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Spontaneous Breathing Improves Lung Aeration in Oleic Acid–induced Lung Injury

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Background: **Experimental and clinical studies have shown reduction in intrapulmonary shunt with improved oxygenation by spontaneous breathing with airway pressure release ventilation (APRV) in acute lung injury. The mechanisms of these findings are not clear. The authors hypothesized that spontaneous breathing results in better aeration of lung tissue and that improvement in oxygenation can be explained by these changes. This hypothesis was studied in a porcine model of oleic acid–induced lung injury.**

Methods: **Two hours after induction of lung injury, 24 pigs were randomly assigned to APRV with or without spontaneous breathing at a positive end-expiratory pressure of 5 cm H_2O. Hemodynamics, spirometry, and end-expiratory lung volume by nitrogen washout were measured at baseline, after 2 h of lung injury, and after 2 and 4 h of mechanical ventilation in the specific mode. Finally, spiral computed tomography of the chest was performed at end-expiratory lung volume in 22 pigs.**

Results: **Arterial carbon dioxide tension and mean and end-inspiratory airway pressures were comparable between settings. Four hours of APRV with spontaneous breathing resulted in improved oxygenation compared with APRV without spontaneous breathing (arterial oxygen tension, 144 ± 65 *vs.* 91 ± 50 mmHg, $P < 0.01$ for interaction time × mode), higher end-expiratory lung volume (786 ± 320 *vs.* 384 ± 148 ml, $P < 0.001$), and better aeration. End-expiratory lung volume and venous admixture were both correlated with the amount of lung reaeration ($r^2 = 0.62$ and $r^2 = 0.61$, respectively).**

Conclusions: **The results support the hypothesis that spontaneous breathing during APRV improves oxygenation mainly by recruitment of nonaerated lung and improved aeration of the lungs.**

PARTIAL ventilatory support is used increasingly, not only to separate patients from mechanical ventilation, but also to provide stable ventilatory assistance of a desired degree during ventilatory failure.[1,2] Spontaneous breathing (SB) with airway pressure release ventilation (APRV) provides adequate ventilatory support in patients with both mild pulmonary insufficiency[3] and severe acute lung injury (ALI).[4,5] In patients with severe ALI, unsupported SB with APRV has been observed to improve arterial blood oxygenation when compared to controlled mechanical ventilation[1,4,5] or breath-to-breath inspiratory assistance with pressure support ventilation.[5]

During controlled mechanical ventilation, the diaphragm is relaxed, and its displacement will mainly be in nondependent, anterior regions—at least with small tidal volumes (V_T)— because of less impedance of abdominal organs in the upper region compared to the lower abdominal regions. On the other hand, during SB, posterior muscular sections of the diaphragm move more than the anterior tendon plate.[6,7] In parallel with the displacement of the diaphragm, ventilation seems to be distributed to upper, nondependent lung regions in the mechanically ventilated subject,[8,9] contrary to the well-known preference of dependent regions during SB.[9] Moreover, computed tomography (CT) of patients during anesthesia[10] and in mechanically ventilated patients with ALI[11–13] shows atelectasis and consolidation of lung in dependent and juxtadiaphragmatic regions. A decrease in atelectasis has also been shown after phrenic nerve stimulation.[14] Thus, recruitment of nonaerated lung and redistribution of gas to dependent, well-perfused lung regions may explain the observed reduction in intrapulmonary shunting and improved ventilation–perfusion matching during SB with APRV.[5,15–17]

Therefore, we hypothesized that SB during APRV will result in better aeration of lung tissue with less collapse or consolidation and improved end-expiratory lung volume (EELV) and that improvement in oxygenation can be explained by aeration changes. These hypotheses were studied using CT densitometry in a porcine model of oleic acid–induced ALI.

Materials and Methods

Animals

Animal experiments were performed in laboratories of the Department of Clinical Physiology at the University Hospital of Uppsala, Uppsala, Sweden. After approval of the local animal ethics committee, 30 healthy pigs (mixed breed of Hampshire, Yorkshire, and Swedish country breed; weight, 30 ± 3 kg) were anesthetized and mechanically ventilated in the supine position. Six animals died after induction of lung injury. Twenty-four pigs were randomized using sealed envelopes to receive APRV either with or without SB. CT measurements of two pigs in the APRV with SB group could not be

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performed for technical reasons, leaving 22 pigs that completed the study.

Anesthesia

Anesthesia was induced with intramuscular atropine (0.04 mg/kg), tiletamine–zolazepam (6 mg/kg), and xylazine (2.2 mg/kg), followed by infusion of 30 $mg \cdot kg^{-1} \cdot h^{-1}$ ketamine, 0.1 $mg \cdot kg^{-1} \cdot h^{-1}$ midazolam, and 1–2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil. Tracheotomy and fluid infusion were performed as previously described.[18] The remifentanil infusion rate was varied between 1 and 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to allow or suppress SB.

Cardiovascular Measurements

Instrumentation of the animals has been described previously.[19] Heart rate and mean systemic, central venous, and pulmonary artery blood pressures were measured using standard techniques.[19] Cardiac output and intrathoracic blood volume were determined with transpulmonary indicator dilution technique as mean of triplicate measurements.[19] Systemic and pulmonary vascular resistances were calculated using standard equations.

