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Individualized Positive End-expiratory Pressure and Regional Gas Exchange in Porcine Lung Injury

Thomas Muders, M.D., Henning Luepschen, M.Sc., Ph.D., Torsten Meier, M.D., Ph.D., Andreas Wolfgang Reske, M.D., Ph.D., Jörg Zinserling, M.Sc., Ph.D., Stefan Kreyer, M.D., Robert Pikkemaat, M.Sc., Ph.D., Enn Maripu, M.Sc., Steffen Leonhardt, Prof., M.D., Ph.D., Göran Hedenstierna, Prof., M.D., Ph.D., Christian Putensen, Prof., M.D., Ph.D., Hermann Wrigge, Prof., M.D., Ph.D.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- In acute lung injury, the optimal positive end-expiratory pressure (PEEP) strategy for mechanical ventilation is not known.

What This Article Tells Us That Is New

- In a porcine model of induced acute lung injury, with increased abdominal pressure caused by intraperitoneal saline infusion, using a crossover design, tracheostomized animals were ventilated using: (1) positive end-expiratory pressure (PEEP) table–based low PEEP without lung recruitment; (2) minimal tidal recruitment PEEP guided by electrical impedance tomography with recruitment; and (3) maximal oxygenation PEEP with recruitment.
- Using a PEEP table and no recruitment, compared with recruitment and either minimal tidal recruitment PEEP or maximal oxygenation PEEP, resulted in less delivered PEEP, and more lung collapse and regional ventilation/perfusion mismatch. The latter two methods had comparable results.

ABSTRACT

Background: In acute respiratory failure elevated intraabdominal pressure aggravates lung collapse, tidal recruitment, and ventilation inhomogeneity. Low positive end-expiratory pressure (PEEP) may promote lung collapse and intrapulmonary shunting, whereas high PEEP may increase dead space by inspiratory overdistension. The authors hypothesized that an electrical impedance tomography–guided PEEP approach minimizing tidal recruitment improves regional ventilation and perfusion matching when compared to a table-based low PEEP/no recruitment and an oxygenation-guided high PEEP/full recruitment strategy in a hybrid model of lung injury and elevated intraabdominal pressure.

Methods: In 15 pigs with oleic acid–induced lung injury intraabdominal pressure was increased by intraabdominal saline infusion. PEEP was set in randomized order: (1) guided by a PEEP/inspired oxygen fraction table, without recruitment maneuver; (2) minimizing tidal recruitment guided by electrical impedance tomography after a recruitment maneuver; and (3) maximizing oxygenation after a recruitment maneuver. Single photon emission computed tomography was used to analyze regional ventilation, perfusion, and aeration. Primary outcome measures were differences in PEEP levels and regional ventilation/perfusion matching.

Results: Resulting PEEP levels were different (mean ± SD) with (1) table PEEP: 11 ± 3 cm H_2O; (2) minimal tidal recruitment PEEP: 22 ± 3 cm H_2O; and (3) maximal oxygenation PEEP: 25 ± 4 cm H_2O; $P < 0.001$. Table PEEP without recruitment maneuver caused highest lung collapse (28 ± 11% *vs.* 5 ± 5% *vs.* 4 ± 4%; $P < 0.001$), shunt perfusion (3.2 ± 0.8 l/min *vs.* 1.0 ± 0.8 l/min *vs.* 0.7 ± 0.6 l/min; $P < 0.001$) and dead space ventilation (2.9 ± 1.0 l/min *vs.* 1.5 ± 0.7 l/min *vs.* 1.7 ± 0.8 l/min; $P < 0.001$). Although resulting in different PEEP levels, minimal tidal recruitment and maximal oxygenation PEEP, both following a recruitment maneuver, had similar effects on regional ventilation/perfusion matching.

Conclusions: When compared to table PEEP without a recruitment maneuver, both minimal tidal recruitment PEEP and maximal oxygenation PEEP following a recruitment maneuver decreased shunting and dead space ventilation, and the effects of minimal tidal recruitment PEEP and maximal oxygenation PEEP were comparable.

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Although positive pressure ventilation is routinely used in critically ill patients with respiratory failure or acute respiratory distress syndrome (ARDS), mechanical ventilation may aggravate lung injury by mechanical stress transferred to lung tissue.[1] Reduction in tidal volumes[2] (V_T), but

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not high positive end-expiratory pressure (PEEP), has been shown to improve survival in ARDS patients.[3] Clinicians tend to increase inspiratory oxygen rather than PEEP[4] and do not consistently follow recommended strategies to adjust PEEP.[4] How to best set PEEP has been hashed out for decades,[5] and yet not a single prospective study has been able to provide a definitive answer.

Lower PEEP/no recruitment strategies aim at finding the lowest possible PEEP that ensures an acceptable oxygenation while limiting plateau pressures and inspiratory overdistension,[2] and tolerating lung collapse (permissive atelectasis).[2,6] Recent clinical guidelines do not recommend the routine use of recruitment maneuvers.[7–9] Derecruitment, however, may promote opening and closure of small airways and alveoli (tidal recruitment)[10,11] and intrapulmonary shunting.

Higher PEEP/full recruitment strategies following a recruitment maneuver aim to optimize oxygenation as surrogate for full lung recruitment,[12,13] and to minimize tidal recruitment, and atelectrauma.[10] However, high PEEP levels may cause high end-inspiratory airway pressure, which might impair regional perfusion.[5,14,15]

Elevated intraabdominal pressure aggravates lung collapse, tidal recruitment, inhomogeneity of regional ventilation, ventilation ($\dot{V}$)/perfusion ($\dot{Q}$) mismatch,[16] and is frequently observed in mixed populations of mechanically ventilated patients,[16,17] especially if lung failure or ARDS is caused by extrapulmonary reasons.[17,18] In patients with potential for lung recruitment, individualized PEEP setting to detect and improve lung recruitment[11] and to minimize tidal recruitment[10] may improve outcomes.

Electrical impedance tomography noninvasively allows bedside monitoring of regional ventilation[19,20] and can be used for individual PEEP titration.[19–21] Electrical impedance tomography–based quantification of inhomogeneity in regional ventilation time courses (regional ventilation delay inhomogeneity)[22,23] has been shown to correlate linearly with tidal recruitment.[22,23] Low tidal recruitment indicates sufficient lung recruitment and may thus enhance homogeneity of ventilation ($\dot{V}$) and perfusion ($\dot{Q}$) and, thus, reduce $\dot{V}/\dot{Q}$ mismatch at the lowest possible PEEP level.

We hypothesized that an electrical impedance tomography–based approach minimizing inhomogeneity of regional ventilation time courses as measure of tidal recruitment improves $\dot{V}/\dot{Q}$ matching when compared to either low PEEP or high PEEP strategies. This hypothesis was studied using single photon emission computed tomography in a porcine hybrid model combining recruitable lung injury with elevated intraabdominal pressure.

Materials and Methods

Animal Preparation, Anesthesia, and Lung Injury

Fifteen healthy pigs (nine males, six females) were anesthetized and mechanically ventilated in supine position. Anesthesia[22,24] was induced with intramuscular atropine (0.04 mg/kg), tiletamin–zolazepam (6 mg/kg), and xylazine (2.2 mg/kg) and maintained by continuous infusion of ketamine (10 mg · kg^{-1} · h^{-1}), midazolam (0.4 mg · kg^{-1} · h^{-1}), fentanyl (10 μg · kg^{-1} · h^{-1}). Depth of anesthesia was verified by paw pinch before animals were continuously paralyzed using pancuronium bromide (0.15 mg · kg^{-1} · h^{-1}) and absence of spontaneous breathing activity was confirmed by observation of continuously displayed gas flow tracing.[22,24] Tracheotomy and instrumentation were performed as previously described.[22,24] To induce lung injury, abdominal pressure (measured in the urinary bladder) was increased to 15 mmHg by infusion of 0.9% saline into the abdominal cavity,[22,24,25] followed by titrated central venous injections of oleic acid, until a stable Pao_2/fractional inspired oxygen concentration (Fio_2) ratio of less than 200 mmHg was reached.[22,24,26]

Measurements

Cardiovascular Measurements. Heart rate and systemic, central venous, and pulmonary artery blood pressures were measured using arterial, central venous, and pulmonary arterial cannulas.[22,24] Cardiac output, extravascular lung water, and intrathoracic blood volume were determined using transpulmonary thermodilution.[22,24] Systemic vascular resistance was calculated using standard equations.

Measurements of Ventilatory Parameters, Lung Mechanics, and Blood Gases. Waveforms were measured using the integrated respiratory monitor of the ventilator (Engström Carestation; GE Healthcare, Germany) and stored for offline analysis.[22] Intraabdominal pressure was measured intermittently in the urinary bladder as described previously.[22,24] Blood gases, oxygen saturation, and hemoglobin levels were measured using a cooximeter (Radiometer, Germany). Venous admixture was calculated using standard equations.[27]

Estimation of Tidal Recruitment. Regional ventilation delay inhomogeneity was measured during a slow inflation (12 ml/kg ideal body weight) using electrical impedance tomography (EIT evaluation KIT II; Dräger Medical, Germany)[22,23] to estimate the amount of tidal recruitment by measuring inhomogeneity in regional ventilatory time courses (fig. 1 and Supplemental Digital Content 1, http://links.lww.com/ALN/C206).

