Therapeutic Range of Spontaneous Breathing during Mechanical Ventilation

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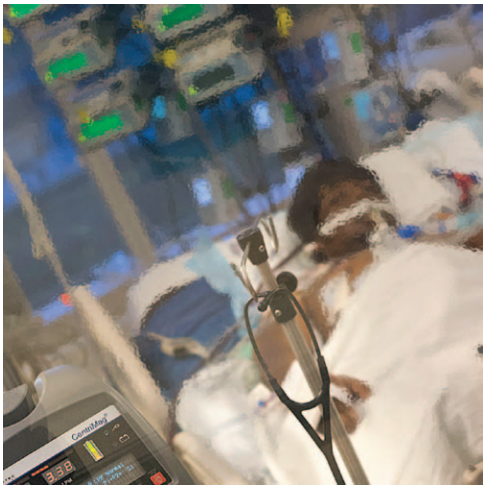
IN the fourth century before the common era (BCE), the Greek philosopher and physician Hippocrates expressed his wisdom on the value of activity to the sick and the healthy by stating that: "The sick will of course profit to a great extent from gymnastics with regard to the restoration of their health and the healthy will profit with regard to its maintenance" (On Regimen in Acute Diseases, 3, 400 BCE). In contemporary critical care medicine, driven by the goal of protecting our patients from self-inflicted injury, pain, and anxiety—and in contrast to Hippocrates' suggestions—we have built a culture of immobilizing our patients: we prescribe high doses of opioids, sedatives, anxiolytics, and antipsychotics, and with the best intentions, we place bed-rest and restraints orders. In patients with severe respiratory failure, we frequently use immobilizing ventilator settings such as volume control ventilation. Recent data have been increasingly challenging this tenet in relation to the fields of neuropsychiatry, rehabilitation, and respiratory medicine.[1–5]

In this issue of ANESTHESIOLOGY, two articles bring new information on why the concept of muscle activity is also relevant to lung biochemistry and regional function. Güldner *et al.*[6] and Bruells *et al.*[7] provide important experimental data on the relationship between the dose of diaphragmatic activity (spontaneous contribution to breathing during mechanical ventilation) and the resulting response in terms of lung mechanical stress, gas exchange, and markers of muscle deconditioning.



"[These studies] support the view that management strategies allowing for diaphragmatic exercise through an increase in spontaneous breathing could result in improved … [global and regional lung] function and help decrease the incidence of respiratory muscle dysfunction in the intensive care unit."

As the main respiratory muscle, the diaphragm contributes 72% for tidal breathing[8] and its role in respiratory mechanics and gas exchange goes well beyond this global number. One of the reasons is its curvature during spontaneous breathing in the supine position, which facilitates expansion of dependent lung regions,[9] optimizes the regional distribution of lung ventilation, and prevents loss of dependent lung aeration and increase in shunt observed when muscle paralysis is produced.[10]

Accordingly, modes of ventilation proposed since the 1970s tried to explore those advantages in patients with acute respiratory failure. The beneficial effects of maintaining continuous spontaneous breathing during mechanical ventilation in patients with acute respiratory failure have been described by Putensen *et al.*[11,12] in two well-designed studies. However, in patients with severe respiratory failure, barriers to spontaneous breathing, including patient–ventilator asynchrony, high oxygen consumption of the respiratory pump muscles, and the risk of barotrauma, have hindered a clear determination of the value of spontaneous breathing during mechanical ventilation.

Both Positive and Negative (Spontaneous) Pressure Ventilation Can Create Harmful Stress and Strain

To characterize ventilator-induced lung injury, it is important to consider the consequences of the mechanical forces acting in the lung parenchyma. The fundamental physical concepts are

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Corresponding articles on page 665 and page 673.

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those of mechanical stress and strain. Stress can be understood as the force per unit of area across a surface within the material under study (*e.g.*, lung tissue), and strain as the relative deformation of that material. Methods to strictly assess lung stress and strain acting on lung cells are currently not available. Consequently, surrogate measurements are used to estimate those quantities. The transpulmonary pressure is a currently used surrogate of lung tissue stress. It is computed as the difference between the airway pressure and the pleural pressure, the latter estimated from the esophageal pressure. For strain, measurements of relative volume change are used, for example, the ratio of the change in lung volume to the resting lung volume during a breathing cycle quantified by imaging techniques.[13,14]

Both positive-pressure mechanical ventilation and spontaneous breathing expose the lung to variable degrees of stress and strain, which result in lung injury.[15] High levels of negative pressure created by respiratory muscles (typically observed in patients with hypercarbic respiratory failure) may critically increase transpulmonary pressure resulting in an increased risk of barotrauma. Indeed, contrasting with reports on the beneficial effects of spontaneous breathing,[11,12] Papazian *et al.* recently suggested that large doses of a neuromuscular-blocking agent (NMBA) could benefit patients in the course of acute respiratory distress syndrome by improving patient–ventilator synchrony and allowing for the accurate adjustment of tidal volume and pressure levels. These authors also reported a lower incidence of new pneumothorax, pneumomediastinum, subcutaneous emphysema, or pneumatocele with administration of cisatracurium, demonstrating the risk of high activity of respiratory pump muscles. It is highly likely that lower transpulmonary pressures due to the use of cisatracurium were responsible for a portion of the reported benefit.