Ventilatory and Lung Mechanics Measurements

Gas flow was measured at the proximal end of the endotracheal tube with a heated pneumotachograph (No. 2; Fleisch, Lausanne, Switzerland), connected to a differential pressure transducer (Huba Control, Würenlos, Switzerland). Airway pressure was measured at the proximal end of the endotracheal tube with another differential gas-pressure transducer (SMT, Munich, Germany). Esophageal pressure was measured with a balloon catheter (International Medical, Zutphen, The Netherlands) connected to a differential pressure transducer (SMT). The validity of the esophageal balloon measurements in the supine subject was tested with the occlusion method of Brunner and Wolff.[20] Because absolute esophageal pressure depends on inflation pressure of the balloon, esophageal pressure was corrected to meet positive end-expiratory pressure (PEEP) at end-expiration, if necessary. All signals were sampled with an analog/digital converter board (PCM-DAS16S/12, Mansfield, MA) installed in a personal computer. Digitized signals were plotted in real time on the computer screen and stored on magnetic media for off-line analysis.

Tidal volume and minute ventilation were derived from the integrated gas flow signal and converted to body temperature pressure saturated conditions. Respiratory rate (RR) and inspiratory and expiratory times were determined from the gas flow signal. Mean and end-inspiratory airway pressures were determined for each respiratory cycle. Transpulmonary pressure was calculated as difference between airway and esophageal pressure. All ventilatory variables were averaged over a period of 5 min.

Gas Analysis

Arterial blood gases were measured with standard blood gas electrodes; oxygen saturation and hemoglobin were analyzed using spectrophotometry; fractions of inspired and expired oxygen, carbon dioxide, and nitrogen were measured with mass spectrometry (for details, see Wrigge *et al.*[18]). Oxygen delivery, oxygen consumption, and venous admixture ($\dot{Q}_{VA}/\dot{Q}_T$) were calculated using standard equations.

Determination of EELV

Multibreath nitrogen washout maneuvers were started consistently from the low continuous positive airway pressure/PEEP level by changing the fraction of inspired oxygen (F_{IO_2}) from baseline level to 1.0. Calculation of EELV has been described in detail previously.[18,21] Briefly, the viscosity-corrected gas flow signal was integrated off-line with the measured nitrogen fraction from the beginning to the end of the washout during both inspiration and expiration. The EELV calculation procedure was started with the first oxygen wash-in breath. Because the first breath usually still contains a certain amount of nitrogen, this inspired nitrogen volume was subtracted from the cumulative nitrogen volume calculated from the washout procedure. Mean values of two consecutive EELV determinations were used for analysis. Coefficient of variation of repeated EELV measurements was 10.4% in this setting.

Ventilatory Setting

APRV without SB. Time-cycled pressure-controlled ventilation (Evita 4; Dräger, Lübeck, Germany) was applied with an RR of 20 breaths/min, an inspiratory-to-expiratory ratio of 1:1, an F_{IO_2} of 0.5, a PEEP of 5 cm H_2O, and an inspiratory pressure that resulted in a V_T of approximately 10 ml/kg. If necessary, inspiratory pressure and RR were adjusted to achieve normocapnia (arterial carbon dioxide tension [Pa_{CO_2}] 35–45 mmHg) guided by end-tidal carbon dioxide monitoring (AS/3; Datex-Engström, Helsinki, Finland) and intermittent arterial blood samples.

After induction of lung injury, inspiratory pressure had to be increased because of decreased compliance, and RR was increased up to 30 breaths/min to maintain normocapnia while keeping the inspiratory-to-expiratory ratio constant. If hypercapnia developed in spite of these adjustments, a Pa_{CO_2} of 60 mmHg was accepted before inspiratory pressure was increased further. If SB occurred during hypercapnia as indicated by negative deflections in the esophageal pressure tracing, remifentanil infusion was increased to 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and if necessary, 2.5 mg/h pancuronium bromide was infused for muscle relaxation. PEEP and F_{IO_2} were kept constant during the entire study.

APRV with SB

Ventilator settings were guided by the principles described above. To allow reinstitution of SB, RR was consistently decreased to 15 breaths/min, resulting in (preset) inspiratory and expiratory times of 2 s, while maintaining inspiratory-to-expiratory ratio constant and remifentanil infusion was lowered.

Lung Injury

Mild-to-moderate lung injury was induced by slow (over 20 min) injection of 0.1 ml/kg oleic acid (Apoteksbolaget, Göteborg, Sweden) suspended in 20 ml isotonic saline *via* the central venous catheter. If the oxygen saturation decreased below 85% during the injection, no further oleic acid was given. During injection, blood pressure was stabilized with titrated doses of adrenaline.

CT Scanning and Analysis

During ventilation, a frontal topogram of the chest was obtained with a Somatom Plus 4 (Siemens, Erlangen, Germany). Guided by observation of airway pressure and flow curves, the tube was clamped strictly at end-expiration immediately followed by a spiral scan (140 kV, 111 mA, 0.75 s for one spin resulting in an acquisition time of 15–20 s), and transverse images were reconstructed with a slice thickness of 8 mm including all of both lungs. Depending on the transversal image seize, the pixel size was 0.25 ± 0.05 mm^2, resulting in a voxel size of 1.96 ± 0.39 mm^3. The craniocaudal scanning direction was randomized.