Single Photon Emission Computed Tomography. Spatial ventilation (^{81m}Krypton gas) and perfusion (^{99m}Tecnetium-labeled macroaggregated albumin) distributions[28,29] were analyzed during ventilation with different PEEP levels. Images were acquired on a dual-head gamma camera and reconstructed after filtering, noise and background correction.[30] For each voxel we calculated:

- regional ventilation/voxel ([$\dot{V}$] gas flow per voxel)
- regional perfusion/voxel ([$\dot{Q}$] blood flow per voxel)
- $\dot{V}/\dot{Q}$ ratio per voxel[30]

All voxels were assigned to one of the following $\dot{V}/\dot{Q}$ compartments according to their $\dot{V}/\dot{Q}$ ratio (using

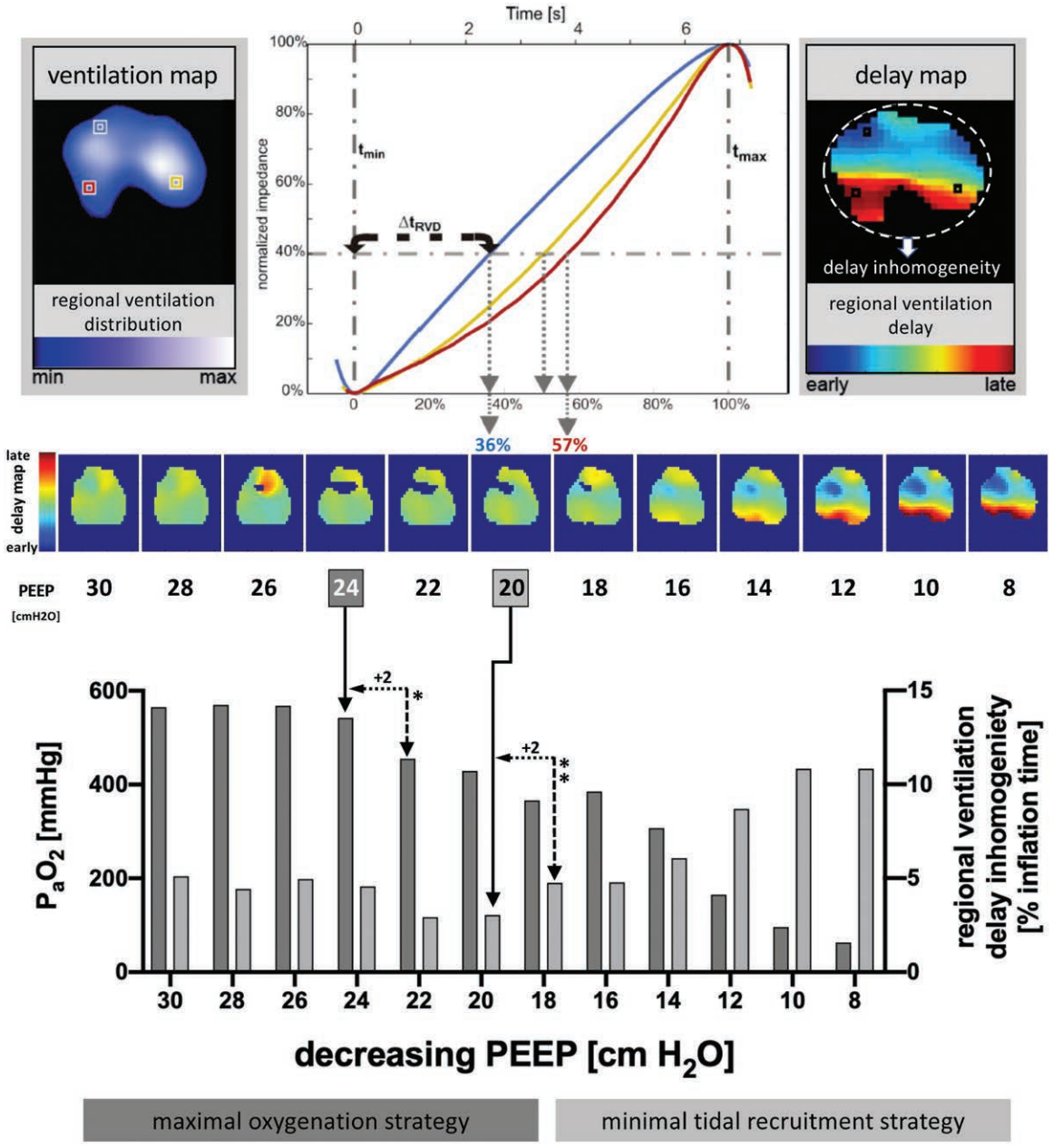

Fig. 1. (*Top*) Calculation of regional ventilation delay inhomogeneity, schematic description. (*Left*) Functional image (ventilation map) recorded by electrical impedance tomography during a slow inflation breath of 12 ml/kg ideal body weight. (*Middle*) Normalized regional impedance/time curves of three exemplary pixels. All curves are normalized to the beginning (t_{min}) and end (t_{max}) of the slow inflation maneuver: *blue*, right ventral pixel; *red*, right dorsal pixel; *yellow*, left dorsal pixel. Ventilation delay time (ΔtRVD) when the regional impedance time curve reaches a threshold of 40% of the maximal local impedance change. (*Right*) Delay map to visualize all regional ventilation delay indices. Regional ventilation delay inhomogeneity expressed as SD of all single pixel regional ventilation delay-values. (*Middle*) Exemplary delay maps from a representative animal (pig No. 13) during decremental titration of positive end-expiratory pressure (PEEP). In each map, *dark red pixels* indicate lung regions that are lately ventilated during a slow inflation maneuver. Very early ventilated lung regions appear as *light blue pixels*. Regional ventilation delay inhomogeneity indicates heterogeneity of ventilation time courses that is well correlated to the amount of tidal recruitment.[22] (*Bottom*) Courses of oxygen partial pressure (Pao_2, *dark gray*, left *y*-axis) and regional ventilation delay inhomogeneity (*light gray*, right *y*-axis) during decremental PEEP trial. At a PEEP of 22 cm H_2O (*dotted arrow* marked with *) Pao_2 decreased more than 5% below the maximal Pao_2 observed during PEEP titration. Hence, a PEEP of 24 cm H_2O was defined as "maximal oxygenation PEEP." At a PEEP of 18 cm H_2O (*dotted arrow* marked with **) regional ventilation delay inhomogeneity increased suggesting an increase in tidal recruitment with decreasing PEEP. Thus, a PEEP of 20 cm H_2O was chosen as "minimal tidal recruitment PEEP."

thresholds known from multiple inert gas elimination technique[31]) (fig. S2, Supplemental Digital Content 2, http://links.lww.com/ALN/C207):

- shunt ($\dot{V}/\dot{Q} < 0.005$)
- low $\dot{V}/\dot{Q}$ ($0.005 \le \dot{V}/\dot{Q} < 0.1$)
- normal $\dot{V}/\dot{Q}$ ($0.1 \le \dot{V}/\dot{Q} < 10$)
- high $\dot{V}/\dot{Q}$ ($10 \le \dot{V}/\dot{Q} < 100$)
- dead space ($\dot{V}/\dot{Q} \ge 100$)

Lung tissue volume, perfusion, and ventilation of $\dot{V}/\dot{Q}$ compartments were calculated (fig. S2, Supplemental Digital Content 2, http://links.lww.com/ALN/C207):

- shunt compartment: lung tissue volume undergoing shunt perfusion
- shunt perfusion: amount of blood flow that is distributed to the shunt compartment
- ventilated lung: all compartments other than shunt compartment
- dead space compartment: lung tissue volume undergoing dead space ventilation
- dead space ventilation: amount of gas flow that is distributed to the dead space compartment
- perfused lung: all compartments other than dead space compartment

Whereas single photon emission computed tomography captured the whole lung and yielded voxels of 4.42 × 4.42 × 4.2 mm (= 0.0821 ml/voxel) electrical impedance tomography analyzed a representative lens-shaped region of approximately 18.5 × 18.5 × 9.25 cm reconstructed to 32 × 32 pixels of approximately 5.8 ×5.8 mm (fig. S3, Supplemental Digital Content 3, http://links.lww.com/ALN/C208).

Computed Tomography. Average lung aeration was measured by low resolution density scans (transmission scans from single photon emission tomography during ongoing ventilation). The lung was manually marked (Osirix v. 5.5, Switzerland) in ten equidistant (cranio-caudal) slices[32] and lung volumes and masses were calculated in differently aerated lung compartments (nonaerated, poorly aerated, normally aerated, overaerated)[22,33] as percentage of total lung volume and total lung mass (Supplemental Digital Content 4, http://links.lww.com/ALN/C209). During all offline image analyses the investigator was blinded to the PEEP.

