightly differed between ventilation modes. However, measurements were performed at three different lung levels and we did observe regional differences. Furthermore, the levels used for CT scans were referred to anatomical landmarks (carina), likely reducing such artifacts. Third, tidal aeration and hyperaeration calculations were of volumetric nature. As hyperaerated areas have proportionally low mass, the absolute amount of lung tissue undergoing cyclic hyperaeration may be reduced. On the other hand, the thresholds for CT compartments most likely resulted in underestimation of hyperaeration in ALI, but they correspond to those internationally recommended [27,28]. Fourth, the assessment of relative ventilation by changes in CT densities may have been skewed by movement of gas within structures with limited participation in gas exchange, like small airways. Nevertheless, stress/strain

of those structures seems to play an important role in ventilator-induced lung injury [29]. Fifth, we did not determine the impact of BIPAP+SB_{mean} and PSV on lung mechanical stress and inflammation directly. However, in experimental ALI, tidal hyperaeration and reaeration seem to be closely related to overdistension and collapse/reopening of lung units, respectively [12,14,30].

Conclusions

In this model of ALI, the reduction of tidal reaeration and hyperaeration during BIPAP+SB_{mean} compared with PSV is not due to decreased nonaerated areas at end-expiration or different distribution of ventilation, but to lower V_T during BIPAP+SB_{spont}.

Key messages

- Compared with PSV, BIPAP+SB_{mean} resulted in: lower mean V_T, comparable oxygenation and hemodynamics, and increased PaCO₂ and inspiratory effort; less nonaerated areas at end-expiration; decreased tidal hyperaeration and reaeration; similar distributions of relative ventilation.
- During BIPAP+SB_{mean}: BIPAP+SB_{spont} had lower V_T and higher rate than BIPAP+SB_{controlled}; BIPAP+SB_{spont} and BIPAP+SB_{controlled} had similar distributions of ventilation and aeration; BIPAP+SB_{controlled} resulted in increased tidal reaeration and hyperaeration, compared with PSV, while BIPAP+SB_{spont} showed an opposite pattern.
- The ratio between spontaneous to controlled breaths could play an important role in reducing tidal reaeration and hyperaeration during BIPAP+SB_{mean}.

Additional material

Additional file 1 Calculation of mean airway pressures. This file shows exactly how the mean airway pressures were calculated for the different modes of assisted ventilation, including the spontaneous and controlled cycles of biphasic positive airway pressure + spontaneous breathing (BIPAP+SB_{mean}).

Additional file 2 Dynamic computed tomography in a representative animal during biphasic positive airway pressure + spontaneous breathing (BIPAP+SB_{mean}). This video shows a dynamic computed tomography scan (grey scale) of the chest taken for approximately 60 seconds at the hilus in one representative animal during assisted ventilation with BIPAP+SB_{mean}. Acute lung injury was induced by surfactant depletion. See Additional file 3 for comparison with pressure support ventilation (PSV).

Additional file 3 Dynamic computed tomography in a representative animal during pressure support ventilation (PSV). This video shows a dynamic computed tomography scan (grey scale) of the chest taken for approximately 60 seconds at the hilus in a representative animal during assisted ventilation with PSV. Acute lung injury was induced by surfactant depletion. See Additional file 2 for comparison with biphasic positive airway pressure + spontaneous breathing (BIPAP+SB_{mean}).

Abbreviations

ALI: acute lung injury; ARDS: acute respiratory distress syndrome; BIPAP+SB_{controlled}: time-cycled controlled breaths at two levels of continuous positive air-

way pressure during BIPAP+SB_{mean}; BIPAP+SB_{mean}: biphasic positive airway pressure with non-assisted spontaneous breathing; BIPAP+SB_{spont}: non-assisted spontaneous breathing during BIPAP+SB_{mean}; CT: computed tomography; CT_{dyn}: dynamic computed tomography; FiO₂: fraction of inspired oxygen; HU: Hounsfield units; I:E: inspiratory:expiratory ratio; P_{0.1}: decay in airway pressure 100 ms after begin of the inspiration; PaCO₂: partial pressure of arterial carbon dioxide; PaO₂: partial pressure of arterial oxygen; P_{aw}: airway pressure; PEEP: positive end-expiratory pressure; PEEP_{idyn}: dynamic intrinsic end-expiratory pressure; Pmean: mean airway pressure; Ppeak: peak airway pressure; Ppl mean: mean transpulmonary pressure; PSV: pressure support ventilation; PTP: pressure versus time product of the inspiratory esophageal pressure; RR: respiratory rate; Ti/Ttot: inspiratory to total respiratory time; V_T: tidal volume.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors made substantial contribution to the study design. MGA and MC drafted the manuscript and helped to perform the experiments. PM, ARC and CS helped to perform the experiments and contributed to drafting the manuscript. MC and VH developed the software for analysis of dynamic computed tomography scans and helped to draft the manuscript. BW performed the more complex multivariate statistical analysis and helped to draft the manuscript. All other authors revised the manuscript for important intellectual content. All authors approved the final version of the manuscript for publication.

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