Computed tomography images were transferred to a personal computer and analyzed with a computer program (Osiris; University of Geneva, Geneva, Switzerland). In all slices, the entire left and right lungs were chosen as the region of interest by drawing the external boundaries of the lungs at the inside of the ribs and the internal boundaries along the mediastinal organs. The investigator was blinded to ventilatory mode. The number of pixels corresponding to each density value in the region of interest of each slice were counted and stored by the computer program. Density values outside the range of −1,000 and +100 Hounsfield units (HU), which constituted less than 1% of all counts, were excluded. Further analysis included three different approaches:

1. Craniocaudal dimensions of the lungs were measured from end-expiratory spiral CT as distances between lung apex and diaphragmatic dome as well as lung apex and costodiaphragmatic recessus.
2. Density counts in regions of interest of all slices were summarized to allow analysis of continuous density distribution of the entire lungs and calculation of mean density. In addition, four groups of density ranges with decreasing air content were defined as described previously[22–24]: range I included densities between −1,000 and −900 HU, previously defined as hyperinflation; range II included densities between −900 and −500 HU, defined as normal aeration; range III included densities between −500 and −100 HU, previously defined as poor aeration; and range IV included densities between −100 and 100 HU, representing atelectasis or lung parenchyma with an air content of 10% or less.
3. The density distribution analysis was limited to two transversal slices: one apical slice located at midpoint of the intrathoracic trachea and another located 1–2 cm above the diaphragm.
4. Pulmonary air content was estimated as the sum of air content of each voxel (CT unit of volume) of the entire lungs. Only voxels with densities ranging from −1,000 to −1 HU were included. Voxel size was calculated as the area of a pixel × 8 mm (slice thickness). Given the known limitations (*e.g.*, underestimation of gas volume due to the partial volume effect),[25] the resulting volume should correspond to EELV.

Protocol

Baseline blood gases, hemodynamics, and ventilatory parameters were obtained 30 min after completing instrumentation and 120 min after completing initiation of ALI. Animals were then randomized either to continue with controlled mechanical ventilation (APRV without SB) or to breathe spontaneously (APRV with SB). After 120 min of ventilation in the specific mode, measurements were repeated. Six hours after randomization, the pigs were transferred to the radiology department without interrupting ventilation or changing ventilatory mode, and another set of measurements was immediately followed by transverse spiral chest CT scans at end-expiration. This resulted in a total study period of approximately 8 h.

Statistics

Primary outcome measures were oxygenation, EELV, and amount of nonaerated lung. Sample size was based on findings of previous studies. To detect differences in these parameters between ventilatory settings with the given two-sided parallel design at a significance level of 5% ($\alpha = 0.05$) with a probability of 82% ($\beta = 0.18$) based on an estimated difference of 0.75 of the parameter's mean SD, at least 20 animals had to be studied.

Results are expressed as mean ± SD. All statistical analyses were performed using a statistical software package (STATISTICA for Windows 6.0; StatSoft, Inc., Tulsa, OK). Normal distribution of data were confirmed by Shapiro-Wilk W test, and data were analyzed using two-way analysis of variance for repeated measures with factors mode and time. Only when a significant F ratio was obtained for a factor (or for the interaction of factors), differences between means were isolated for the specific factor (or for all factors in case of significant interaction) with the *post hoc* Tukey multiple compari-

Table 1. Hemodynamics

Parameter	Group	Baseline	Lung Injury	2-h Treatment	4-h Treatment	Lung Injury	Time	Mode	Interaction
HR, beats/min	SB−	92 ± 16	95 ± 15	98 ± 15	98 ± 21				
	SB+	85 ± 15	93 ± 20	102 ± 20	105 ± 18				
MAP, mmHg	SB−	88 ± 20	86 ± 10	81 ± 12	81 ± 15				
	SB+	82 ± 14	87 ± 12	90 ± 19	92 ± 17				
CVP, mmHg	SB−	8 ± 2	11 ± 2	11 ± 2	10 ± 4		*		
	SB+	7 ± 2	11 ± 2	10 ± 1	10 ± 2				
SVR, dyn · s · cm^{-5}	SB−	1,967 ± 725	1,610 ± 353	1,538 ± 377	1,593 ± 383	†			
	SB+	2,089 ± 724	1,553 ± 314	1,493 ± 349	1,488 ± 352				
MPAP, mmHg	SB−	19 ± 3	34 ± 5	33 ± 6	33 ± 6	‡	‡	*	
	SB+	16 ± 2	35 ± 6	31 ± 5#	30 ± 6#				
PVR, dyn · s · cm^{-5}	SB−	260 ± 47	480 ± 136	467 ± 138	485 ± 142	‡			
	SB+	239 ± 83	464 ± 95	407 ± 113	394 ± 135				
CO, l/min	SB−	3.2 ± 0.8	3.8 ± 0.6	3.8 ± 0.9	3.8 ± 1.2	†			*
	SB+	3.1 ± 0.8	3.9 ± 0.9	4.4 ± 0.9	4.5 ± 0.9§				
ITBV, ml	SB−	582 ± 93	615 ± 64	601 ± 55	588 ± 81	*			
	SB+	592 ± 70	634 ± 45	637 ± 55	644 ± 57				

Baseline was only tested against Lung Injury. *Post hoc* testing was always performed if a significant F ratio for a factor or the interaction of factors was obtained by repeated-measures analysis of variance (* $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$), but only significant differences are marked: § $P < 0.05$, ‖ $P < 0.01$, # $P < 0.001$ for within-group differences and ** $P < 0.05$ for between-group differences (*post hoc* Tukey multiple comparison test).

CO = cardiac output, CVP = central venous blood pressure, HR = heart rate, ITBV = intrathoracic blood volume, MAP = mean arterial blood pressure, MPAP = mean pulmonary artery blood pressure, PVR = pulmonary vascular resistance, SB−/SB+ = airway pressure release ventilation *without/with* spontaneous breathing, SVR = systemic vascular resistance.

son test. Data of the first measurement set (before induction of ALI) were only compared with data of the second measurement set (after ALI). Differences were considered to be statistically significant if P was less than 0.05.