Experimental Protocol

Baseline Ventilatory Setting. Volume-controlled mechanical ventilation was applied with a V_T of 6 to 8 ml/kg, an inspiratory-to-expiratory ratio of 1:1, an F_{IO_2} of 0.5, and a PEEP of 5 cm H_2O. Respiratory rate was 25 to 30 breaths/min.[22]

After induction of lung injury, respiratory rate had to be increased to 30 to 40 breaths/min to avoid severe hypercapnic acidosis (P_{aCO_2} greater than 60 mmHg; pH less than 7.25), while keeping inspiratory-to-expiratory ratio constant and ensuring complete expiration as observed by a zero end-expiratory flow.[22] Spontaneous breathing efforts were continuously suppressed by muscle paralysis, which was confirmed by absence of spontaneous breathing activity in the continuously displayed airway pressure and flow tracings.

PEEP Strategies. Individualized PEEP levels were guided by three different strategies to be compared later in a crossover design (fig. 2 and Supplemental Digital Content 5, http://links.lww.com/ALN/C210).

Table PEEP Strategy. PEEP and F_{IO_2} were adjusted according to the ARDS Network protocols lower PEEP/ F_{IO_2} table[2] without a preceding recruitment maneuver[2] aiming at lung rest and tolerating "permissive atelectasis." Resulting PEEP was defined as "table PEEP."

Maximal Oxygenation PEEP Strategy and Minimal Tidal Recruitment PEEP Strategy. A lung recruitment maneuver[13] was performed targeting a P_{aO_2} greater than 400 mmHg at F_{IO_2} = 1.0 while using pressure-controlled ventilation with a driving pressure of 15 cm H_2O and increasing PEEP from 30 up to 45 cm H_2O in steps of 5 cm H_2O every 2 min. Then, PEEP titration was performed using volume-controlled ventilation (6 to 8 ml/kg ideal body weight) starting at 30 cm H_2O. Every 4 min blood gases were taken and tidal recruitment[22] was measured during a single low flow breath using electrical impedance tomography (fig. 2), as previously described, before PEEP was decreased in steps of 2 cm H_2O.

Deterioration of oxygenation was defined as P_{aO_2} decrease of more than 5% from the individual maximum with decreasing PEEP. "Maximal oxygenation PEEP" was defined as the lowest PEEP level that avoided this decrease and was set 2 cm H_2O above the PEEP that caused a P_{aO_2} decrease (fig. 1). Deterioration of temporal homogeneity was defined as increase in regional ventilation delay inhomogeneity with decreasing PEEP. "Minimal tidal recruitment PEEP" was defined as the lowest PEEP level that avoids this increase and was set 2 cm H_2O above the PEEP that caused an increase in regional ventilation delay inhomogeneity (fig. 1).

PEEP Studies at the Scanner Laboratory. After transfer to the scanner laboratory without interrupting mechanical ventilation using baseline settings, table PEEP, maximal oxygenation PEEP, and minimal tidal recruitment PEEP (based on previous titration) were studied in randomized order (blockwise randomization, blocks of six, sealed envelopes), while keeping all other ventilator settings constant.

Before every measurement point, stability of lung injury was checked, and carry-over effects of lung volume history were prevented by following standard sequence (fig. 2):

- Table PEEP: derecruitment (disconnection from the ventilator, PEEP 5 for 1 min), stability check (table PEEP for 10 min, blood gas analysis), complete sets of measurements including single photon emission computed tomography after additional 20 min of ventilation with table PEEP.

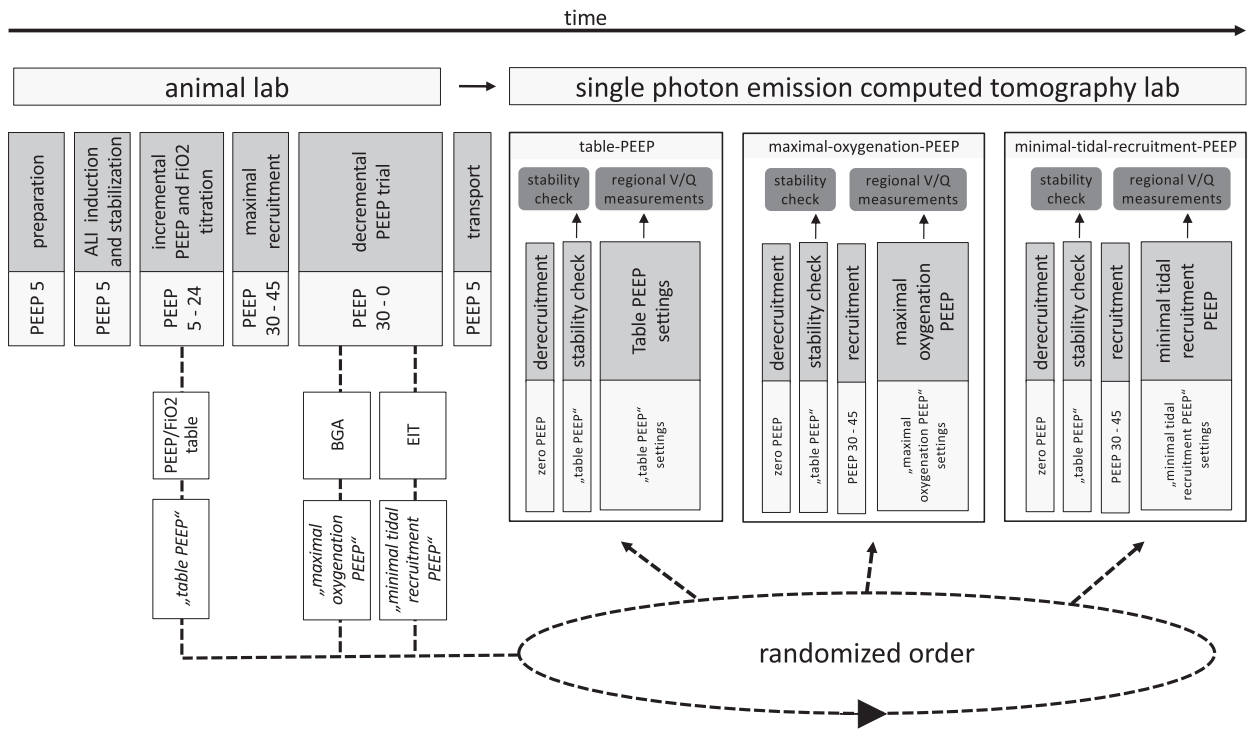

Fig. 2. Experimental protocol: animal preparation and lung injury induction. Incremental PEEP- and FIO_2-titration without a preceding recruitment maneuver according to the ARDS Network lower PEEP/FIO_2 table to define table PEEP. Maximal recruitment maneuver until PaO_2 > 400 mmHg. Blood gas measurements and electrical impedance tomography during decremental PEEP titration to define "maximal oxygenation PEEP" and "minimal tidal recruitment PEEP." Animals were transported to the single photon emission computed tomography lab without interrupting mechanical ventilation using baseline settings. Investigation of the previously defined table PEEP, maximal oxygenation PEEP, and minimal tidal recruitment PEEP in a block-wise randomized order. To prevent influences of lung volume history, systematic derecruitment and/or recruitment and a stability check were performed before every measurement cycle. During all regional $\dot{V}/\dot{Q}$ measurements FIO_2 was kept constant as set according to the PEEP/FIO_2 table during table PEEP. ALI, acute lung injury; ARDS, acute respiratory distress syndrome; BGA, blood gas analysis; EIT, electrical impedance tomography; FIO_2, fractional inspired oxygen concentration; PEEP, positive end-expiratory pressure; $\dot{V}/\dot{Q}$, ventilation/perfusion.

- Maximal oxygenation PEEP: derecruitment and stability check as described above (table PEEP for 10 min, blood gas analysis), recruitment maneuver using the previously used pressures (during maximal recruitment in the lab), complete sets of measurements including single photon emission computed tomography after 20 min of ventilation with maximal oxygenation PEEP.
- Minimal tidal recruitment PEEP: derecruitment and stability check as described above (table PEEP for 10 min, blood gas analysis), recruitment as described above, complete sets of measurements including single photon emission computed tomography after 20 min of ventilation with minimal tidal recruitment PEEP.

Ethics and Statistical Analysis

After approval by the local Animal Research Ethics Committee (approval No. C274/7), this study was performed in the Hedenstierna Laboratory, Department of Clinical Physiology, Uppsala University Hospital, Uppsala, Sweden, in adherence with the Guide for the Care and Use of Laboratory Animals (National Academy of Science 1996).

For this exploratory study, no reliable pilot data or data from publications were available. Based on experiences with other animal model studies using different ventilatory settings,[22,24] we assumed differences between levels in the range of 75% of the SD at each level and a correlation of 0.5 between levels. A target power of 80% was used. With a sample size of 15, the test of a single contrast between two PEEP settings at a 0.05 α level in a one-way repeated measures ANOVA with three levels was found to have 80.3% power to detect a contrast C of 3, assuming SD = 4 at each level, a between-level correlation of 0.5, and an a resulting effect size of 0.752. We followed the Animal Research: Reporting of *In Vivo* Experiments (ARRIVE) guidelines[34] (Supplemental Digital Content 6, http://links.lww.com/

ALN/C211). Primary outcome measures were differences in PEEP levels and amounts of gas and blood flow to different compartments.