When spontaneous-breathing activity is allowed during mechanical ventilation, the increase in transpulmonary pressure in dependent lung zones may lead to recruitment of atelectatic lung tissue and reduction in lung elastance. Güldner *et al.* demonstrate[2] that such improvement in dependent lung aeration is associated with a reduction in transpulmonary pressure when spontaneous breathing represents a larger percentage of total ventilation with a biphasic positive airway pressure ventilation/airway pressure-release ventilation mode. The resulting increase in end-expiratory lung volumes resulted in a reduction in the ratio of regional inspired lung volume to end-expired lung volume, their surrogate measure of strain. By using imaging methods, the authors additionally established that the consequent oxygenation benefit was likely more associated with changes in aeration than in perfusion distribution. Overall, the findings imply that a larger contribution of spontaneous ventilation resulted in an improvement in the mechanical conditions in those injured lungs with reduction in lung stress and strain.

Ventilator-induced Diaphragmatic Dysfunction

Another mechanism of spontaneous breathing on the ventilator relates to protective effects on ventilator-induced diaphragmatic dysfunction, which is defined as the loss of diaphragmatic force-generating capacity specifically related to the use of passive mechanical ventilation. It is characterized by structural damage to muscle fibers from oxidative stress, mitochondrial dysfunction, and lipid accumulation as well as muscle atrophy.[16] Atrophy from prolonged inactivity heavily affects the most active skeletal muscles and respiratory muscles are susceptible to disuse atrophy given their constant high activity levels.

Respiratory depressants decrease the drive to the phrenic nerve and may lead to diaphragm atrophy. Recent data suggest that the time course and the mechanisms of immobilization-induced diaphragmatic weakness observed in preclinical models, including early disruption of the myofilament protein structure, translate to intensive care unit patients.[16–18] In a clinical scenario, high-dose opioids and propofol infusions do not allow for the appropriate diaphragmatic contractions required to avoid ventilator-induced diaphragmatic weakness that delays weaning from the ventilator. Bruells *et al.*[7] suggest that high doses of anesthetic agents such as propofol are sufficient to abolish the beneficial effects of spontaneous breathing.

Neuromuscular-blocking agents add significantly to the effects of immobilizing ventilator modes to worsen ventilator-induced diaphragmatic dysfunction,[19] which is the reason why the long-term use of NMBA to facilitate mechanical ventilation should be avoided in critical care medicine. Of note, the harmful effects of NMBA resulting in ventilator-induced diaphragmatic dysfunction occur while the drive of the phrenic nerve remains high (in contrast to the effects of centrally acting respiratoy depressants such as propofol). This clinical scenario increases vulnerability to posttraumatic stress disorder,[20] particularly if NMBAs are given in the absence of monitoring of cognitive function.

Limitations

Both studies were quite circumspect in acknowledging their limitations. Ultimately, the results will need further clarification of mechanisms in experimental models and confirmation in clinical investigations. Importantly, respiratory mechanics, distribution of lung ventilation and perfusion, and consequent gas exchange will vary in different presentations of clinical respiratory failure. Those could lead to different results in terms of lung mechanical forces, and optimal range of spontaneous-breathing contribution. Indeed, the relatively small differences in transpulmonary pressures, oxygenation, aeration, and perfusion observed by Güldner *et al.* at the different levels of spontaneous breathing during biphasic positive airway pressure ventilation/airway pressure-release ventilation suggest that different functional conditions could shift the optimal setpoint for that spontaneous-breathing contribution in individual cases.

Clinical Implications

Rapid recovery of spontaneous breathing should be the goal in patients requiring intubation and mechanical ventilation,

and it is important to optimize the level of diaphragmatic contractions during mechanical ventilation (fig. 1). Güldner *et al.* and Bruells *et al.*'s works are consistent with the concept that NMBA or high doses of respiratory depressants that minimize or even abolish diaphragmatic activity during mechanical ventilation should be avoided due to the risk for ventilator-induced diaphragmatic dysfunction, increased lung stress, and suboptimal gas exchange. However, excessive diaphragmatic contractions leading to increased work of breathing and increased lung stress should also be prevented. This concept has been recently emphasized by the finding in injured lungs of increased transpulmonary pressures in dependent lung regions, which resulted in air shift from nondependent to dependent regions (Pendelluft) and risk for local overstretch.[21]

In summary, the works by Güldner *et al.*[6] and Bruells *et al.*[7] support the view that management strategies allowing for diaphragmatic exercise through an increase in spontaneous breathing could result in improved respiratory mechanics, gas exchange, and diaphragmatic function and help decrease the incidence of respiratory muscle dysfunction in the intensive care unit. They point toward an approach of judicious use of respiratory-depressant anesthetics, NMBAs, and ventilation modes that allow for spontaneous breathing or noninvasive ventilation whenever possible.