Results

Lung Injury

Two hours after oleic acid injection, heart rate and mean arterial and central venous pressures were not different from baseline, whereas systemic vascular resistance decreased, and cardiac output and intrathoracic blood volume increased similarly ($P < 0.05$; table 1) in both groups. Mean pulmonary artery pressure and pulmonary vascular resistance both increased in response to induction of lung injury ($P < 0.001$). Arterial oxygen tension (Pa_{O_2}) and arterial and venous oxygen saturation decreased significantly ($P < 0.01$), whereas $\dot{Q}_{VA}/\dot{Q}_T$ increased ($P < 0.001$) following induction of lung injury, and 18 of 22 animals had a Pa_{O_2}/F_{IO_2} of less than 300 mmHg of which 8 pigs even had a Pa_{O_2}/F_{IO_2} lower than 150 mmHg (table 2). Oxygen delivery remained unchanged, but oxygen consumption increased ($P < 0.001$).

After induction of lung injury, RR and inspiratory pressure had to be increased to maintain alveolar ventilation. This resulted in shorter inspiratory and expiratory times and higher end-inspiratory, mean airway, and mean

Table 2. Oxygenation

Parameter	Group	Baseline	Lung Injury	2-h Treatment	4-h Treatment	Lung Injury	Time	Mode	Interaction
Pa_{O_2}, mmHg	SB−	242 ± 18	115 ± 32	90 ± 37	91 ± 50	‡			†
	SB+	240 ± 36	104 ± 41	110 ± 47	144 ± 65§				
Sa_{O_2}, %	SB−	98.9 ± 0.5	95.9 ± 2.3	88.8 ± 11.1	84.0 ± 13.4‖	†	*		*
	SB+	98.6 ± 0.3	91.5 ± 9.9	90.9 ± 9.6	91.3 ± 11.3				
$\dot{D}_{O_2}$, ml/min	SB−	365 ± 96	374 ± 64	345 ± 84	339 ± 98				*
	SB+	331 ± 74	365 ± 93	409 ± 111	438 ± 115				
$\dot{V}_{O_2}$, ml/min	SB−	142 ± 43	185 ± 36	172 ± 42	160 ± 41	‡			†
	SB+	132 ± 24	172 ± 14	181 ± 29	186 ± 32				
Sv_{O_2}, %	SB−	60.0 ± 7.9	48.3 ± 7.8	44.3 ± 12.6	43.0 ± 11.8	†			*
	SB+	58.3 ± 7.0	46.6 ± 13.7	49.3 ± 10.6	55.3 ± 12.1				
Q_{VA}/Q_T, %	SB−	5.0 ± 1.9	14.4 ± 3.8	24.2 ± 13.4	30.8 ± 18.4‖	‡	*		*
	SB+	5.6 ± 2.9	21.1 ± 13.5	22.7 ± 14.6	21.0 ± 10.9				

Baseline was only tested against Lung Injury. *Post hoc* testing was always performed if a significant F ratio for a factor or the interaction of factors was obtained by repeated-measures analysis of variance (* $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$), but only significant differences are marked: § $P < 0.05$, ‖ $P < 0.01$, # $P < 0.001$ for within-group differences. and ** $P < 0.05$ for between-group differences (*post hoc* Tukey multiple comparison test).

$\dot{D}_{O_2}$ = oxygen delivery, Pa_{O_2} = arterial oxygen partial pressure, Q_{VV}/Q_T = venous admixture, Sa_{O_2} = arterial oxygen saturation, SB−/SB+ = airway pressure release ventilation *without/with* spontaneous breathing, Sv_{O_2} = venous oxygen saturation, $\dot{V}_{O_2}$ = oxygen consumption.

Table 3. Ventilation

Parameter	Group	Baseline	Lung Injury	2-h Treatment	4-h Treatment	Lung Injury	Time	Mode	Interaction
RR, l/min	SB−	25 ± 4	29 ± 3	32 ± 3	34 ± 5	†	‡		*
	SB+	25 ± 4	30 ± 0	41** ± 5	39 ± 9				
V_T, ml	SB−	341 ± 62	269 ± 62	237 ± 43	231 ± 48	†	‡		
	SB+	344 ± 45	293 ± 64	208 ± 35	234 ± 56				
V_E, l	SB−	8.0 ± 1.2	8.3 ± 1.9	8.1 ± 1.6	8.0 ± 1.6	*			
	SB+	8.2 ± 0.9	9.4 ± 1.1	8.5 ± 1.2	8.7 ± 1.6				
$Paco_2$, mmHg	SB−	40 ± 6	52 ± 7	57 ± 7	56 ± 15	‡			
	SB+	41 ± 7	52 ± 12	59 ± 15	57 ± 16				
Ti, s	SB−	1.4 ± 0.2	1.2 ± 0.2	1.1 ± 0.3	1.0 ± 0.1	†	*		
	SB+	1.4 ± 0.2	1.2 ± 0.2	1.0 ± 0.4	0.9 ± 0.3				
Te, s	SB−	1.3 ± 0.2	1.0 ± 0.3	0.8 ± 0.3	0.9 ± 0.2	†	*		
	SB+	1.2 ± 0.2	1.0 ± 0.3	0.6 ± 0.2	0.7 ± 0.3				
$P_{aw.ei}$ cm H_2O	SB−	17.5 ± 1.2	24.4 ± 3.9	23.6 ± 3.7	24.0 ± 3.8	‡			
	SB+	16.9 ± 1.3	24.7 ± 4.2	24.7 ± 4.2	24.8 ± 4.0				
$P_{aw.mean}$, cm H_2O	SB−	10.0 ± 1.2	14.1 ± 3.0	14.2 ± 2.1	13.8 ± 2.3	‡			
	SB+	9.8 ± 1.0	14.6 ± 2.4	14.8 ± 3.0	14.6 ± 2.5				
$P_{trans.mean}$, cm H_2O	SB−	3.9 ± 1.3	7.3 ± 3.3	7.2 ± 2.8	6.8 ± 2.8	‡			
	SB+	4.0 ± 0.9	8.1 ± 2.2	8.8 ± 3.0	8.5 ± 3.7				

All values are mean ± SD, including spontaneous breaths when present.