Data (expressed as mean ± SD) were tested for normal distribution (Shapiro–Wilk test) and analyzed using two-tailed testing. Paired *t* tests, one- or two-way repeated-measures ANOVA) and consecutive *post hoc* tests (Newman–Keuls, repeated-measures ANOVA), were performed if appropriate. Results from blood gas analyses, shunt, and atelectasis were compared using linear correlation (Pearson) and Bland–Altman analysis. (STATISTICA for Windows 6.0; StatSoft, Inc., USA). $P < 0.05$ was considered to be statistically significant (for details see Supplemental Digital Content 7, http://links.lww.com/ALN/C212).

Results

All animals finished the whole study protocol. Due to invalid $\dot{V}/\dot{Q}$ raw data, one pig (No. 1) had to be excluded. No outlier data were excluded. Finally, 14 animals were analyzed.

Lung Injury Model Effects and Stability

Our lung injury model caused in all animals an oxygenation and lung mechanics impairment compatible with the current criteria for moderate human ARDS[35] (table S1, Supplemental Digital Content 8, http://links.lww.com/ALN/C213) and was stable throughout the entire study period (table S2, Supplemental Digital Content 9, http://links.lww.com/ALN/C214). Randomization resulted in homogeneous distribution of all orders of measurements (table S3, Supplemental Digital Content 10, http://links.lww.com/ALN/C215).

Cardiorespiratory Effects of the Different PEEP Strategies

Table PEEP resulted in the lowest PEEP (table PEEP, 11 ± 3; minimal tidal recruitment PEEP, 22 ± 3; maximal oxygenation PEEP, 25 ± 4 cm H_2O; $P < 0.001$; table 1) and plateau (33 ± 6 *vs.* 37 ± 6 *vs.* 41 ± 7 cm H_2O; $P < 0.001$; table 1), but highest driving pressure (22 ± 6 *vs.* 15 ± 4 *vs.* 16 ± 6 cm H_2O; $P < 0.001$; table 1), whereas PEEP and plateau pressure were highest with maximal oxygenation PEEP. Driving pressure was lower using both minimal tidal recruitment and the maximal oxygenation PEEP. As indicated by a decrease in regional ventilation delay inhomogeneity measured by electrical impedance tomography, minimal tidal recruitment PEEP reduced tidal recruitment, when compared to table PEEP. Of note, further increase of PEEP using maximal oxygenation PEEP did not further decrease regional ventilation delay inhomogeneity (table PEEP, 9.0 ± 3.6; minimal tidal recruitment PEEP, 4.8 ± 1.3; maximal oxygenation PEEP, 5.6 ± 2.2%; $P < 0.001$; table 1).

Higher PEEP levels during minimal tidal recruitment PEEP and maximal oxygenation PEEP improved venous admixture (table 1) and arterial oxygenation (table PEEP, 85 ± 20; minimal tidal recruitment PEEP, 257 ± 94; maximal oxygenation PEEP, 240 ± 100 mmHg; $P < 0.001$; table 1). Intrathoracic blood volume was comparable between all PEEP settings (table S4, Supplemental Digital Content 11, http://links.lww.com/ALN/C216).

During PEEP titration, which lasted 4 min at any PEEP level, maximal oxygenation PEEP, as intended, resulted in the highest Pao_2 when compared to minimal tidal recruitment PEEP (483 ± 126 *vs.* 441 ± 125 mmHg; $P = 0.0192$; paired *t* test). These short-term differences were not sustained when respective PEEP levels were used for a longer period (20 min) during single photon emission tomography scans (table 1) which may be explained by extrapulmonary long-term effects such as lower cardiac output at highest PEEP levels (table 1).

Effects of Different PEEP Strategies on Lung Volume, Lung Mass, and Aeration

Pulmonary gas volume was comparable between minimal tidal recruitment and maximal oxygenation PEEP (table 2). In contrast, the table PEEP, which was not preceded by a recruitment maneuver, resulted in a reduced gas volume (table 2). Total lung mass was comparable between all three PEEP settings (table 2). (For detailed results of quantitative computed tomography analyses see figs. S4 to S6, Supplemental Digital Content 12, http://links.lww.com/ALN/C217.)

Effects of Different PEEP Strategies on Pulmonary Ventilation and Perfusion

Volume of Lung Compartments Referring to Shunt Flow, Low, Normal, and High $\dot{V}/\dot{Q}$ and Dead Space Ventilation. Figure 3 shows spatial distribution of regional ventilation and perfusion. Volumes, ventilation, and perfusion of lung compartments are given in figure 4. Ventilated lung volume was reduced with table PEEP (fig. 3A) and normal $\dot{V}/\dot{Q}$ compartment amounted to about 25% of total lung (fig. 4A). In contrast, normal $\dot{V}/\dot{Q}$ compartment was more than doubled with minimal tidal recruitment and maximal oxygenation PEEP (fig. 4A). Using table PEEP, the largest lung proportion was perfused but not ventilated (shunt compartment, fig. 4A). In contrast, ventilation was redistributed to the dorsal lung regions (fig. 3D) and the shunt compartment decreased during both minimal tidal recruitment and maximal oxygenation PEEP (fig. 4A). The volume of ventilated, but not perfused, lung tissue (dead space compartment) was largest using maximal oxygenation PEEP (fig. 4A).

Blood Flow Distribution to Different Lung Compartments. During table PEEP, the perfusion of normal $\dot{V}/\dot{Q}$ compartment was lower when compared to both other strategies, whereas perfusion of shunt compartment was tripled and amounted to more than 50% of cardiac output (fig. 4B). With higher PEEP during both minimal tidal recruitment

Table 1. Cardio-respiratory Results

Parameter	PEEP Table	Minimal Tidal Recruitment	Maximal Oxygenation	*P* Value ANOVA *Post Hoc* Tests a	b	c
RR (1/min)	35 ± 2	35 ± 2	35 ± 2	-	0.999 -	-
V_T (ml)	215 ± 18	211 ± 15	209 ± 22	-	0.134 -	-
V_T ([ml/kg] body weight)	7.7 ± 0.3	7.5 ± 0.3	7.5 ± 0.4	-	0.138 -	-
V_E (l/min)	7.3 ± 0.8	7.1 ± 0.9	7.4 ± 0.9	-	0.101 -	-
P_{ACO_2} (mmHg)	54 ± 12	48 ± 9	51 ± 15	-	0.141 -	-
PEEP (cm H_2O)	11 ± 3	22 ± 3	25 ± 4	< 0.001 < 0.001	< 0.001	0.004
Airway driving pressure (cm H_2O)	22 ± 6	15 ± 4	16 ± 6	< 0.001 < 0.001	< 0.001	0.571
$P_{aw.mean}$ (cm H_2O)	19 ± 3	27 ± 3	31 ± 4	< 0.001 < 0.001	< 0.001	0.002
$P_{aw.plat}$ (cm H_2O)	33 ± 6	37 ± 6	41 ± 7	0.008	< 0.001 < 0.001	0.043
Regional ventilation delay inhomogeneity (%)	9.0 ± 3.6	4.8 ± 1.3	5.6 ± 2.2	< 0.001 < 0.001	< 0.001	0.936
Cdyn (l/cm H_2O)	10 ± 3	14 ± 4	14 ± 5	< 0.001 < 0.001	< 0.001	0.968
CO (l/min)	6.3 ± 1.2	4.8 ± 1.3	4.3 ± 1.0	< 0.001 < 0.001	< 0.001	0.153
MAP (mmHg)	98 ± 17	94 ± 21	92 ± 17	-	0.306 -	-
MPAP (mmHg)	38 ± 8	36 ± 6	39 ± 8	-	0.212 -	-
S_aO_2 (%)	88 ± 5	97 ± 1	97 ± 2	< 0.001 < 0.001	< 0.001	0.970
Pao_2 (mmHg)	85 ± 20	257 ± 94	240 ± 100	< 0.001 < 0.001	< 0.001	0.758
Pao_2/Fio_2 (mmHg)	141 ± 41	417 ± 115	388 ± 120	< 0.001 < 0.001	< 0.001	0.603
Fio_2	0.64 ± 0.17	0.62 ± 0.15	0.62 ± 0.15	-	0.382 -	-
Q_s/Q_t (%)	34 ± 6	11 ± 5	12 ± 6	< 0.001 < 0.001	< 0.001	0.784
Oxygen delivery (ml/min)	626 ± 142	495 ± 121	463 ± 117	< 0.001 < 0.001	< 0.001	0.338
Intraabdominal pressure (cm H_2O)	18 ± 6	20 ± 5	20 ± 5	-	0.251 -	-

Statistics: upper row: one-way repeated-measures ANOVA, PEEP-effect; lower row: *post hoc* (Newmann-Keuls) tests (if appropriate): a: table-PEEP vs. minimal-tidal-recruitment-PEEP, b: table-PEEP vs. maximal-oxygenation-PEEP, c: minimal-tidal-recruitment-PEEP *vs* maximal-oxygenation-PEEP.