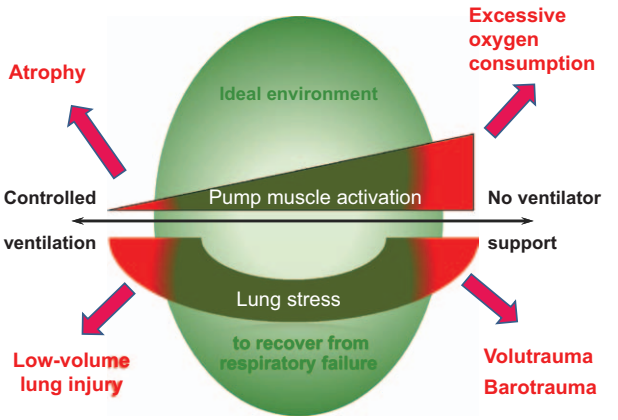

Fig. 1. Effects of the different contribution of spontaneous breathing on the ventilator on different factors influencing the recovery from respiratory failure. Increasing levels of ventilatory support achieved with neuromuscular blockade, anesthetics, and ventilator settings, suppress diaphragmatic contractions, leading to ventilator-induced diaphragmatic dysfunction and increased mechanical stress in the lungs. Among the several mechanisms leading to ventilator-induced lung injury present in this condition, those associated with low-volume lung injury and increased lung stress are presented by Güldner *et al.*[6] In contrast, minimal or no ventilator support in severe respiratory failure leads to excessive diaphragmatic contractions that require a high oxygen delivery resulting from the increased work of breathing. In addition, excessive spontaneous-breathing efforts with increased negative pleural pressures may lead to undesirably high levels of transpulmonary pressures and expose the patient to increased risk of barotrauma and volutrauma. The *green region* represents the mid-path, that is, optimized diaphragmatic contractions that provide the ideal environment for recovery from respiratory failure.

One of Hippocrates' heuristics was that "things which can be done well or properly should all be done properly" (On Regimen in Acute Diseases, 400 BCE). As far as mechanical ventilation in the intensive care unit is concerned, we agree with his statement that "If we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have found the safest way to health." (Regimen Book 1, 2).

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Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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References

1. Lipshutz AK, Gropper MA: Acquired neuromuscular weakness and early mobilization in the intensive care unit. Anesthesiology 2013; 118:202–15
2. Meyer MJ, Stanislaus AB, Lee J, Waak K, Ryan C, Saxena R, Ball S, Schmidt U, Poon T, Piva S, Walz M, Talmor DS, Blobner M, Latronico N, Eikermann M: Surgical Intensive Care Unit Optimal Mobilisation Score (SOMS) trial: A protocol for an international, multicentre, randomised controlled trial focused on goal-directed early mobilisation of surgical ICU patients. BMJ Open 2013; 3:e003262
3. Camargo Pires-Neto R, Fogaça Kawaguchi YM, Sayuri Hirota A, Fu C, Tanaka C, Caruso P, Park M, Ribeiro Carvalho CR: Very early passive cycling exercise in mechanically ventilated critically ill patients: Physiological and safety aspects—A case series. PLoS One 2013; 8:e74182
4. Sasaki N, Meyer MJ, Eikermann M: Postoperative respiratory muscle dysfunction: Pathophysiology and preventive strategies. Anesthesiology 2013; 118:961–78
5. Eikermann M, Latronico N: What is new in prevention of muscle weakness in critically ill patients? Intensive Care Med 2013; 39:2200–3
6. Güldner A BA, Carvalho NC, Beda A, Zeidler S, Wiedemann B, Wunderlich G, Andreeff M, Uhlig C, Spieth PM, Koch T, Pelosi P, Kotzerke J, Gama de Abreu M: Higher levels of spontaneous breathing induce lung recruitment and reduce global stress/strain in experimental lung injury. Anesthesiology 2014; 120:673–82
7. Bruells CS Maes K, Rossaint R, Thomas D, Cielen N, Bergs I, Bleilevens C, Weis J, Gayan-Ramirez G: Sedation using propofol induces similar diaphragm dysfunction and atrophy during spontaneous breathing and mechanical ventilation in rats. Anesthesiology 2014; 120:665–72
8. Jones JG, Minty BD: The relative contribution to tidal breathing of the chest wall and the abdomen in awake and anaesthetized subjects. Br J Anaesth 1976; 48:812

9. Reber A, Nylund U, Hedenstierna G: Position and shape of the diaphragm: Implications for atelectasis formation. Anaesthesia 1998; 53:1054–61
10. Tokics L, Hedenstierna G, Strandberg A, Brismar B, Lundquist H: Lung collapse and gas exchange during general anesthesia: Effects of spontaneous breathing, muscle paralysis, and positive end-expiratory pressure. ANESTHESIOLOGY 1987; 66:157–67
11. Putensen C, Mutz NJ, Putensen-Himmer G, Zinserling J: Spontaneous breathing during ventilatory support improves ventilation-perfusion distributions in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 1999; 159(4 Pt 1):1241–8
12. Putensen C, Zech S, Wrigge H, Zinserling J, Stüber F, Von Spiegel T, Mutz N: Long-term effects of spontaneous breathing during ventilatory support in patients with acute lung injury. Am J Respir Crit Care Med 2001; 164:43–9
13. Protti A, Cressoni M, Santini A, Langer T, Mietto C, Febres D, Chierichetti M, Coppola S, Conte G, Gatti S, Leopardi O, Masson S, Lombardi L, Lazzerini M, Rampoldi E, Cadringher P, Gattinoni L: Lung stress and strain during mechanical ventilation: Any safe threshold? Am J Respir Crit Care Med 2011; 183:1354–62
14. Wellman TJ, Winkler T, Costa EL, Musch G, Harris RS, Venegas JG, Melo MF: Measurement of regional specific lung volume change using respiratory-gated PET of inhaled ^{13}N-nitrogen. J Nucl Med 2010; 51:646–53
15. Yoshida T, Uchiyama A, Matsuura N, Mashimo T, Fujino Y: The comparison of spontaneous breathing and muscle paralysis in two different severities of experimental lung injury. Crit Care Med 2013; 41:536–45
16. Picard M, Jung B, Liang F, Azuelos I, Hussain S, Goldberg P, Godin R, Danialou G, Chaturvedi R, Rygiel K, Matecki S, Jaber S, Des Rosiers C, Karpati G, Ferri L, Burelle Y, Turnbull DM, Taivassalo T, Petrof BJ: Mitochondrial dysfunction and lipid accumulation in the human diaphragm during mechanical ventilation. Am J Respir Crit Care Med 2012; 186:1140–9
17. Grosu HB, Lee YI, Lee J, Eden E, Eikermann M, Rose KM: Diaphragm muscle thinning in patients who are mechanically ventilated. Chest 2012; 142:1455–60
18. Jaber S, Petrof BJ, Jung B, Chanques G, Berthet JP, Rabuel C, Bouyabrine H, Courouble P, Koechlin-Ramonatxo C, Sebbane M, Similowski T, Scheuermann V, Mebazaa A, Capdevila X, Mornet D, Mercier J, Lacampagne A, Philips A, Matecki S: Rapidly progressive diaphragmatic weakness and injury during mechanical ventilation in humans. Am J Respir Crit Care Med 2011; 183:364–71
19. Testelmans D, Maes K, Wouters P, Gosselin N, Deruisseau K, Powers S, Sciot R, Decramer M, Gayan-Ramirez G: Rocuronium exacerbates mechanical ventilation-induced diaphragm dysfunction in rats. Crit Care Med 2006; 34:3018–23
20. Nelson BJ, Weinert CR, Bury CL, Marinelli WA, Gross CR: Intensive care unit drug use and subsequent quality of life in acute lung injury patients. Crit Care Med 2000; 28:3626–30
21. Yoshida T, Torsani V, Gomes S, De Santis RR, Beraldo MA, Costa EL, Tucci MR, Zin WA, Kavanagh BP, Amato MB: Spontaneous effort causes occult Pendelluft during mechanical ventilation. Am J Respir Crit Care Med 2013; 188:1420–7

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

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_20, 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 $\dot{Q}_{rel}$ $\left(A_e / \dot{Q}_{rel}\right)$, 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_20; 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.

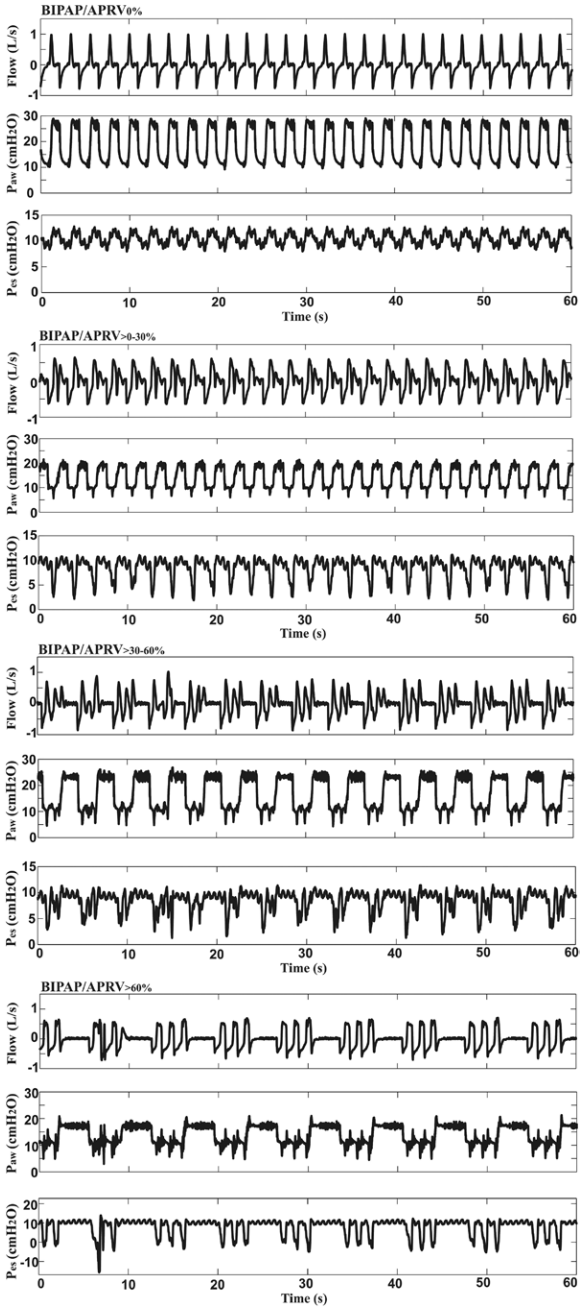

Fig. 1. Respiratory tracings of airflow (Flow), airway pressure (P_{aw}), and esophageal pressure (P_{es}) during biphasic positive airway pressure/airway pressure release ventilation (BIPAP/APRV) at four different levels of spontaneous breathing in total minute ventilation (0%, >0 to 30%, >30 to 60%, 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_2O)	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_2O)					13.4 ± 1.2	12.8 ± 1.1	13.4 ± 1.1
$P_{aw,peak; contr. cycles}$ (cm H_2O)					19.6 ± 1.4	19.4 ± 2.5	20.1 ± 1.4
$P_{aw,peak; mixed cycles}$ (cm H_2O)					19.4 ± 2.8	19.8 ± 2.8	20.7 ± 1.9
$P_{aw,mean}$ (cm H_2O)	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_2O)					10.9 ± 0.9	10.9 ± 1.1	10.5 ± 0.2
$P_{aw,mean; contr. cycles}$ (cm H_2O)					14.8 ± 0.8	15.9 ± 1.4	17.1 ± 1.1#
$P_{aw,mean; mixed cycles}$ (cm H_2O)					14.2 ± 1.2	15.8 ± 1.6#	16.5 ± 1.3#†
$P_{L,peak}$ (cm H_2O)	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_2O)					5.3 ± 1.3	5.8 ± 2.5	6.8 ± 2.4
$P_{L,peak; contr. cycles}$ (cm H_2O)					9.2 ± 2.1	9.2 ± 2.1	10.3 ± 1.7
$P_{L,peak; mixed cycles}$ (cm H_2O)					10.1 ± 2.3	10.8 ± 2.6	13.0 ± 3.1
$P_{L,mean}$ (cm H_2O)	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_2O)					3.1 ± 0.8	2.9 ± 1.4	3.4 ± 0.9
$P_{L,mean; contr. cycles}$ (cm H_2O)					4.9 ± 1.5	5.8 ± 1.5	7.4 ± 1.4#†
$P_{L,mean; mixed cycles}$ (cm H_2O)					5.2 ± 1.3	6.1 ± 1.7#	7.4 ± 1.9#†
PTP (cm H_2O × s/min)					28.6 ± 24.4	45.5 ± 31.0#	58.2 ± 39.6#
$PTP_{spont cycles}$ (cm H_2O × s/min)					2.7 ± 2.7	25.0 ± 15.8#	42.8 ± 24.9#†
$PTP_{mixed cycles}$ (cm H_2O × 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.

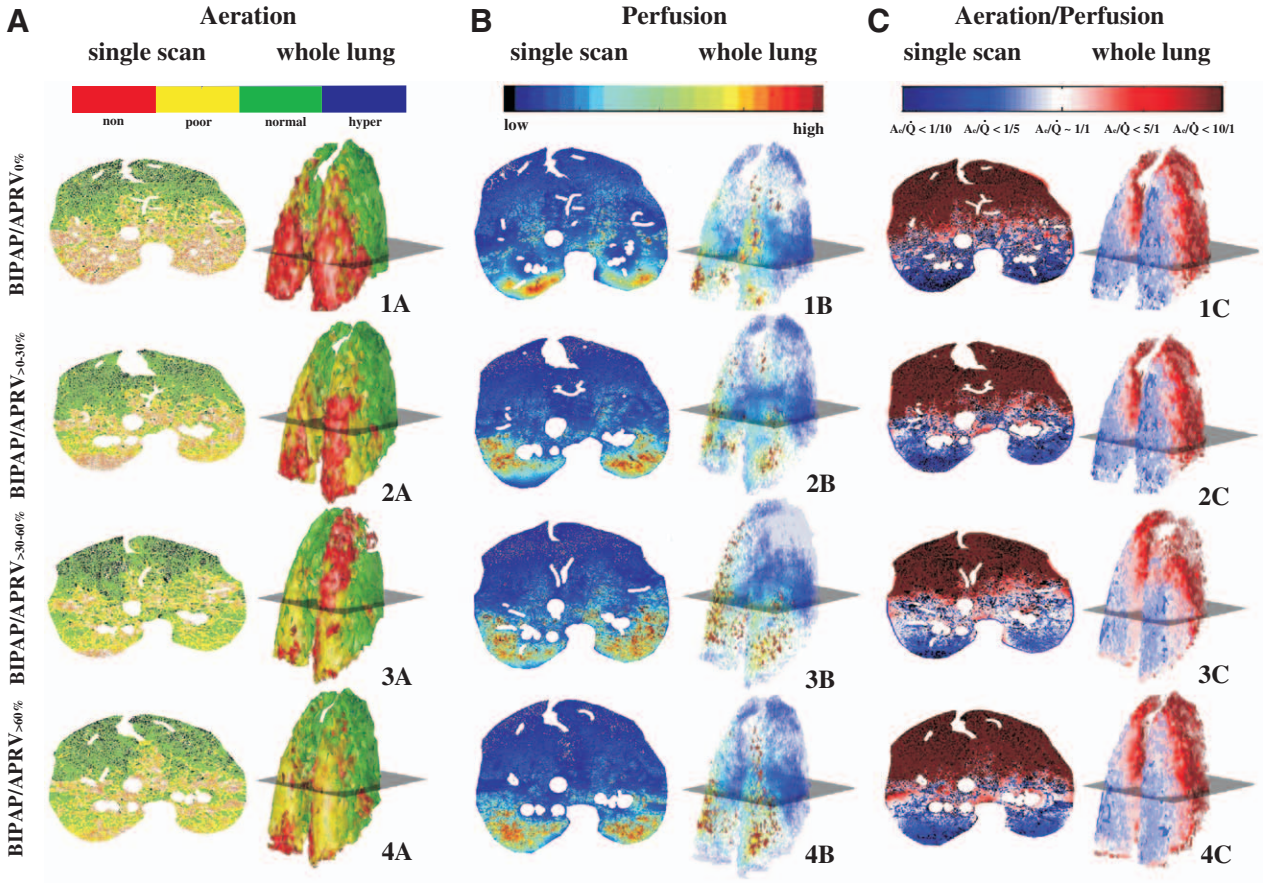

Fig. 2. Distributions of aeration (column *A*), perfusion (column *B*), and aeration/perfusion ($A_a/\dot{Q}$, column *C*) during biphasic positive airway pressure/airway pressure release ventilation (BIPAP/APRV) at four different levels of spontaneous breathing in total minute ventilation (0%, >0 to 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 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.

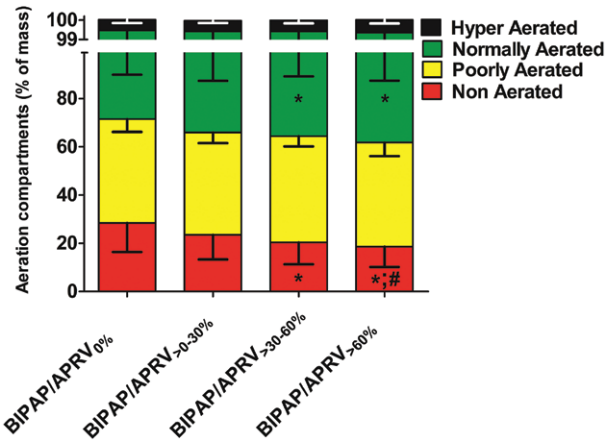

Fig. 3. Distributions of nonaerated (*red*), poorly aerated (*yellow*), normally aerated (*green*), and hyperaerated compartments (*black*). Values are given as mean (*bar*) and SD (*error bar*) and were calculated as percentage of mass of whole lungs during biphasic positive airway pressure/airway pressure 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/$APRV_{>0–30\%}$.

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_2O, 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

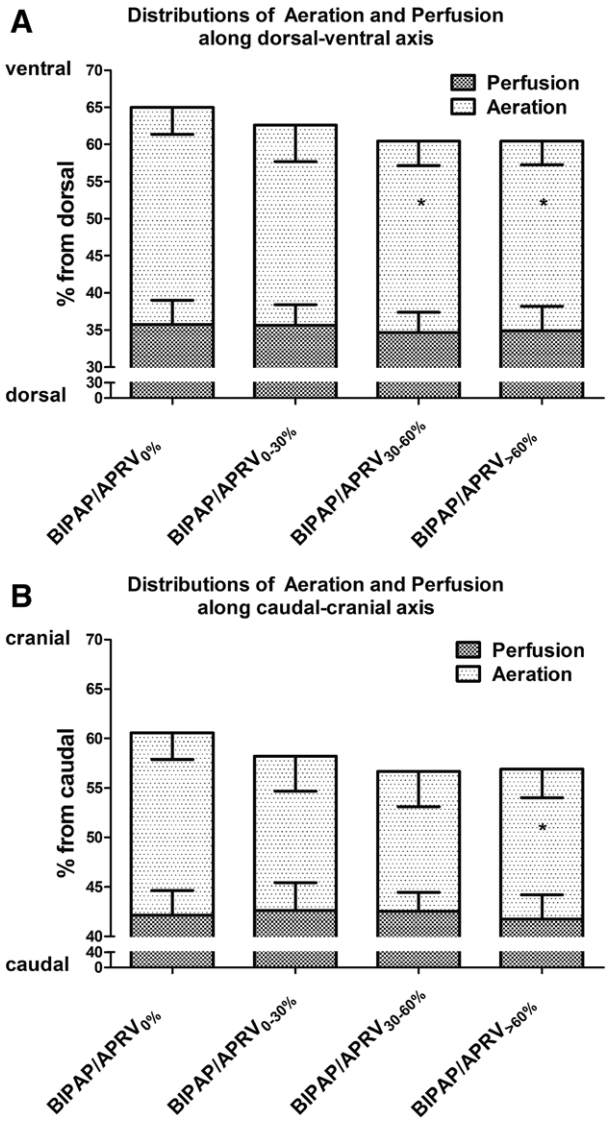

Fig. 4. Distributions of aeration and perfusion, along the dorsal-ventral axis (*A*) and the cranial-caudal axis (*B*) during biphasic positive airway pressure/airway pressure release ventilation (BIPAP/APRV) at four different levels of spontaneous breathing in total minute ventilation (0%, >0 to 30%, >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$_{0\%}$.

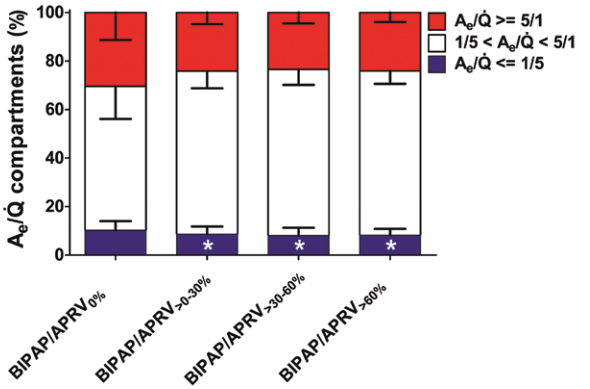

Fig. 5. Distributions of aeration/perfusion $\left(A_e/\dot{Q}\right)$ compartments in whole lungs during biphasic positive airway pressure/airway pressure release ventilation (BIPAP/APRV) at four different levels of spontaneous breathing in total minute ventilation (0%, >0 to 30%, >30 to 60%, and >60%).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

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Competing Interests

The authors declare no competing interests.

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References

1. Puybasset L, Cluzel P, Gusman P, Grenier P, Preteux F, Rouby JJ; The CTSASG: Regional distribution of gas and tissue in acute respiratory distress syndrome. I. Consequences for lung morphology. Intensive Care Med 2000; 26:857–69
2. Pelosi P, Rocco PR, de Abreu MG: Use of computed tomography scanning to guide lung recruitment and adjust positive-end expiratory pressure. Curr Opin Crit Care 2011; 17:268–74
3. Putensen C, Wrigge H: Clinical review: Biphasic positive airway pressure and airway pressure release ventilation. Crit Care 2004; 8:492–7
4. Neumann P, Wrigge H, Zinserling J, Hinz J, Maripuu E, Andersson LG, Putensen C, Hedenstierna G: Spontaneous breathing affects the spatial ventilation and perfusion distribution during mechanical ventilatory support. Crit Care Med 2005; 33:1090–5
5. Carvalho AR, Spieth PM, Pelosi P, Beda A, Lopes AJ, Neykova B, Heller AR, Koch T, Gama de Abreu M: Pressure support ventilation and biphasic positive airway pressure improve oxygenation by redistribution of pulmonary blood flow. Anesth Analg 2009; 109:856–65
6. Gama de Abreu M, Guldner A, Pelosi P: Spontaneous breathing activity in acute lung injury and acute respiratory distress syndrome. Curr Opin Anaesthesiol 2012; 25:148–55
7. Putensen C, Mutz NJ, Putensen-Himmer G, Zinserling J: Spontaneous breathing during ventilatory support improves ventilation-perfusion distributions in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 1999; 159(4 Pt 1):1241–8
8. Lanteri CJ, Kano S, Sly PD: Validation of esophageal pressure occlusion test after paralysis. Pediatr Pulmonol 1994; 17:56–62
9. Vieira SR, Puybasset L, Richecoeur J, Lu Q, Cluzel P, Gusman PB, Coriat P, Rouby JJ: A lung computed tomographic assessment of positive end-expiratory pressure-induced lung overdistension. Am J Respir Crit Care Med 1998; 158(5 Pt 1):1571–7
10. Kotzerke J, Andreeff M, Wunderlich G, Wiggermann P, Zöphel K: [Ventilation-perfusion-lungscintigraphy using PET and ^{68}Ga-labeled radiopharmaceuticals]. Nuklearmedizin 2010; 49:203–8
11. Lachmann B, Robertson B, Vogel J: *In vivo* lung lavage as an experimental model of the respiratory distress syndrome. Acta Anaesthesiol Scand 1980; 24:231–6
12. Gama de Abreu M, Spieth P, Pelosi P, Carvalho AR, Walter C, Schreiber-Ferstl A, Aikele P, Neykova B, Hübler M, Koch T: Noisy pressure support ventilation: A pilot study on a new assisted ventilation mode in experimental lung injury. Crit Care Med 2008; 36:818–27
13. Matute-Bello G, Frevert CW, Martin TR: Animal models of acute lung injury. Am J Physiol Lung Cell Mol Physiol 2008; 295:L379–99
14. Putensen C, Räsänen J, López FA: Ventilation-perfusion distributions during mechanical ventilation with superimposed spontaneous breathing in canine lung injury. Am J Respir Crit Care Med 1994; 150:101–8

15. Wrigge H, Zinserling J, Neumann P, Defosse J, Magnusson A, Putensen C, Hedenstierna G: Spontaneous breathing improves lung aeration in oleic acid-induced lung injury. Anesthesiology 2003; 99:376–84
16. Henzler D, Pelosi P, Bensberg R, Dembinski R, Quintel M, Pielen V, Rossaint R, Kuhlen R: Effects of partial ventilatory support modalities on respiratory function in severe hypoxemic lung injury. Crit Care Med 2006; 34:1738–45
17. Putensen C, Zech S, Wrigge H, Zinserling J, Stüber F, Von Spiegel T, Mutz N: Long-term effects of spontaneous breathing during ventilatory support in patients with acute lung injury. Am J Respir Crit Care Med 2001; 164:43–9
18. Zin WA, Milic-Emili J: Esophageal pressure measurement, Principles and Practice of Intensive Care Monitoring. Edited by Tobin MJ. New York, McGraw-Hill, 1997, pp 545–52
19. Yoshida T, Uchiyama A, Matsuura N, Mashimo T, Fujino Y: The comparison of spontaneous breathing and muscle paralysis in two different severities of experimental lung injury. Crit Care Med 2013; 41:536–45
20. Carvalho AR, Spieth PM, Güldner A, Cuevas M, Carvalho NC, Beda A, Spieth S, Stroczynski C, Wiedemann B, Koch T, Pelosi P, de Abreu MG: Distribution of regional lung aeration and perfusion during conventional and noisy pressure support ventilation in experimental lung injury. J Appl Physiol (1985) 2011; 110:1083–92
21. Pinto Da Costa N, Di Marco F, Lyazidi A, Carteaux G, Sarni M, Brochard L: Effect of pressure support on end-expiratory lung volume and lung diffusion for carbon monoxide. Crit Care Med 2011; 39:2283–9
22. Rimensberger PC, Cox PN, Frndova H, Bryan AC: The open lung during small tidal volume ventilation: Concepts of recruitment and "optimal" positive end-expiratory pressure. Crit Care Med 1999; 27:1946–52
23. Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, Jaber S, Arnal JM, Perez D, Seghboyan JM, Constantin JM, Courant P, Lefrant JY, Guérin C, Prat G, Morange S, Roch A; ACURASYS Study Investigators: Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010; 363:1107–16
24. Braune A, Güldner A, Carvalho N, Adreeff M, Oehme L, Spieth P, Zeidler S, Kerber S, Koch T, Pelosi P, Kotzerke J, Gama de Abreu M: Measurement of regional lung perfusion using ^{68}Ga-labelled and fluorescent-labelled microshperes In experimental lung injury: A comparative analysis. Am J Respir Crit Care Med 2013; 187: A4901