Baseline was only tested against Lung Injury. *Post hoc* testing was always performed if a significant F ratio for a factor or the interaction of factors was obtained by repeated-measures analysis of variance (* $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$), but only significant differences are marked: § $P < 0.05$, ‖ $P < 0.01$, # $P < 0.001$ for within-group differences and ** $P < 0.05$ for between-group differences (*post hoc* Tukey multiple comparison test).

$P_{aw.ei}$ = end-inspiratory airway pressure; $P_{aw.mean}$ = mean airway pressure, $P_{trans.mean}$ = mean transpulmonary pressure; $Paco_2$ = arterial carbondioxide partial pressure; RR = respiratory rate, SB−/SB+ = airway pressure release ventilation *without/with* spontaneous breathing, Te = expiratory time, Ti = inspiratory time, V_E = minute ventilation, V_T = tidal volume.

transpulmonary pressures, whereas V_T decreased ($P < 0.05$; table 3). Despite a small increase in minute ventilation ($P < 0.05$), $Paco_2$ was significantly higher 2 h after induction of lung injury ($P < 0.001$). EELV was reduced in all animals (fig. 1) after induction of ALI.

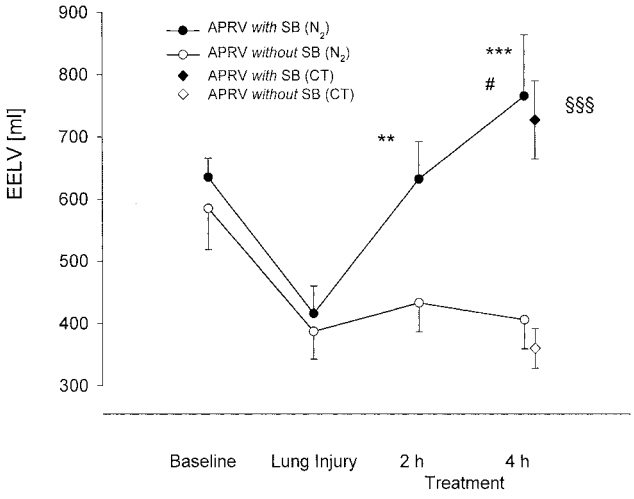

Fig. 1. Time course of end-expiratory lung volume (EELV) for airway pressure release ventilation (APRV) with and without spontaneous breathing (SB) measured by nitrogen (N_2) washout and after 4 h of specific treatment using computed tomography (CT) densitometry. **$P < 0.01$ and ***$P < 0.001$ compared with Lung Injury. #$P < 0.05$ APRV with *versus* without SB measured by nitrogen washout. §§§$P < 0.001$ APRV with *versus* without SB determined by CT analysis.

APRV with and without Spontaneous Breathing

Hemodynamics. Cardiac output increased during APRV with SB ($P < 0.05$ after 4 h of treatment) but not during APRV without SB ($P < 0.05$ interaction time × mode; table 1). All other systemic hemodynamics (except central venous pressure, which decreased slightly over time) remained unchanged after 2 and 4 h of treatment, regardless of ventilatory mode. In contrast, mean pulmonary artery pressure decreased significantly ($P < 0.001$) after 2 and 4 h only during APRV with SB ($P < 0.05$).

Oxygenation

We observed significant interactions of time and ventilatory mode in all measured oxygenation variables (table 2). Pao_2 increased with SB after 2 h, reaching statistical significance after 4 h ($P < 0.05$), whereas Pao_2 remained low during APRV without SB. Oxygen saturation decreased and $\dot{Q}_{VA}/\dot{Q}_T$ increased in the absence of SB ($P < 0.01$ at 4 h). Time courses of oxygen delivery and consumption were both significantly modified by SB with higher values during APRV with SB ($P < 0.05$ and $P < 0.01$, respectively). Improvement of oxygen delivery with SB was explained by an increase in both cardiac output and Pao_2.

Ventilation

All ventilatory data are given in table 3. According to the protocol, RR had to be increased during APRV without SB, whereas RR increased due to SB during APRV

with SB ($P < 0.0001$ for both modes). However, increase in RR was larger during APRV with SB after 2 h of treatment with SB ($P < 0.05$) and tended to be higher after 4 h with significant interaction of time and mode ($P < 0.05$). Increase in RR was accompanied by decreases in inspiratory and expiratory times in both groups. V_T decreased significantly in both settings. Minute and alveolar ventilation (as indicated by $Paco_2$) were not significantly different over time or between ventilatory modes. PEEP was set at 5 cm H_2O during the entire study; end-inspiratory, mean airway, and mean transpulmonary pressures were comparable between groups and did not change significantly over time. The proportion of minute ventilation due to SB during APRV with SB could not be measured directly because SB activity partially coincides with mechanical breaths. However, the mechanical ventilation should have been halved by the 50% reduction of RR down to 15/min during APRV with SB. Still, minute ventilation was comparable between both settings, suggesting a 50% contribution of SB to the total ventilation.