Cdy, dynamic compliance of the respiratory system; CO, cardiac output; Fio_2 inspiratory oxygen fraction; MAP, mean arterial blood pressure; MPAP, mean pulmonary arterial blood pressure; P_{ACO_2}, arterial carbon dioxide partial pressure; Pao_2/Fio_2, Horowitz index; P_aO_2, arterial oxygen partial pressure; $P_{aw.mean}$, mean airway pressure; $P_{aw.plat}$, plateau airway pressure; PEEP, positive end-expiratory pressure; Q_s/Q_t, shunt (Berggren); RR, respiratory rate; S_aO_2 arterial oxygen saturation; V_E, minute ventilation; V_T, tidal volume.

and maximal oxygenation PEEP, overall pulmonary perfusion was reduced (figs. 3B and 4B) mainly reflected by reduction in shunt perfusion (fig. 4B) in dependent lung regions (fig. 3C). Whereas absolute blood flows were different (fig. 3B), relative regional perfusion distribution along the normalized ventral-to-dorsal axis was not affected by these PEEP strategies (fig. 3B).

Ventilation Distribution to Different Lung Compartments. On the normalized ventral to dorsal axis, ventilation was redistributed from nondependent to dependent lung regions during both minimal tidal recruitment and maximal oxygenation PEEP when compared to table PEEP (figs. 3D and 5, second row). Ventilation of the normal $\dot{V}/\dot{Q}$ compartment was reduced with table PEEP (fig. 4C), and dead space ventilation (gas flow to the dead space compartment) in the ventral lung regions was nearly doubled when compared to both other PEEP strategies (figs. 3E and 4C) and contributed to more than one third of the total minute ventilation.

Table 2. Lung Volumes and Aeration

Parameter	PEEP Strategy			*P* Value ANOVA		
				I	II	I*II
	PEEP Table	Minimal Tidal Recruitment	Maximal Oxygenation	*Post Hoc* Test		
				a	b	c
Total lung volume (ml)	902 ± 234	1376 ± 205	1413 ± 278	I < 0.001	–	–
				a < 0.001	b < 0.001	c = 0.617
Distribution of total lung volume to different degrees of aeration				I < 0.001	II < 0.001	I*II < 0.001
Nonaerated (%)	28 ± 11	5 ± 5	4 ± 4	a < 0.001	b < 0.001	c = 0.935
Poorly aerated (%)	40 ± 7	27 ± 13	24 ± 15	a = 0.009	b = 0.003	c = 0.586
Normally aerated %)	32 ± 1	69 ± 15	71 ± 17	a < 0.001	b < 0.001	c = 0.531
Hyperaerated (%)	<1	<1	<1	–	–	–
Total lung mass (g)	590 ± 143	597 ± 110	600 ± 95	I = 0.935	–	–
				–	–	–
Distribution of total lung volume to different degrees of aeration				I < 0.001	II <0.001	I*II < 0.001
Nonaerated (%)	40 ± 12	9 ± 9	9 ± 8	a < 0.001	b < 0.001	c = 0.932
Poorly aerated (%)	42 ± 7	36 ± 15	33 ± 17	a = 0.488	b = 0.248	c = 0.469
Normally aerated %)	18 ± 9 [a, b]	55 ± 19 [a]	58 ± 20 [b]	a = 0.007	b < 0.001	c = 0.419
Hyperaerated (%)	<1	<1	<1	–	–	–
Pulmonary gas volume (ml)	315 ± 136	779 ± 197	814 ± 258	I < 0.001		
				a < 0.001	b < 0.001	c = 0.597
Ventilated lung volume (%)	53 ± 7	78 ± 6	83 ± 9	I < 0.001		
				a < 0.001	b < 0.001	c = 0.121
Ventilated lung volume (ml)	577 ± 206	1287 ± 278	1404 ± 430	I < 0.001		
				a < 0.001	b < 0.001	c = 0.201
Perfused lung volume (%)	78 ± 6	78 ± 7	72 ± 8		I = 0.007	
				a = 0.724	b < 0.010	c = 0.009
Perfused lung volume (ml)	822 ± 182	1270 ± 308	1190 ± 321		I < 0.001	
				a < 0.001	b < 0.001	c = 0.334

Distribution of total lung volume and lung mass on different degrees of aeration and pulmonary gas volume, measured by computed tomography (transmission scans during single photon emission computed tomography); amount of ventilated and perfused lung volume (in % lung volume and ml), measured by single photon emission computed tomography. One-way (I, PEEP effect) or two-way repeated-measures ANOVA (I, PEEP effect; II, distribution to different degrees of aeration; I*II, interaction). *Post hoc* (Newmann–Keuls) test: a, table-PEEP *vs.* minimal tidal recruitment PEEP; b, table PEEP *vs.* maximal oxygenation PEEP; c, minimal tidal recruitment PEEP *vs.* maximal oxygenation PEEP. Data as mean ± SD. PEEP, positive end-expiratory pressure.

With decreasing aerated lung volume during table PEEP, regional ventilation (gas flow per voxel) of the remaining aerated voxels reached up to 2 ml · min^{-1} · $voxel^{-1}$, primarily in the more ventral lung regions, whereas regional ventilation remained less than 1 ml · min^{-1} · $voxel^{-1}$ in all lung regions using the minimal tidal recruitment and maximal oxygenation PEEP (figs. 3F and 5, second row).

Figure 5 shows two- and three-dimensional reconstructions of regional ventilation and perfusion analyses from a representative animal for the three PEEP strategies (of note: this illustrative example is not necessarily representative for all quantitative results of the whole study population). Comparison of PEEP titrations based on electrical impedance tomography and driving pressure are given in the online supplement (figs. S7 and S8; table S5; Supplemental Digital Content 13, http://links.lww.com/ALN/C218). A comparison of regional $\dot{V}/\dot{Q}$ measurements and blood gas analyses is provided in the online supplement (figs. S9 to S11, Supplemental Digital Content 14, http://links.lww.com/ALN/C219).

Discussion

This animal study comparing three strategies for individualized PEEP titration in a porcine model of recruitable lung injury and elevated intraabdominal pressure showed that different strategies resulted in different PEEP levels. Minimal tidal recruitment and maximal oxygenation PEEP caused and maintained alveolar recruitment, decreased regional ventilation/voxel, reduced both shunt compartment and shunt perfusion, and diminished dead space ventilation, when compared to table PEEP. Dead space compartment was highest with maximal oxygenation PEEP.

Shunt and Dead Space

Single photon emission tomography enables discrimination of shunt perfusion (blood flow to nonventilated lung volume) from the size of shunt compartment (volume of shunt-perfused lung tissue). The high amounts of both shunt compartment and shunt perfusion during table PEEP were reduced with higher airway pressures during both other