Aeration

Time course of EELV (fig. 1) after induction of lung injury was significantly different between ventilatory modes ($P < 0.001$ for interaction). EELV, measured by nitrogen washout, remained low in animals during APRV without SB after 2 and 4 h (411 ± 165 and 384 ± 148 ml, respectively) but improved during APRV with SB (652 ± 200 and 786 ± 320 ml; $P < 0.01$ and $P < 0.001$, respectively) with significant differences between ventilatory modes after 4 h ($P < 0.05$). EELV calculated from spiral CT scans was also higher during APRV with SB compared with APRV without SB (752 ± 203 *vs.* 353 ± 104 ml; $P < 0.001$).

Distances between lung apex and diaphragmatic dome or costodiaphragmatic recessus at end-expiration were 142 ± 7 and 202 ± 18 mm during APRV with SB *versus* 133 ± 11 and 170 ± 25 mm during APRV without SB ($P < 0.05$ and $P < 0.01$, respectively).

Mean overall lung density was significantly lower during APRV with SB (−462 ± 70 HU) compared with APRV without SB (−329 ± 87 HU; $P < 0.001$), indicating better aeration with SB. Density distributions from end-expiratory spiral CT scans of the whole lung are shown in figure 2. No hyperinflated lung tissue was detected in either ventilatory mode. The proportion of normally aerated tissue was much higher with SB ($P < 0.001$; fig. 2), whereas the normalized amount of poorly aerated tissue was not significantly different. Absence of SB resulted in a significantly higher relative amount of nonaerated lung ($P < 0.05$).

Examples of end-expiratory CT slices close to the diaphragm during APRV without and with SB are shown in figure 3. Analysis of the apical slice showed a tendency to more normally aerated tissue ($P = 0.061$) and less poorly aerated tissue ($P < 0.05$) with SB compared with APRV without SB (fig. 4, *A*). The amount of nonaerated lung was low and not significantly different between the two modes in this region. In the slice close to the diaphragm, similar qualitative differences between the modes were observed as in the density distribution of the whole lung, *i.e.*, a higher proportion of normally aerated lung tissue, no significant differences in poorly aerated tissue, and less nonaerated tissue with SB (fig. 4, *B*). Comparison of apical and diaphragmatic slices revealed a craniocaudal difference in aeration with more normally aerated and less nonaerated lung tissue in the apical region as compared with the region close to the diaphragm ($P < 0.001$; fig. 5). Although this craniocaudal difference in aeration was observed during both ventilator settings, its magnitude was dependent on ventilatory mode ($P < 0.01$) because aeration was better during APRV with SB.

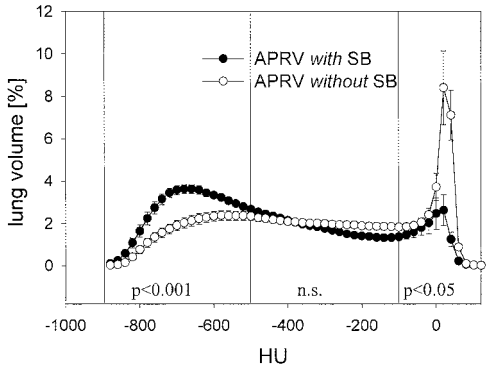

Fig. 2. Densitometry of the whole lungs from spiral computed tomography at end-expiration. Histogram shows normalized lung volume in Hounsfield units (HU) ranging from −1,000 to 100 plotted as mean ± SEM of all animals. Aeration categories (hyperinflated, normally aerated, poorly aerated, nonaerated; see text for details) are marked and were statistically compared between airway pressure release ventilation (APRV) with and without spontaneous breathing (SB).

The variables EELV and amount of nonaerated tissue, both measured by CT densitometry, were found to be significantly correlated (fig. 6; EELV = −1410 × nonaerated lung + 833, $r^2 = 0.62$, $P < 0.001$, or $r^2 = 0.38$ for EELV measured by nitrogen washout), suggesting that recruitment of atelectasis and consolidated lung is a major factor to explain improvement of EELV with SB. In addition, nonaerated lung explained 61% of venous admixture ($\dot{Q}_{VA}/\dot{Q}_T$ = 99 × nonaerated lung + 5.7, r^2 = 0.61, $P = 0.001$).

Discussion

Our studies in porcine oleic acid–induced lung injury are the first investigating effects of SB on aeration of lung tissues. The results confirm previous experimental and clinical data[1,4,5,15,16] showing improved oxygenation and hemodynamics during SB with APRV in ALI. Further-

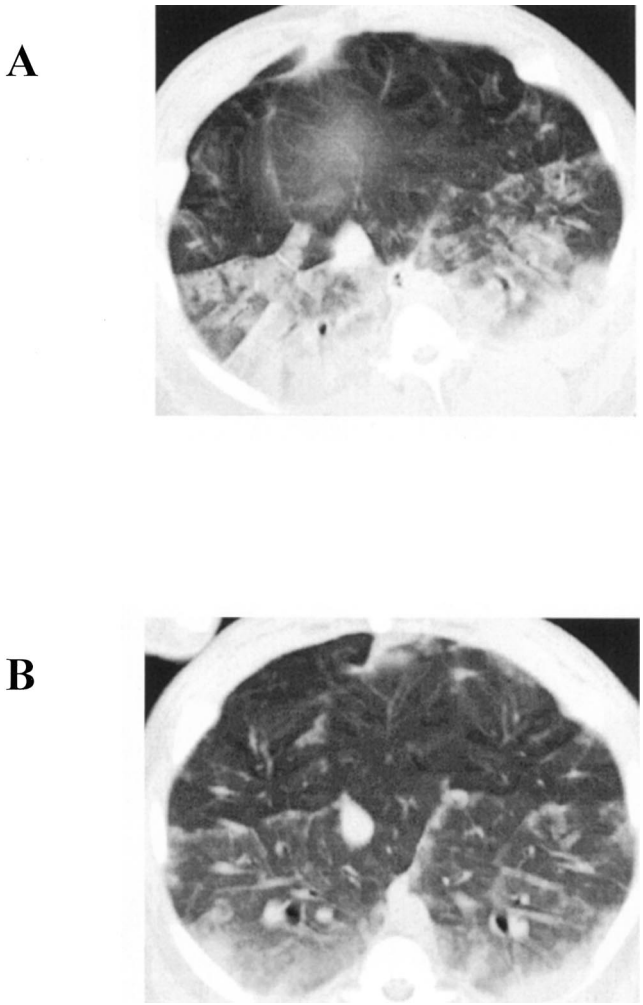

Fig. 3. Original computed tomography scans close to the diaphragm of pig 2 (*A*) during airway pressure release ventilation without spontaneous breathing and pig 3 (*B*) during airway pressure release ventilation with spontaneous breathing. Note differences in aeration and lung consolidation related to spontaneous breathing activity.

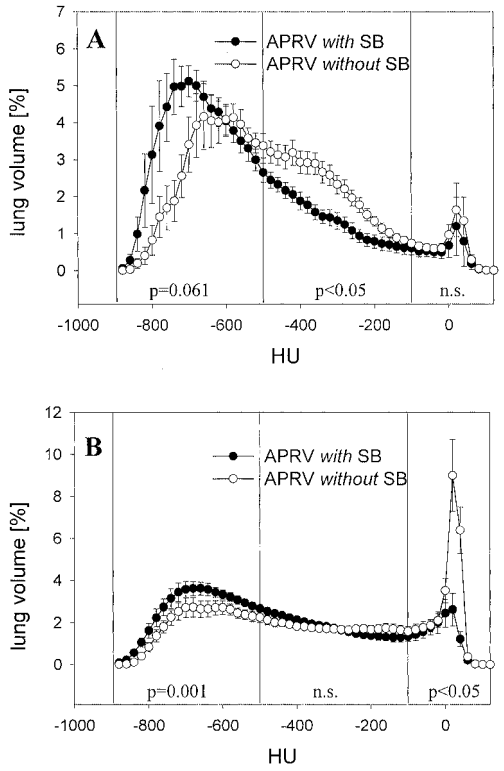

Fig. 4. Density histograms of defined slices located at lung apex (*A*) and close to the diaphragm (*B*) taken from end-expiratory spiral computed tomography of each animal at end-expiration. Histograms show normalized lung volume in Hounsfield units (HU) ranging from −1,000 to 100 plotted as mean ± SEM of all animals. Aeration categories (hyperinflated, normally aerated, poorly aerated, nonaerated; see text for details) are marked and were statistically compared between airway pressure release ventilation (APRV) with and without spontaneous breathing (SB).

more, APRV with SB was associated with a progressive increase in EELV, less atelectasis/consolidation, and a larger amount of normally aerated lung tissue predominantly in juxtadiaphragmatic lung regions compared with APRV without SB.

Spontaneous breathing in any phase of the mechanical ventilator cycle is possible with APRV, a technique that provides ventilatory support by time-cycled switching between two continuous positive airway pressure levels.[26–28] During APRV, spontaneous breaths are mechanically supported only when they coincide with the restoration of the high continuous positive airway pressure level. When SB is abolished, APRV is not different from conventional pressure-controlled ventilation.[28]

Effects of Spontaneous Breathing on Hemodynamics and Oxygen Uptake

In line with previous data,[1,4,5,15,16] our study showed improvement in cardiac output with SB during APRV. This is in agreement with the concept that a decrease in intrathoracic pressure during spontaneous inspiration with APRV may improve venous return and thereby cardiac output.[5,29] However, intrathoracic blood volume and central venous pressure were not different between groups, indicating comparable volume status. Changes in cardiac output caused by mechanical ventilation have been reported to correlate positively with intrapulmonary shunt.[30] In contrast, during APRV with SB, increased cardiac output was associated with less $\dot{Q}_{VA}/\dot{Q}_T$, an increased Pa_{O_2}, and a higher oxygen delivery.

Oxygen consumption tended to increase during APRV with SB and tended to decrease during APRV without SB with significant interaction of ventilatory mode and time. Previous studies did not report measurable increases in total oxygen consumption due to inspiratory muscle activity during APRV.[4,5] However, the estimated fraction of spontaneous ventilation was higher in our study as compared with previous studies.[4,5]

Effects of Spontaneous Breathing on Oxygenation, Aeration, and EELV

Spontaneous breathing during APRV resulted consistently in improved $\dot{Q}_{VA}/\dot{Q}_T$ and arterial blood oxygen-