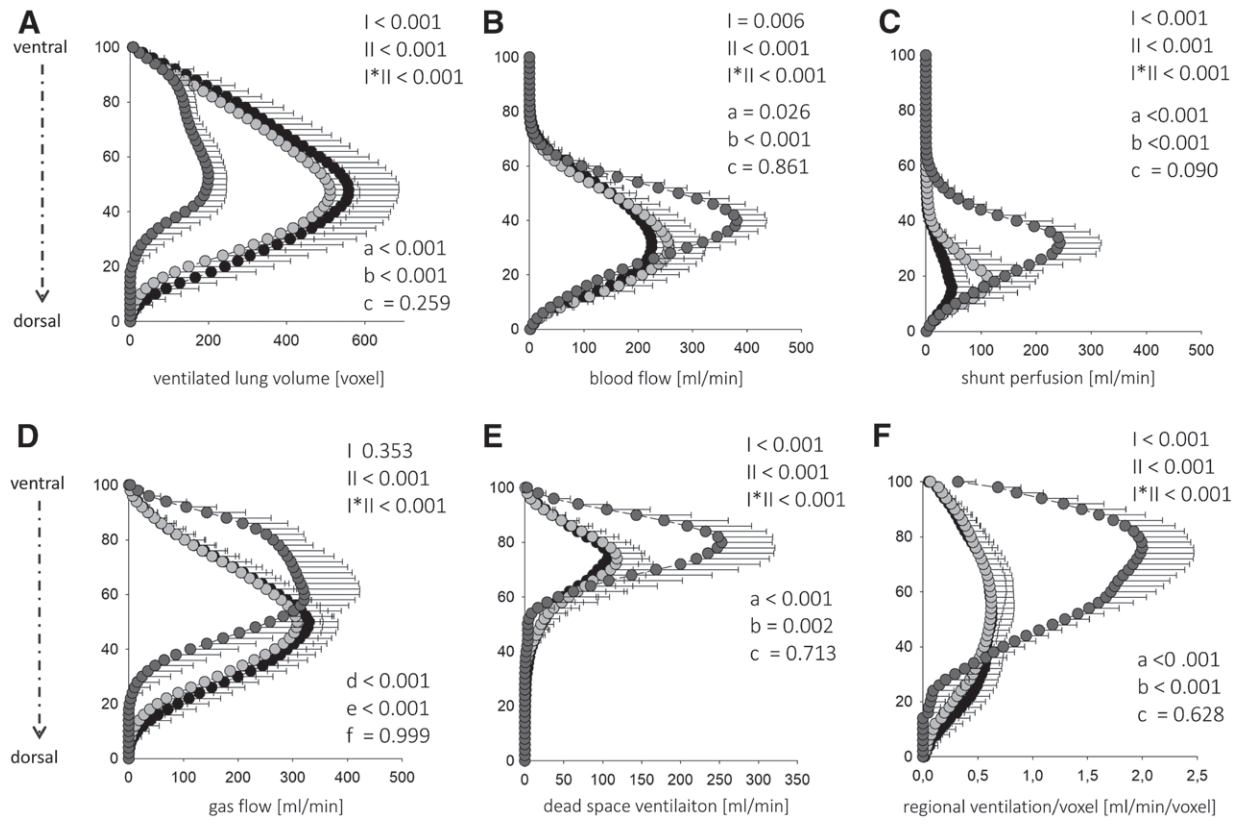

Fig. 3. Regional distribution (on a dorsal-to-ventral axis) of (*A*) ventilated lung volume (in voxel), (*B*) pulmonary blood flow (perfusion in ml/min), (*C*) shunt perfusion (in ml/min), (*D*) pulmonary gas flow (ventilation in ml/min), (*E*) dead space ventilation (in ml/min), and (*F*) regional ventilation/voxel (in ml · min^{-1} · $voxel^{-1}$) during ventilation with table PEEP (*dark gray circles*), minimal tidal recruitment PEEP (*light gray circles*), and maximal oxygenation PEEP (*black circles*), respectively. Statistics: two-way repeated-measure ANOVA; I, repeated-measures-factor "PEEP strategy"; II, repeated-measures factor "ventral-to-dorsal-distribution" and interaction I*I of both factors. *Post hoc* (repeated-measures ANOVA) for differences in regional distribution between PEEP-strategies: a, table PEEP *vs.* minimal tidal recruitment PEEP (factor PEEP); b, table PEEP *vs.* maximal oxygenation PEEP (factor PEEP); c, maximal oxygenation PEEP *vs.* minimal tidal recruitment PEEP (factor PEEP); d, table PEEP *vs.* minimal tidal recruitment PEEP (interaction); e, table PEEP *vs.* maximal oxygenation PEEP (interaction); f, maximal oxygenation PEEP *vs.* minimal tidal recruitment PEEP (interaction). Data are presented as mean and SD.

PEEP settings. Two different (recruitment-dependent and recruitment-independent) but concordant mechanisms can explain this finding. First, alveolar recruitment decreased the size of the shunt compartment (figs. 4A and 5) and, hence the corresponding blood flow (fig. 3B) no longer appeared as shunt perfusion (fig. 3C). Second, as previously shown, a decreased cardiac output resulting from reduced cardiac preload[36] with higher intrathoracic pressures may cause a disproportionately higher reduction in shunt perfusion,[37] which is in agreement with our data (fig. 3, B and C). In contrast to experimental data from a lavage model,[38] we did not find redistribution of pulmonary blood flow toward dorsal regions with increase in PEEP. This may be explained by an already increased perfusion of these regions due to attenuated hypoxic pulmonary vasoconstriction in our model.[39]

In analogy, regional $\dot{V}/\dot{Q}$ analyses allow discrimination of the size of the dead space compartment (volume of ventilated but nonperfused lung tissue) from dead space ventilation (gas flow to this dead space compartment). Dead space, as defined here, is where ventilation exceeds perfusion by the factor 100.[31,40] This implies that the dead space compartment, or part of it, can be ventilated by a very small gas flow as long as it exceeds blood flow by the factor 100. Depending on the presence of high or low gas flows, the same amount of dead space ventilation can either be caused by low regional ventilation/voxel (fig. 3F) of large dead space compartment (implicating a static distension of aerated lung tissue) or by high regional ventilation/voxel (fig. 3F) of small dead space compartment (implicating a more dynamic intratidal distension of aerated lung tissue). Following the aforementioned considerations, impairment of oxygenation and carbon dioxide elimination is rather affected by the amount of shunt perfusion and dead space ventilation than by the sizes of the shunt and dead space compartments.

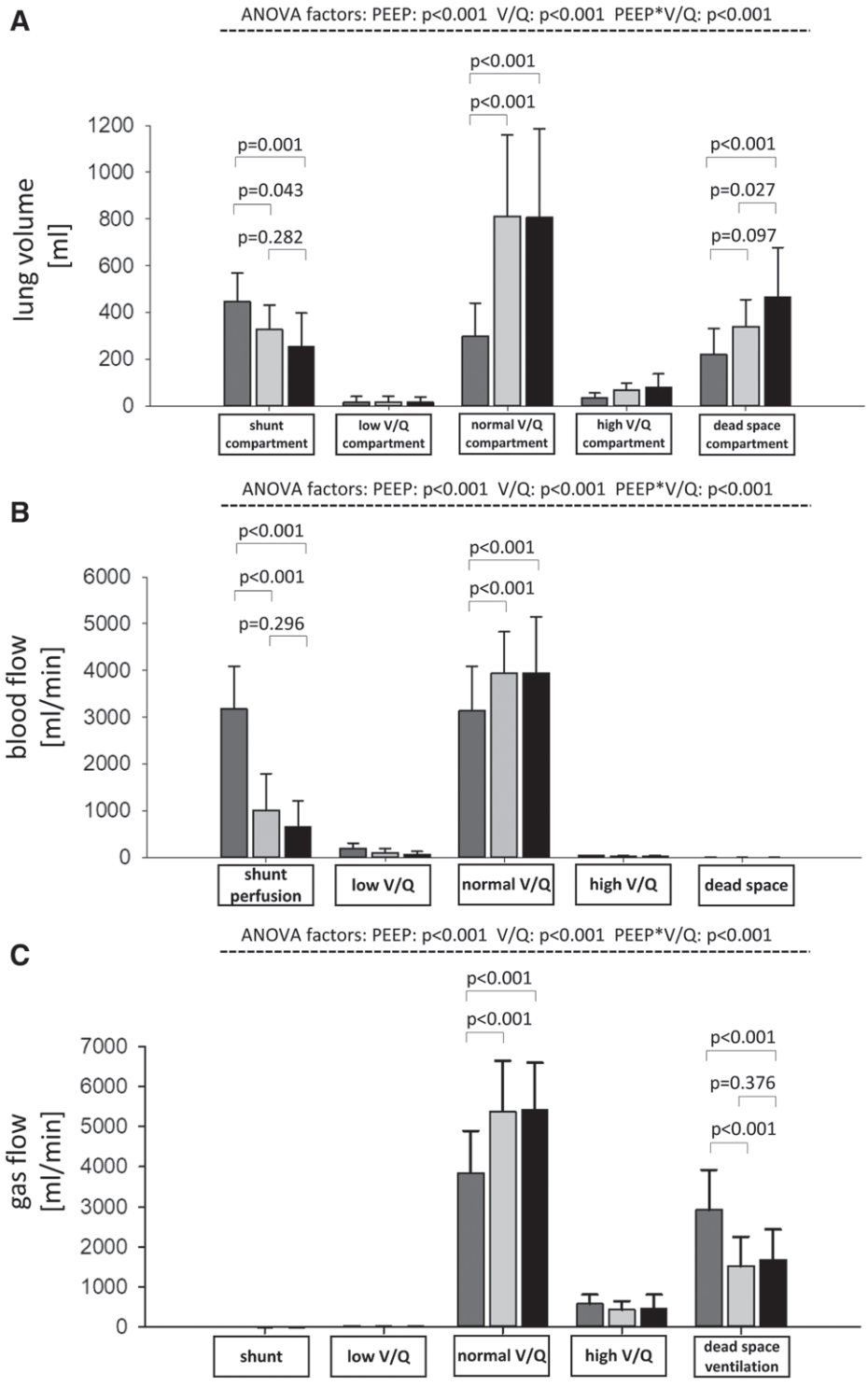

Fig. 4. Distribution of (*A*) lung volume (in ml), (*B*) pulmonary blood flow (perfusion in ml/min), and (*C*) pulmonary gas flow (ventilation in ml/min) to shunt, low $\dot{V}/\dot{Q}$, normal $\dot{V}/\dot{Q}$, high $\dot{V}/\dot{Q}$., and dead space compartments during ventilation with table PEEP (*dark gray bars*), minimal tidal recruitment PEEP (*light gray bars*), and maximal oxygenation PEEP (*black bars*), respectively. Two-way repeated-measures ANOVA. Repeated-measures factor; PEEP strategy, II repeated-measures factor: "$\dot{V}/\dot{Q}$ class," and interaction PEEP-strategy * $\dot{V}/\dot{Q}$ class. *Post hoc* (Newmann–Keuls) test for differences between PEEP strategies within $\dot{V}/\dot{Q}$ classes (*square brackets).* Data are presented as mean and SD. PEEP, positive end-expiratory pressure; $\dot{V}/\dot{Q}$, ventilation/perfusion.