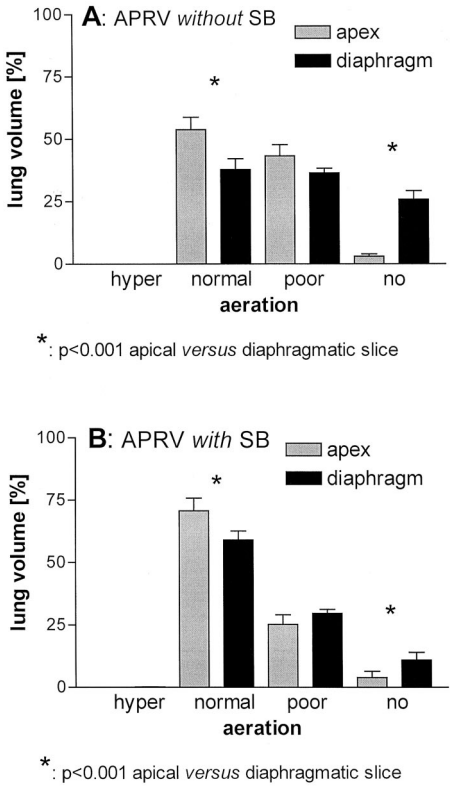

Fig. 5. Relative amount of lung volume for each aeration category calculated from the defined apical and diaphragmatic slices of end-expiratory spiral computed tomography during airway pressure release ventilation (APRV) without spontaneous breathing (SB) (*A*) and APRV with SB (*B*) are compared. Differences between lung regions were also dependent on spontaneous breathing ($P < 0.01$ for interaction lung region and ventilatory mode).

ation. These observations are in agreement with experimental[15,16] and clinical[1,4,5] findings that SB with APRV reduces intrapulmonary shunting.

A major finding of this study is the substantial and progressive improvement of EELV with SB, whereas EELV remained low in the absence of SB (fig. 1). This EELV improvement may be explained recruitment of nonaerated lung during APRV with SB. In this group, EELV even exceeded baseline level before induction of lung injury in some animals (fig. 1). Although previous studies in pigs showed no occurrence of atelectasis caused by induction of anesthesia,[31] we cannot exclude that EELV was already impaired due to decreased muscle tone at baseline.[32] Because expiratory time and V_T were not significantly different between groups, it is unlikely that relevant differences in air trapping due to incomplete expiration can explain the remarkable increase in EELV with SB.

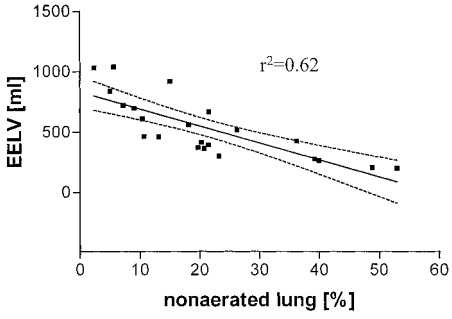

Fig. 6. Linear correlation of end-expiratory lung volume (EELV) and relative amount of nonaerated lung revealed the equation EELV = −1410 × nonaerated lung + 833, $r^2 = 0.62$, $P < 0.001$.

The level of external PEEP used in this study was the same used in previous animal studies.[15,16] PEEP of 5 cm H_2O in combination with controlled mechanical ventilation was obviously not able to restore EELV after induction of mild-to-moderate lung injury in our model. Although no widely accepted strategy to optimize PEEP in pigs exists, higher PEEP levels might have favored restoration of EELV[12,33] but could have decreased systemic blood flow.[34] However, aim of this study was not to compare different alveolar recruitment strategies but to study the effects of unrestricted SB on lung aeration which required comparable PEEP levels in both treatment groups. Our study design resulted in comparable end-inspiratory and mean airway pressures between groups.

Another major finding is that SB was associated with considerably less atelectasis/consolidation (fig. 2 and fig. 4, *B*). The fairly good negative correlation ($r^2 = 0.62$) between EELV and amount of nonaerated lung (fig. 6) suggests that alveolar recruitment is an important factor for improvement of EELV during APRV with SB. Progressive improvement in EELV in combination with the correlation of $\dot{Q}_{VA}/\dot{Q}_T$ and nonaerated lung ($r^2 = 0.61$) suggests that reopening of nonaerated lung areas mainly explains improved oxygenation during SB.

Although other inspiratory muscles may also contribute to improvement in aeration during SB, the craniocaudal gradient in aeration and aeration differences (fig. 5) as well as the marked differences in aeration in regions close to the diaphragm between APRV with and without SB (fig. 3, *B* and fig. 4, *B*) suggest a role of diaphragmatic muscular tone and/or contractions on the observed aeration differences. This is further supported by the observed decreased craniocaudal lung dimensions, which may indicate a cephalad shift of the diaphragm in absence of SB and muscle paralysis. Diaphragmatic contractions have been shown to reduce the size of atelectasis in dependent lung areas of patients with normal lungs during general anesthesia.[14] Previous radiographic observations have suggested that contractions of the diaphragm result in distribution of ventilation to dependent, usually well-perfused lung areas in normal subjects[6,7,35] and in chronic obstructive pulmonary disease patients.[7] This might at least partially be explained by a regional increase in transpulmonary pressure caused by active diaphragmatic excursions predominantly in dependent parts of the lung, despite the fact that hydrostatic pressure of the lungs and abdomen is

highest in these regions. Different portions of diaphragmatic muscles with different orientation to the chest wall and different force–length relationships may be seen as anatomic basis for the observed functional effects.[36,37] However, we can only speculate on regional differences in transpulmonary pressure in our model, and we did not observe differences in mean transpulmonary pressure.

Conclusion

Our data show that SB with APRV promotes reopening of collapsed and consolidated lung and increased EELV, and these may be major mechanisms of improved oxygenation. Although these results cannot be directly transferred to patients with ALI, they are in line with clinical studies in these patients showing improved oxygenation and systemic blood flow if SB is not suppressed.

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