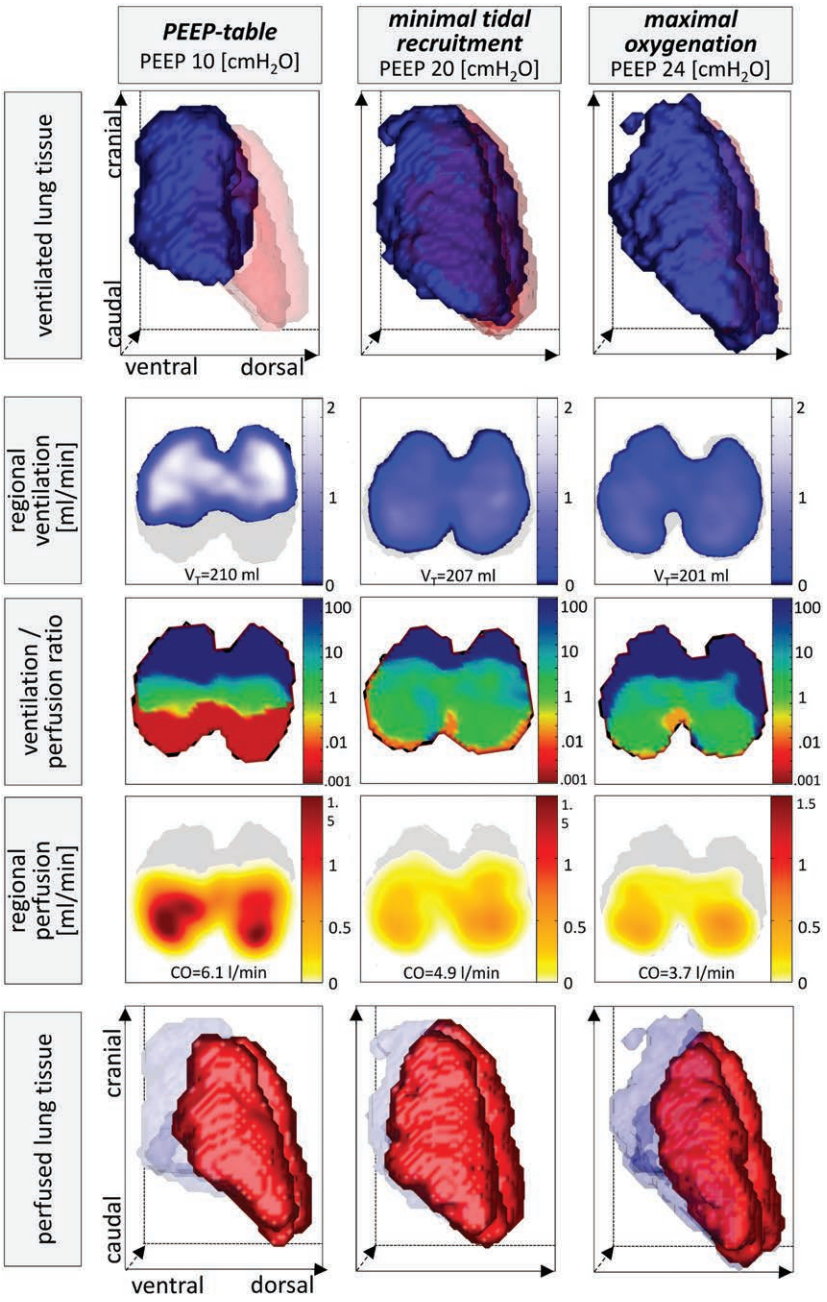

Fig. 5. Regional ventilation and perfusion analyses from single photon emission computed tomography during ventilation with table PEEP (10 cm H_2O [*left*]), minimal tidal recruitment PEEP (20 cm H_2O [*middle*]), and maximal oxygenation PEEP (24 cm H_2O [*right*]), respectively; representative animal (pig No. 13). (*Top row*) Three-dimensional reconstruction of the ventilated (*blue*) and perfused but not ventilated (*light red*) lung tissue (view from the left dorsal); (*second row*) regional ventilation distribution within a transverse slice (view from caudal), blue-scaled in ml · min^{-1} · $voxel^{-1}$, and global tidal volume in ml/min; (*middle row*) regional ventilation/perfusion relation within the same transversal slice; (*fourth row*) regional perfusion distribution within the same slice, red-scaled in ml · min^{-1} · $voxel^{-1}$ and global cardiac output in ml/min; (*bottom row*) three-dimensional reconstruction of the perfused (*red*) and ventilated but not perfused (*light blue*) lung tissue (view from the left dorsal). Table-PEEP: small ventral part of the lung is ventilated and has to accommodate the whole tidal volume. Regional ventilation/voxel dramatically increases, as indicated by the light blue to white spots. Perfusion is increased but shifted to the very dorsal lung regions, resulting in gross $\dot{V} / \dot{Q}$ mismatch. Only a small lung fraction contributes to pulmonary gas exchange. Minimal tidal recruitment PEEP: ventilated lung volume is increased by recruitment of dorsal lung regions. As a consequence, regional ventilation/voxel decreases and homogenizes substantially. Additionally, total and regional perfusion decreased. $\dot{V} / \dot{Q}$ substantially improved. Both shunt perfusion and dead space ventilation decrease. Maximal oxygenation PEEP further increases lung volume, but results in a further decrease in pulmonary perfusion, especially in ventral lung regions. Thus, dead space compartment in the ventral part of the lung increases. CO, cardiac output; PEEP, positive end-expiratory pressure; $\dot{V} / \dot{Q}$, ventilation/perfusion.

Regional Ventilation/Voxel and Strain

Since V_T, minute ventilation, and respiratory rate remained constant between the different PEEP strategies, changes in regional ventilation/voxel (fig. 3F) were mainly a function of differences in ventilated lung volume (fig. 3A). Aeration data suggest that differences in lung volume were mainly caused by recruitment of collapsed lung rather than by changes in edema because lung masses were similar between PEEP settings (figs. S5 and S6, Supplemental Digital Content 12, http://links.lww.com/ALN/C217).

At lowest airway pressures during table PEEP without a preceding recruitment maneuver, the derecruited, small lung (table 2; fig. 3A) had to accommodate the total V_T, which resulted in higher regional ventilation/voxel (fig. 3F). This suggests increased specific ventilation (volume change/resting volume) related to strain,[41–43] which causes ventilator-induced lung injury.[41,44] Increased driving pressure is associated with poor outcome in ARDS patients.[4,45] Highest driving pressures were observed with table PEEP due to lowest respiratory system compliance and lung volume ("baby lung")[46] promoting cyclic inspiratory distention[5] even with "protective" V_T. This is supported by previous findings in ARDS patients[47] and data from a ventilator-induced lung injury model showing inflammation[48] of ventilated ventral lung regions, whereas collapsed regions are "protected" by being non- or poorly-ventilated.[48] In our study, increased regional ventilation/voxel during table PEEP (fig. 3F) was associated with dead space ventilation (fig. 3E), which causes mechanical stress without contributing to gas exchange (wasted ventilation).[49] Increased dead space ventilation has been shown to be associated with impaired outcome.[50]

In our model characterized by a recruitable lung injury, both high PEEP strategies, minimal tidal recruitment PEEP and maximal oxygenation PEEP, were comparably associated with sustained alveolar recruitment (table 2) increasing ventilated lung volume (fig. 3A) and respiratory system compliance while reducing driving pressures. However, the preceding recruitment maneuver may at least partially explain these results. Redistribution of ventilation to recruited lung regions caused reduction in regional ventilation/voxel of ventral lung regions (fig. 3F) which might decrease cyclic strain. Dead space compartment (fig. 4A) increased with higher PEEP levels and was highest with maximal oxygenation PEEP. Whether this is attributable to static strain cannot be derived from our data, since we did not measure lung distension. Finally, minimal tidal recruitment PEEP ensured comparable lung recruitment and volume, regional ventilation/voxel, and regional gas exchange at lower PEEP levels when compared to the maximal oxygenation PEEP strategy, but requires additional technical equipment which makes this impedance tomography–based strategy less clinically compelling.

Clinical data suggest increased mortality in patients with high amount of collapsed but recruitable lung tissue undergoing tidal recruitment.[11] Decreased mortality has been associated with lung recruitment and reduced tidal recruitment at higher PEEP levels,[3,10] whereas patients with less recruitable lungs may face harm from inspiratory overdistension.[10] Although increasing airway pressures to facilitate lung recruitment before PEEP titration seems physiologically reasonable—at least in patients with recruitment potential—recruitment maneuvers with pressures up to 60 cm H_2O followed by PEEP titration aimed at the highest global compliance in patients with mainly pneumonia-associated, less recruitable ARDS increased mortality,[51] and recent clinical guidelines do not recommend the routine use of recruitment maneuvers. In patients with less recruitable lungs (*e.g.,* due to pneumonia), application of high PEEP and airway pressures to facilitate recruitment as performed in our study maybe harmful. Hence, identification of recruitability is crucial.

PEEP setting according to respiratory system or lung mechanics (*e.g.,* by using esophageal pressure-guided approaches) improved oxygenation,[52] but not survival.[53] Minimizing temporal lung inhomogeneity guided by impedance tomography may not individually result in the same PEEP levels as found by using measures of global lung mechanics (Supplemental Digital Content 13, http://links.lww.com/ALN/C218), suggesting that global and regional information on lung function might differ. PEEP titration was also performed in different animal models and humans measuring lung volume, ventilation distribution, and regional lung mechanics by impedance tomography.[19] Whether impedance tomography–based strategies are clinically advantageous warrants further investigations.

Limitations. Our study has limitations. Firstly, acute lung failure and ARDS summarize several pathophysiologic entities, which cannot be mimicked by a single experimental model. Elevated intraabdominal pressure is frequently observed in ventilated patients.[16–18] Whereas its incidence in all ARDS patients is unknown, elevated intraabdominal pressure is prevalently seen in respiratory failure or ARDS caused by extrapulmonary reason[16–18] (*e.g.*, abdominal sepsis).

We used intraabdominal saline infusion to increase intraabdominal pressure as previously reported.[22,24,54] Others used air insufflation[25] or intraabdominal balloons.[26,55] We combined oleic acid injection,[56] which causes endothelial lung injury,[56] with moderately elevated intraabdominal pressure,[25] as done before.[22,24,26,55] Adding elevated intraabdominal pressure[22,24,26] aggravates experimental lung injury[26] and increases collapse and tidal recruitment.[22,24] Thus, our hybrid model allows stable lung collapse and recruitability over time. However, our results are not necessarily transferrable to all ventilated patients, and especially not to pulmonary-induced ARDS characterized by less recruitability. Since intraabdominal pressure affects transpulmonary pressure, our model might favor higher PEEP levels and results might differ with other intraabdominal pressure levels. However, comparable effects on recruitment and global gas exchange were recently reported when applying these

PEEP strategies in aspiration-induced lung injury without elevated intraabdominal pressure.[21] Moreover, PEEP according to the PEEP/FIO_2 table is frequently used as a reference strategy when studying different PEEP strategies in patients with[57,58] and without[59–61] elevated intraabdominal pressure.

Second, due to the lack of a recruitment maneuver, the table PEEP strategy started from a different volume history (derecruited lung) than both other strategies (fully recruited lung). Using the ARDS Network higher PEEP/FIO_2 table, and/or using table PEEP after a recruitment maneuver would likely result in lung recruitment and less $\dot{V}/\dot{Q}$ mismatch. Thus, by design, our study is biased in this regard, and we cannot differentiate between effects of a recruitment maneuver and high PEEP. We compared clinically relevant strategies aiming at lung recruitment or lung rest and "permissive" atelectasis. The ARDS Network studies neither proposed recruitment maneuvers nor excluded patients with elevated intraabdominal pressure.[2]

Third, the impedance tomography–based method of PEEP titration was previously validated in different lung injury models characterized by low to high recruitability.[21,22,24] In animals without lung injury, PEEP titration resulted in low regional ventilation delay inhomogeneity already at low PEEP levels providing evidence that the impedance tomography–based method is sensitive in nonrecruiters as well (fig. S1, Supplemental Digital Content 1, http://links.lww.com/ALN/C206). Although increased inhomogeneity values at high PEEP levels (fig. 1) can be explained by delayed inflation of distended lung tissue,[22] the method is not validated to detect alveolar hyperdistention.

Fourth, different arbitrary thresholds of oxygen decline have been reported (Pao_2, 10% decrease; less than 450 to 400 mmHg)[13,62] to ensure "optimal gas exchange."[12] We used a 5% decrease in Pao_2 to assume maximum recruitment as an upper extreme. Using other oxygenation thresholds, the maximal oxygenation PEEP level might have been different.

Fifth, results for dead space may have been different using pressure-controlled ventilation. Additionally, by design, we could not study effects of PEEP strategies on ventilation-induced lung injury and outcome.

Last, shunt values from regional $\dot{V}/\dot{Q}$ measurement correlated well to shunt values measured by blood gas analysis and atelectasis. However, we found less accuracy with higher shunt values which can be explained by basically differences between both methods (see Supplemental Digital Content 14, http://links.lww.com/ALN/C219). We cannot validate dead space ventilation from our regional $\dot{V}/\dot{Q}$ data. Single photon emission computed tomography does not enable detection of all anatomical dead space. However, the gross appearance of the $\dot{V}/\dot{Q}$ distribution is similar to that of the classic multiple inert gas elimination technique.[40] Although dead space ventilation and dead space compartments might suggest dynamic or static hyperinflation of the lung, our densitometric analysis did not show hyperaerated lung tissue. This might be explained by interaction between density thresholds, slice thickness, and reconstruction parameters impairing the detection of hyperinflation.[63]

Conclusion

In a pig model of recruitable lung injury and elevated intraabdominal pressure, three PEEP strategies resulted in different PEEP levels. When compared to table PEEP without a recruitment maneuver, both minimal tidal recruitment PEEP and maximal oxygenation PEEP following a recruitment maneuver induced lung recruitment, which decreased shunt perfusion, dead space ventilation, and regional ventilation/voxel. Effects of minimal tidal recruitment PEEP and maximal oxygenation PEEP were comparable, but with lower PEEP in the minimal tidal recruitment PEEP setting.

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Competing Interests

Drs. Leonhardt, Putensen, Wrigge, and Reske received lecture honoraria from Draeger Medical (Lübeck, Germany). Dr. Pikkermaat reports financial relationships with Draegerwerk AG and CoKGaA (Lübeck, Germany). Dr. Wrigge reports consultant honoraria from Draeger Medical. The remaining authors declare no competing interests.

Correspondence

Address correspondence to Dr. Muders: Department of Anesthesiology and Intensive Care Medicine, University Hospital Bonn, D - 53105 Bonn, Germany. t.muders@uni-bonn.de.

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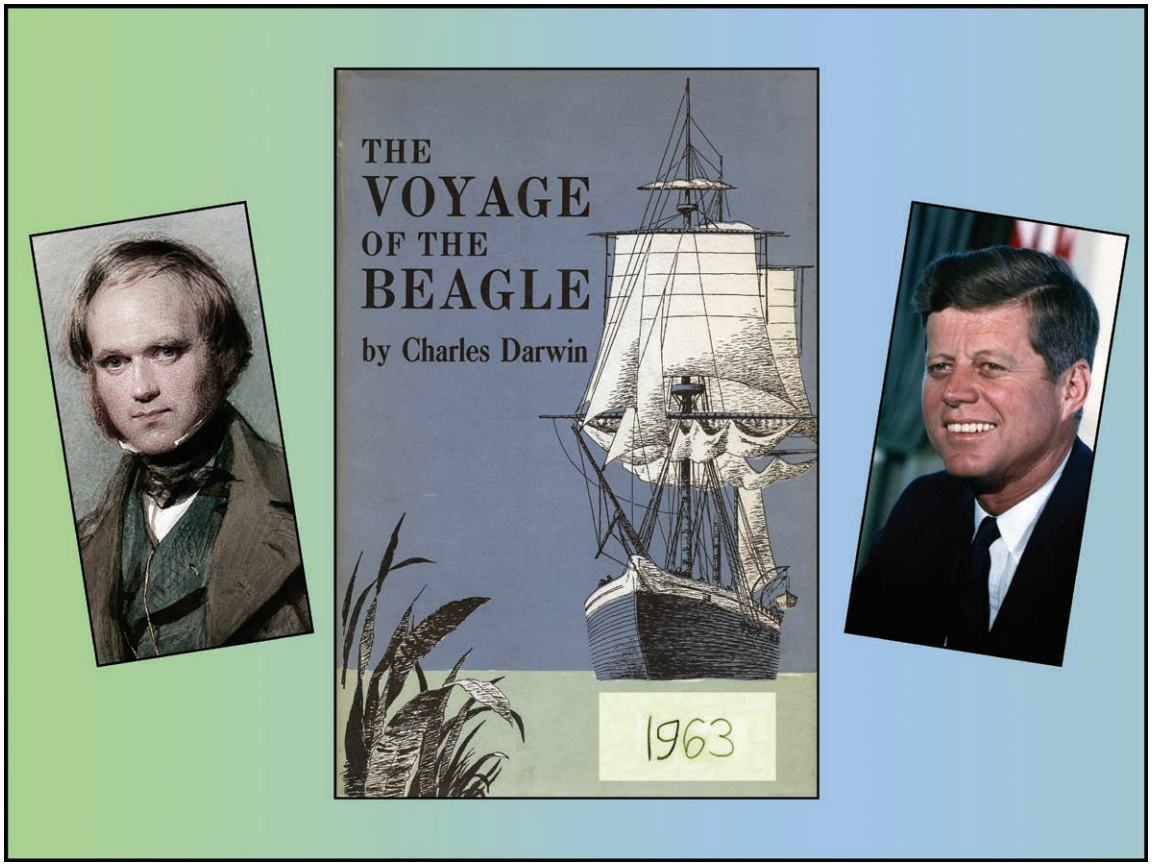
Byline Backstory No. 3: An Assassination Transforms an Aspiring Naturalist into a Future Physician



With astronauts blasting off from my extended backyard next to Cape Canaveral, I remember scrawling "1963" on the dust jacket (*middle*) of the book that I read in second grade, my 328-page copy of *The Voyage of the Beagle* by Charles Darwin (*left*). A second inspiration encouraging me to become a naturalist was my third-grade teacher, Mrs. Ruby Gammage, who was ranked as one of the nation's top 100 "Elementary Science and Mathematics" educators. However, on November 22, 1963, a tearful Mrs. Gammage asked the class to suspend calculating cylindrical volumes in order to hear the radio broadcasting news of the assassination of President John F. Kennedy (*right*). I resolved on that day, my eighth birthday, to become a physician. Twenty-four years later, at the Wood Library-Museum Board Meeting, the last anesthesiologist who had attended that mortally wounded president, Dr. Marion T. "Pepper" Jenkins, would welcome my start as acting curator for the Wood Library-Museum. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

George S. Bause, M.D., M.P.H., Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio.