

# Computed tomographic assessment of lung aeration at different positive end-expiratory pressures in a porcine model of intra-abdominal hypertension and lung injury

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## Research

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# Abstract

## Background

Intra-abdominal hypertension (IAH) is common in critically ill patients and is associated with increased morbidity and mortality. High positive end-expiratory pressures (PEEP) can reverse lung volume and oxygenation decline caused by IAH in the setting of injured lungs. The impact of high PEEP levels on alveolar overdistension in IAH and lung injury is unknown. We aimed to define an optimal PEEP range during IAH and lung injury that would be high enough to reduce atelectasis formation while low enough to minimize alveolar overdistention.

## Methods

Five anesthetized pigs received standardized anesthesia and mechanical ventilation. Peritoneal insufflation of air was used to generate intra-abdominal pressure of 27cmH<sub>2</sub>O (20 mmHg). Lung injury was created by intravenous oleic acid. PEEP levels of 5, 12, 17, 22, and 27cmH<sub>2</sub>O were applied. We performed computed tomography and measured arterial oxygen levels, respiratory mechanics, and cardiac output 5 min after each new PEEP level. The proportion of overdistended, normally aerated, poorly aerated, and non-aerated atelectatic lung tissue was calculated based on Hounsfield units.

## Results

PEEP decreased poorly aerated and atelectatic lung whilst increasing normally aerated lung. Overdistension increased with each incremental increase in applied PEEP.

## Conclusions

Our findings in a large animal model suggest that an optimal PEEP level which maximally recruits atelectatic lung without causing overdistension or hemodynamic compromise may not exist.

## Background

Intra-abdominal hypertension (IAH) is defined as a sustained intra-abdominal pressure (IAP) above or equal to 12 mmHg (1) and occurs in around 30% of critically-ill patients. Mortality increases in proportion to the degree of IAH (2). IAH impairs function and causes permanent histological changes of various organ systems (3–5). Furthermore, due to a cephalad shift of the diaphragm, IAH causes pulmonary atelectasis, impaired lung function and chest wall compliance as well as reduced oxygenation (4, 6–11).

The optimal mechanical ventilation, and more specifically, the optimal level of PEEP in patients with IAH remains unknown (7, 12–14). Previous experimental results of our group show that high PEEP levels counteract the negative respiratory effects of IAH (8, 11, 15). However, high PEEP levels might cause alveolar over-distension in the non-dependent lung regions, which is associated with ventilator-induced lung injury (13, 16).

Lung computed tomography (CT) is the only method besides electrical impedance tomography that informs on alveolar overdistension by quantification of lung volumes and tissue density (17–19). We aimed to define an optimal PEEP range that would be high enough to reduce atelectasis formation while low enough to minimize overdistention

from analysis of CT lung images obtained from a pig model of IAH and lung injury. We hypothesized that the inflection point for atelectasis would be lower than for over-distension in the presence of IAH.

## Methods

Additional details of the study methodology are provided in the online supplement (Online supplement 1 – methods unabridged).

The study conformed to the regulations of the Australian Code for the care and use of animals for scientific purposes (20) and was approved by the Animal Ethics Committees, Murdoch University (R2588/13).

## Preparation Of Animals And Ventilation

Five anesthetized and paralyzed female pigs (Large White) with a median (IQR) weight of 29.3 (29.0-30.6) kg were included in this study.

The pigs were mechanically ventilated (Babylog VN500, Draeger, Lübeck, Germany) using the following settings: volume guaranteed pressure-controlled continuous mandatory ventilation (PC-CMV/VG),  $F_iO_2$  0.6, tidal volume 8 mL/kg. The initial PEEP setting was 5cmH<sub>2</sub>O and altered according to the experimental protocol (see below). The initial respiratory rate was adjusted to maintain an end-tidal CO<sub>2</sub> of 35–45 mmHg. Subsequently, PEEP was the only ventilation setting altered throughout the remainder of the protocol.

## Respiratory Mechanics

Esophageal pressure was measured as previously described (11). The optimal position in the esophagus was confirmed from the pressure trace and ultimately using CT-guidance.

End-inspiratory and end-expiratory airway and esophageal pressures were obtained and the static elastances of the respiratory system ( $E_{rs}$ ), chest wall ( $E_w$ ) and lung ( $E_l$ ) and the transpulmonary pressures were derived as described previously (11).

Arterial oxygen and carbon dioxide tension were measured with a blood gas analyzer immediately following blood collection (Rapidlab 1200, Siemens, Leverkusen, Germany). PaO<sub>2</sub> over fractional inspiratory oxygen concentration (P/F ratio), was calculated (11).

## Hemodynamic Parameters

The animals remained supine throughout the study. Mean arterial blood pressure was measured at the femoral artery and cardiac output was measured by transpulmonary thermodilution (11).

Pigs were stabilized hemodynamically with 4% succinylated gelatin solution (500 mL over the first 30 min followed by 1 mL/kg/h, Gelofusine®, Braun, Bella Vista NSW, Australia). Noradrenalin infusion (3 mg/50 mL) was administered if required to maintain a mean arterial pressure  $\geq$  70 mmHg.

## Intra-abdominal Pressure

A large bore orogastric tube was inserted to allow continuous gastric drainage. Intra-abdominal hypertension of 27cmH<sub>2</sub>O (20 mmHg) was created by the insufflation of air into the peritoneal cavity through an air-tight catheter. A three-way tap connected to a transducer allowed direct measurement of IAP.

## Experimental Protocol

Measurements, including a CT scan, were performed initially at baseline IAP (abdomen not inflated) and again after peritoneal inflation of air to an IAP of 27cmH<sub>2</sub>O (20 mmHg). The initial PEEP level was set at 5 cmH<sub>2</sub>O. PEEP was incremented subsequently to 12, 17, 22, and 27cmH<sub>2</sub>O (“ascending”). PEEP levels were then decreased (“descending”) to ascertain an optimal “deflation” PEEP. Hysteresis was assessed by comparing measurements obtained at ascending and descending PEEP levels. Recruitment maneuvers were not used. CT images and physiological measurements (see below) were obtained five minutes after a stabilization period. Ventilation settings were kept constant except for PEEP.

## Lung Injury

The experimental protocol was carried out first with healthy lungs and then with injured lungs. To create lung injury, we used oleic acid as previously described (11) until a P/F ratio of 200–300 mmHg was established.

## Computed Tomography

A whole-lung helical CT scan (Siemens Somatom Emotion 16, Erlangen, Germany) was performed during an inspiratory and an expiratory pause (each about 20 seconds) (21). The scan parameters were standardized to 130 kV, 110 mA, 1.0 pitch, and 3 mm slice thickness at each tested PEEP level.

Image analyses was performed with Maluna® software (MALUNA 3.17, Peter Herrmann, University of Göttingen, Göttingen, Germany) (6). Based on the degree of density of lung tissue, four aeration compartments were computed: overdistended tissue (-1,000 to -901 Hounsfield units [HU]), normally aerated tissue (-900 to -501 HU), poorly aerated tissue (-500 to -101 HU), and non-aerated (atelectatic) tissue (-100 to 200 HU) (6, 22).

CT lung volumes were analyzed further in Excel (v16 for Mac, Microsoft, Redmond, Washington, USA). Three different equations including the Venegas equation were applied (Supplemental Digital Content 1 (23, 24)). The accuracy of each equation was assessed for describing the effect of different PEEP levels on CT volumes. The best fit was defined as a curve resulting in the smallest root mean square between the measured and calculated pressure-volume points.

## Statistics

A linear mixed model was applied to assess the effect of factors (IAH, lung injury, ascending vs descending PEEP) and covariates (PEEP) on different variables using SPSS (v25, IBM, St Leonards NSW, Australia). This approach accounted for the correlation between the repeated measures on each pig. Main effect was used for analysis of respiratory and hemodynamic outcomes. Main effect plus an interaction with lung segments (PEEP and lung injury) was used for CT measured lung volumes. Laterality (left/right) was included as a fixed factor in the linear mixed model. Differences between pigs were accounted for as a random effect. Missing values were imputed based on the

average relative differences between any pig with missing data and the other animals. Linear regression was performed to assess for correlations. A p-value of < 0.05 was considered statistically significant. For descriptive statistics, median (IQR) is reported.

## Results

One pig died during the protocol after lung injury was induced at the highest PEEP level of 27cmH<sub>2</sub>O. Therefore, we were unable to perform CT analysis or cardio-respiratory measurements with descending PEEP levels. The remaining results of this pig were used as described above. All other pigs survived to study completion.

## Effect Of Oleic Acid

To create lung injury, we required 0.4 (0.4–0.8) mL/kg IV oleic acid. The resulting P/F ratio of injured lungs before abdominal inflation was 153 (146–232) mmHg (Online supplement 2 – Table: Effect of IAH and lung injury on cardio-respiratory variables, Online supplement 3 – Figure: P/F ratio at different experimental conditions). Lung injury increased plateau airway and expiratory esophageal pressure, and increased  $E_{rs}$  consequent to increased  $E_L$ .

## Effect Of IAH

Median (IQR) baseline IAP were 2 (0–5) cmH<sub>2</sub>O [2 (0–4) mmHg] with healthy lungs and 3 (3–3) cmH<sub>2</sub>O [3 (2–3) mmHg] after oleic acid (lung injury). Overall IAH decreased oxygenation but this finding was not confirmed in a subgroup analyzes of healthy or sick lungs (Online supplement 2 – Table: Effect of IAH and lung injury on cardio-respiratory variables, Online supplement 3 – Figure: P/F ratio at different experimental conditions). Plateau airway and inspiratory esophageal pressures,  $E_w$  and  $E_L$  increased in the presence of IAH (Online supplement 2 – Table: Effect of IAH and lung injury on cardio-respiratory variables).

## Effect Of Lung Injury And IAH On CT Parameters

Because lung aeration at end-inspiration paralleled those at end-expiration we only describe lung aeration measured during end-expiration. While lung injury decreased gas volumes, IAH decreased gas volumes only in healthy but not in injured lungs (Table 1). Neither lung injury nor IAH affected tissue mass. The effect of lung injury and IAH were more pronounced on a segmental level (Fig. 1, Table 1, Online supplement 4 - Effect of IAH and lung injury on segmental lung aeration). In the dorsal dependent lung segments, lung injury and IAH decreased the segmental proportion of normally aerated lung due to an increase in atelectatic lung.

Table 1  
Effect of intra-abdominal hypertension (IAH) and lung injury on end-expiratory lung parameters measured by computed tomography

Abdomen	Baseline	IAH	Baseline	IAH		Baseline	IAH	
Lungs	Healthy	Healthy	Injured	Injured	Healthy	Injured		
P					Baseline vs IAH	Baseline vs IAH	healthy vs lung injury	healthy vs lung injury
Total lung volume, L	1.2 (1.1,1.2)	0.8 (0.7,0.8)	1.0 (1.0,1.0)	1.0 (0.9,1.1)	<b>&lt;0.01</b>	1.0	0.6	0.5
Lung gas volume, mL	721 (698,791)	378 (370,418)	522 (519,596)	428 (281,449)	<b>&lt;0.01</b>	0.1	<b>0.02</b>	1.0
Lung tissue mass, g	393 (356,412)	338 (316,354)	397 (372,399)	446 (361,454)	1.0	1.0	1.0	0.9
Overdistended, %	2 (2,2)	1 (1,2)	2 (2,3)	2 (1,2)	1.0	0.9	0.8	1.0
Normally aerated %	82 (79,85)	56 (50,65)	61 (57,66)	44 (35,51)	<b>&lt;0.01</b>	0.1	<b>0.03</b>	0.5
Poorly aerated, %	14 (11,16)	32 (27,36)	24 (22,26)	26 (22,31)	<b>0.01</b>	1.0	0.3	1.0
Atelectatic, %	2 (1,4)	10 (7,15)	11 (8,13)	26 (15,35)	0.1	<b>&lt;0.01</b>	0.1	<b>&lt;0.01</b>
Intra-abdominal pressure (IAP) of 27 cmH <sub>2</sub> O (20 mmHg) was applied. P, significance. Median (IQR) are given. Mixed linear model was used for statistical testing.								

## Effect Of PEEP

### Healthy lungs

In the presence of IAH and healthy lungs, high PEEP did not affect oxygenation but increased airway plateau and esophageal pressure, and decreased  $E_{rs}$  due to decreased  $E_L$  (Fig. 2, Online supplement 5 - Effect of PEEP on cardio-respiratory variables).

Higher PEEP levels increased gas volumes but did not affect tissue mass (Table 2). The overall proportion of normally aerated lungs increased due to a decrease in poorly aerated and atelectatic lung, with a parallel increase in the overall proportion of overdistended lung.

Table 2

Effect of different levels of positive end-expiratory pressure (PEEP) on end-expiratory lung parameters measured by computed tomography in the presence of intra-abdominal hypertension

PEEP, cmH <sub>2</sub> O	5	12	17	22	27	P,
PEEP, % of IAP	19	44	63	81	100	PEEP
<b>Healthy lungs</b>						
Total lung volume, L	0.8 (0.7,0.8)	0.9 (0.9,1.0)	1.0 (1.0,1.0)	1.1 (1.1,1.2)	1.3 (1.2,1.3)	< 0.01
Lung gas volume, mL	378 (370,418)	511 (501,561)	620 (611,649)	761 (743,788)	903 (856,908)	< 0.01
Lung tissue mass, g	338 (316,354)	355 (334,358)	352 (329,361)	353 (338,369)	351 (322,367)	0.6
Overdistended, %	1 (1,2)	2 (1,3)	2 (2,4)	4 (3,5)	5 (4,7)	< 0.01
Normally aerated, %	56 (50,65)	68 (63,74)	75 (70,80)	79 (76,83)	82 (82,86)	< 0.01
Poorly aerated, %	32 (27,36)	23 (20,38)	18 (15,22)	14 (10,16)	9 (8,11)	< 0.01
Atelectatic, %	10 (7,15)	5 (4,7)	3 (2,4)	3 (2,3)	2 (1,2)	< 0.01
<b>Injured lungs</b>						
Total lung volume, L	1.0 (0.9,1.1)	1.2 (1.0,1.2)	1.3 (1.0,1.4)	1.5 (1.2,1.5)	1.7 (1.3,1.7)	< 0.01
Lung gas volume, mL	428 (381,449)	569 (482,609)	744 (570,762)	885 (732,933)	1024 (827,1104)	< 0.01
Lung tissue mass, g	446 (361,454)	489 (381,521)	526 (392,546)	546 (424,557)	548 (429,560)	0.01
Overdistended, %	2 (1,2)	2 (2,3)	3 (2,3)	3 (3,3)	5 (4,6)	< 0.01
Normally aerated, %	44 (35,51)	55 (45,59)	60 (53,65)	63 (58,70)	69 (65,74)	< 0.01
Poorly aerated, %	26 (22,31)	25 (22,29)	24 (21,29)	24 (18,27)	19 (15,25)	< 0.01
Atelectatic, %	26 (15,35)	18 (10,23)	11 (7,15)	6 (3,7)	3 (24)	< 0.01
Intra-abdominal pressure (IAP) of 27 cmH <sub>2</sub> O (20 mmHg) was applied. Median (IQR) are given. Mixed linear model was used for statistical testing.						

PEEP reduced normally aerated, poorly aerated and atelectatic lung predominantly in the dorsal lung segments but led to overdistension predominantly in the ventral lung segments (Fig. 3, Online supplement 6 – Table: Effect of PEEP on segmental lung aeration).

## Injured lungs

In the presence of IAH and injured lungs, increased PEEP improved oxygenation. The effect of PEEP on plateau airway, end-expiratory, and end-inspiratory esophageal pressures as well as  $E_{rs}$  and  $E_L$  paralleled those found in healthy lungs (Fig. 1, Online supplement 5 – Table: Effect of PEEP on cardio-respiratory variables).

The effect of increased PEEP in the presence of IAH and injured lungs on gas volumes as well as on the overall and segmental aeration compartments (overdistended, normally aerated, poorly aerated and atelectatic lung) paralleled those found in healthy lungs (Table 2, Fig. 3, Online supplement 6 – Table: Effect of PEEP on segmental lung aeration). In contrast, PEEP increased tissue mass in the presence of IAH and injured lungs.

## Inflection Points And Regression Analysis

The Venegas equation best described the pressure-volume data sets when compared with the exponential and linear equations (smallest root mean square) (Online supplement 7 – Table: Tested equations to fit pressure-volume data). The proportion of atelectatic lung correlated best with oxygenation,  $E_{rs}$  and  $E_L$  (Online supplement 8 – Table: Correlation between lung aeration and different lung parameters).

Throughout the different experimental conditions, atelectatic and poorly aerated lung were dominant in the dorsal dependent lung segments (Online supplement 9 - Table: Segmental lung aeration distribution at different experimental conditions). In contrast, overdistended lung was most prominent in the ventral lung segments. Normally aerated lung had a more even distribution and remained greatest in the medial lung segments.

## Hemodynamic Effects

Higher PEEP levels were associated with decreased blood pressure and cardiac output (Online supplement 5 – Table: Effect of PEEP on cardio-respiratory variables).

## Discussion

We aimed to define an optimal PEEP range that would be high enough to reduce atelectasis formation while low enough to minimize overdistention in the setting of IAH and lung injury using analysis of CT lung images obtained from pigs. In contrast to our hypothesis, inflections points for atelectasis and overdistension were not identifiable. Instead, we found that PEEP decreased atelectasis but simultaneously increased overdistension with each incremental increase in applied PEEP.

## Healthy Lungs

Previously, we showed that the IAH induced lung changes including reduced end-expiratory lung volumes and raised  $E_{CW}$  are reversed by increasing PEEP (8, 15). The effect of different PEEP levels on CT measured lung parameters in the context of IAH was unknown.

## Overall lung changes

Our findings that IAH is associated with reduced lung gas volumes (as measured by CT) without affecting tissue mass and increased atelectatic lung is consistent with previous studies (6, 25). In general, we were able to demonstrate that higher PEEP levels reversed the above changes induced by IAH. However, increasing PEEP also

increased the proportion of overdistended lung in the ventral non-dependent lung segments, thereby increasing the risk of ventilator-induced lung injury (13, 16).

## Segmental lung changes

Although PEEP appeared to reverse the changes in lung aeration and volume linearly (Fig. 3), the Venegas equation showed a better fit than the linear equation. However, the Venegas equation does not adequately describe the “pressure-volume” data as the resulting constants representing residual volume, vital capacity, and inflection points were highly variable across the different experimental conditions without following any physiological rationale. Thus, in our experiment, we were unable to identify inflections points for any of the lung aeration compartments.

The distribution of aeration compartments along the different lung segments appeared constant throughout the different experimental conditions while lung volumes decreased by lung injury and IAH and increased with incremental PEEP. Although lung injury, IAH and PEEP significantly affected this distribution, these differences were small. The consequence of a relatively constant segmental distribution of aeration compartments suggests that a PEEP level that solely decreases atelectasis without increasing overdistension does not exist.

## Clinical consequences

We examined the effect of PEEP in the presence of IAH and healthy lung to allow comparison with the results obtained in injured lungs. As IAH and PEEP only minimally affect oxygenation in healthy lungs, the role of PEEP is to provide safe protective lung ventilation and not to improve oxygenation (14). Whether patients with IAH and healthy lungs may benefit from higher PEEP levels to reduce the risk of atelectotrauma and ventilator-induced lung injury remains unknown (3, 14, 16).

## Injured Lungs

### Overall lung changes

Oleic acid is directly toxic to endothelial cells causing a varying degree of interstitial and alveolar edema, hemorrhagic infiltration and fibrin deposition (26). An increase in tissue mass measured by CT is a surrogate marker for lung edema (27). Our finding that oleic acid reduced gas volume without affecting tissue mass suggests that alveolar collapse and not lung edema predominated in our animal model. This finding contrasts with an increase in lung tissue mass in IAH following oleic acid described by other investigators (6, 11, 28). The disparity between our results and previous studies may reflect different experimental protocols. We aimed to avoid fluid overload during the current protocol to align with contemporary clinical practice as fluid overload is associated with impaired lung function and increased duration of mechanical ventilation (29).

Surprisingly, higher PEEP levels increased lung tissue mass in injured but not in healthy lungs. The oleic acid induced increase in  $E_L$  resulted in higher plateau airway and intra-thoracic pressures for a given tidal volume, which may itself decrease thoracic lymph drainage (30) or increase intra-thoracic blood volume (14). However, whether higher PEEP in patients with IAH and lung injury increases the risk of lung edema remains debatable.

### Segmental lung changes

The effect of IAH on normally aerated and atelectatic lung was more pronounced in the injured lung compared with health lung. In contrast to poorly aerated lung, atelectatic lung represents a shunt region that does not take part in

gas exchange (18). We found the proportion of atelectatic lung to correlate best with oxygenation,  $E_{rs}$  and  $E_L$  suggesting that oxygenation improved due to a reduction in atelectasis.

## Clinical consequences

In the presence of injured lungs, PEEP was able to reverse the IAH induced deoxygenation, lung volume reduction and alveolar collapse. However, the proportion of overdistended lung also increased with increasing level of PEEP. Therefore, we were not able to find an ideal PEEP level that maximally reduced atelectasis without increasing overdistension.

Thus, to find an optimal PEEP level in patients with IAH and injured lungs, the clinician has to balance the potential benefit of improving oxygenation by increasing lung volumes and reducing atelectasis with the potential risks of alveolar distension, lung injury and hemodynamic compromise when applying higher PEEP levels. Medical and surgical treatment options to reduce IAH (14, 31, 32) are equally important when aiming to improve the outcome of patients with IAH and lung injury.

## Study Limitations

This study has several limitations. Our findings were obtained in an animal experiment, which may incompletely represent lung injury. However, we aimed to use a large animal model with highest possible similarity to human anatomy pertinent to our study and designed our methodology to best mimic clinical practice. Our sample size was relatively small and one pig died mid-experiment so inferred data were used. Therefore, some of our results may have been underpowered. For obvious methodological reasons (e.g. non-reversibility of lung injury) our experiment was not randomized and change over time might have influenced our results. However, in our previous animal experiment using oleic acid, time did not appear to affect our results (11). Examining more than five PEEP levels may have yielded physiologically more plausible Venegas equations. However, our findings of increased PEEP on bedside cardio-respiratory parameters are consistent with the literature in healthy (8, 14, 33) and in injured lungs (8, 11, 33–35), providing some confidence in the validity of our experimental model.

## Conclusions

In this animal model, PEEP in the presence of IAH variably decreased the proportion of poorly aerated and atelectatic lung whilst increasing the proportion of normally aerated lung. However, this lung recruitment was achieved at the cost of an increased proportion of overdistended lung in both healthy and in injured lungs. Our findings suggest that an optimal PEEP level which maximally recruits atelectatic lung without causing overdistension or hemodynamic compromise may not exist.

## List Of Abbreviations

CT = computed tomography,  $E_{rs}$  = elastance of the respiratory system,  $E_W$  = elastance of the chest wall,  $E_L$  = elastance of the lung, IAH = Intra-abdominal hypertension, IAP = intra-abdominal pressure, PEEP = positive end-expiratory pressures, P/F ratio = arterial oxygen tension in mmHg over fractional inspiratory oxygen concentration

## Declarations

## Ethics approval and consent to participate

The study conformed to the regulations of the Australian Code for the care and use of animals for scientific purposes and was approved primarily by the Animal Ethics Committees of Murdoch University (R2588/13) and secondarily by the University of Western Australia (RA/3/900/77). Studies were performed at Murdoch University Veterinary Hospital.

## Consent for publication

Not applicable.

## Availability of data and material

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

## Competing interests

The authors declare that they have no competing interests.

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## Authors' contributions

AR drafted and JP, GM, and DR reviewed research protocol. AR, SA, GM and DR performed the animal experiment. PH and DR advised on CT analysis. SA analyzed hemodynamic and AR all other data. MF advised and reviewed statistical analysis. AR drafted manuscript. All authors reviewed and contributed to the final manuscript.

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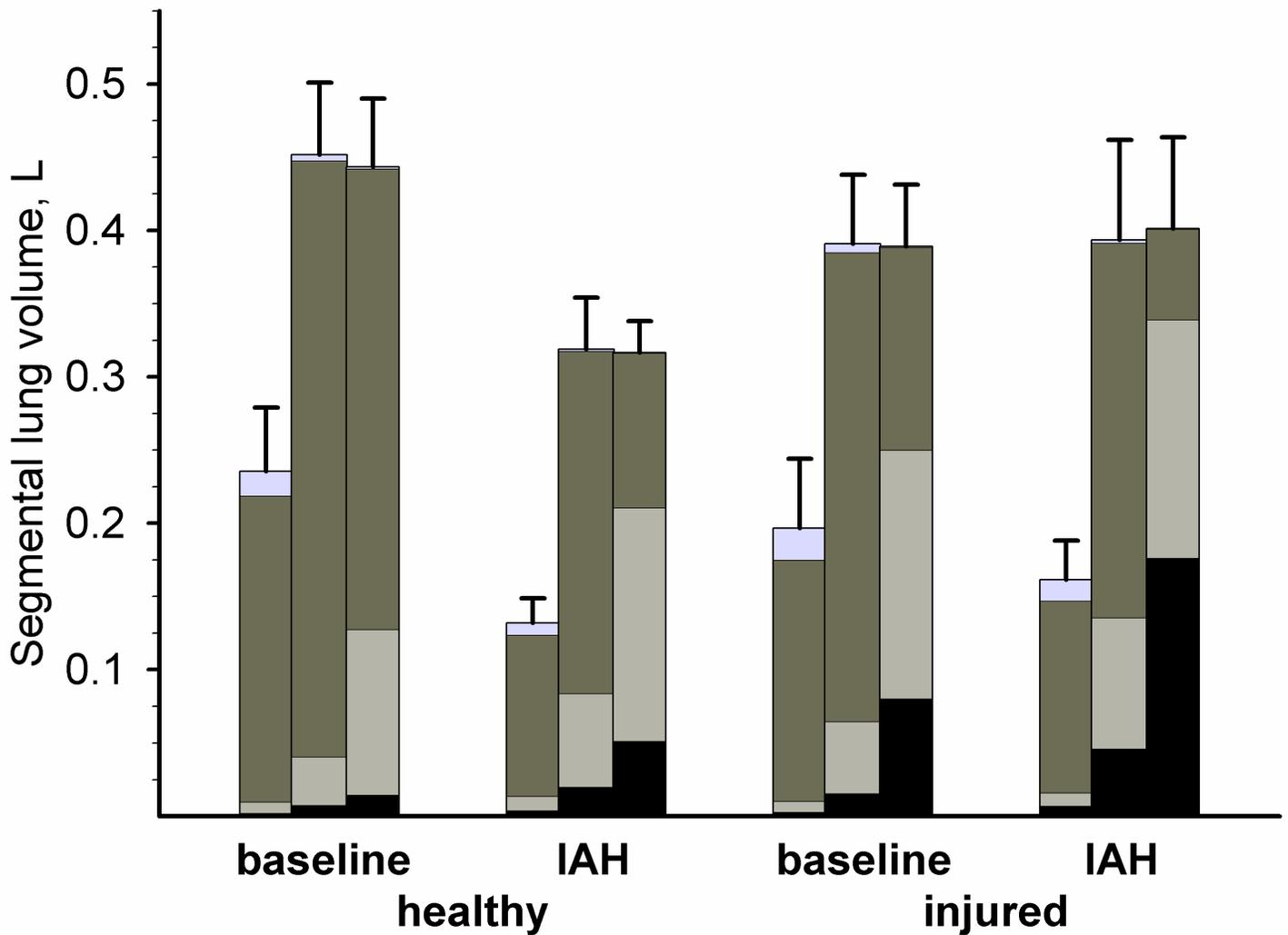
## References

1. Kirkpatrick AW, Roberts DJ, De Waele J et al (2013) Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. *Intensive Care Med* 39:1190–1206
2. Reintam Blaser A, Regli A, De Keulenaer B et al (2019) Incidence, Risk Factors, and Outcomes of Intra-Abdominal Hypertension in Critically Ill Patients-A Prospective Multicenter Study (IROI Study). *Crit Care Med* 47:535–542
3. Schachtrupp A, Toens C, Hoer J, Klosterhalfen B, Lawong AG, Schumpelick V (2002) A 24-h pneumoperitoneum leads to multiple organ impairment in a porcine model. *J Surg Res* 106:37–45
4. Schachtrupp A, Lawong G, Afify M, Graf J, Toens C, Schumpelick V (2005) Fluid resuscitation preserves cardiac output but cannot prevent organ damage in a porcine model during 24 h of intraabdominal hypertension. *Shock* 24:153–158
5. Malbrain ML, De Waele JJ, De Keulenaer BL (2015) What every ICU clinician needs to know about the cardiovascular effects caused by abdominal hypertension. *Anaesthesiol Intensive Ther* 47:388–399

6. Quintel M, Pelosi P, Caironi P et al (2004) An increase of abdominal pressure increases pulmonary edema in oleic acid-induced lung injury. *Am J Respir Crit Care Med* 169:534–541
7. Pelosi P, Quintel M, Malbrain ML. Effect of intra-abdominal pressure on respiratory mechanics. *Acta Clin Belg Suppl.* 200778–88
8. Regli A, Hockings LE, Musk GC et al (2010) Commonly applied positive end-expiratory pressures do not prevent functional residual capacity decline in the setting of intra-abdominal hypertension: a pig model. *Crit Care* 14:R128
9. Henzler D, Hochhausen N, Bensberg R et al (2010) Effects of preserved spontaneous breathing activity during mechanical ventilation in experimental intra-abdominal hypertension. *Intensive Care Med* 36:1427–1435
10. Strang CM, Freden F, Maripuu E, Hachenberg T, Hedenstierna G (2010) Ventilation-perfusion distributions and gas exchange during carbon dioxide-pneumoperitoneum in a porcine model. *Br J Anaesth* 105:691–697
11. Regli A, Mahendran R, Fysh ET et al (2012) Matching positive end-expiratory pressure to intra-abdominal pressure improves oxygenation in a porcine sick lung model of intra-abdominal hypertension. *Crit Care* 16:R208
12. Cheatham ML, Malbrain ML. Cardiovascular implications of abdominal compartment syndrome. *Acta Clin Belg Suppl.* 200798–112
13. Pelosi P, Vargas M (2012) Mechanical ventilation and intra-abdominal hypertension: 'Beyond Good and Evil'. *Crit Care* 16:187
14. Regli A, Pelosi P, Malbrain MLNG (2019) Ventilation in patients with intra-abdominal hypertension: what every critical care physician needs to know. *Ann Intensive Care* 9:52
15. Regli A, Chakera J, De Keulenaer BL et al (2012) Matching positive end-expiratory pressure to intra-abdominal pressure prevents end-expiratory lung volume decline in a pig model of intra-abdominal hypertension. *Crit Care Med* 40:1879–1886
16. Pinhu L, Whitehead T, Evans T, Griffiths M (2003) Ventilator-associated lung injury. *Lancet* 361:332–340
17. Muders T, Luepschen H, Zinserling J et al (2012) Tidal recruitment assessed by electrical impedance tomography and computed tomography in a porcine model of lung injury\*. *Crit Care Med* 40:903–911
18. Gattinoni L, Caironi P, Pelosi P, Goodman LR (2001) What has computed tomography taught us about the acute respiratory distress syndrome? *Am J Respir Crit Care Med* 164:1701–1711
19. Puybasset L, Gusman P, Muller JC, Cluzel P, Coriat P, Rouby JJ (2000) Regional distribution of gas and tissue in acute respiratory distress syndrome. III. Consequences for the effects of positive end-expiratory pressure. *CT Scan ARDS Study Group. Adult Respiratory Distress Syndrome. Intensive Care Med* 26:1215–1227
20. National Health and Medical Research Council (Australia), Australian Research Council, Universities Australia, CSIRO (Australia). Australian code for the care and use of animals for scientific purposes. National Health and Medical Research Council National Health and Medical Research Council, Universities Australia, CSIRO; 2013:8th Edition
21. Gattinoni L, Caironi P, Cressoni M et al (2006) Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med* 354:1775–1786
22. Grasso S, Terragni P, Mascia L et al (2004) Airway pressure-time curve profile (stress index) detects tidal recruitment/hyperinflation in experimental acute lung injury. *Crit Care Med* 32:1018–1027
23. Venegas JG, Harris RS, Simon BA (1998) A comprehensive equation for the pulmonary pressure-volume curve. *J Appl Physiol* 84:389–395

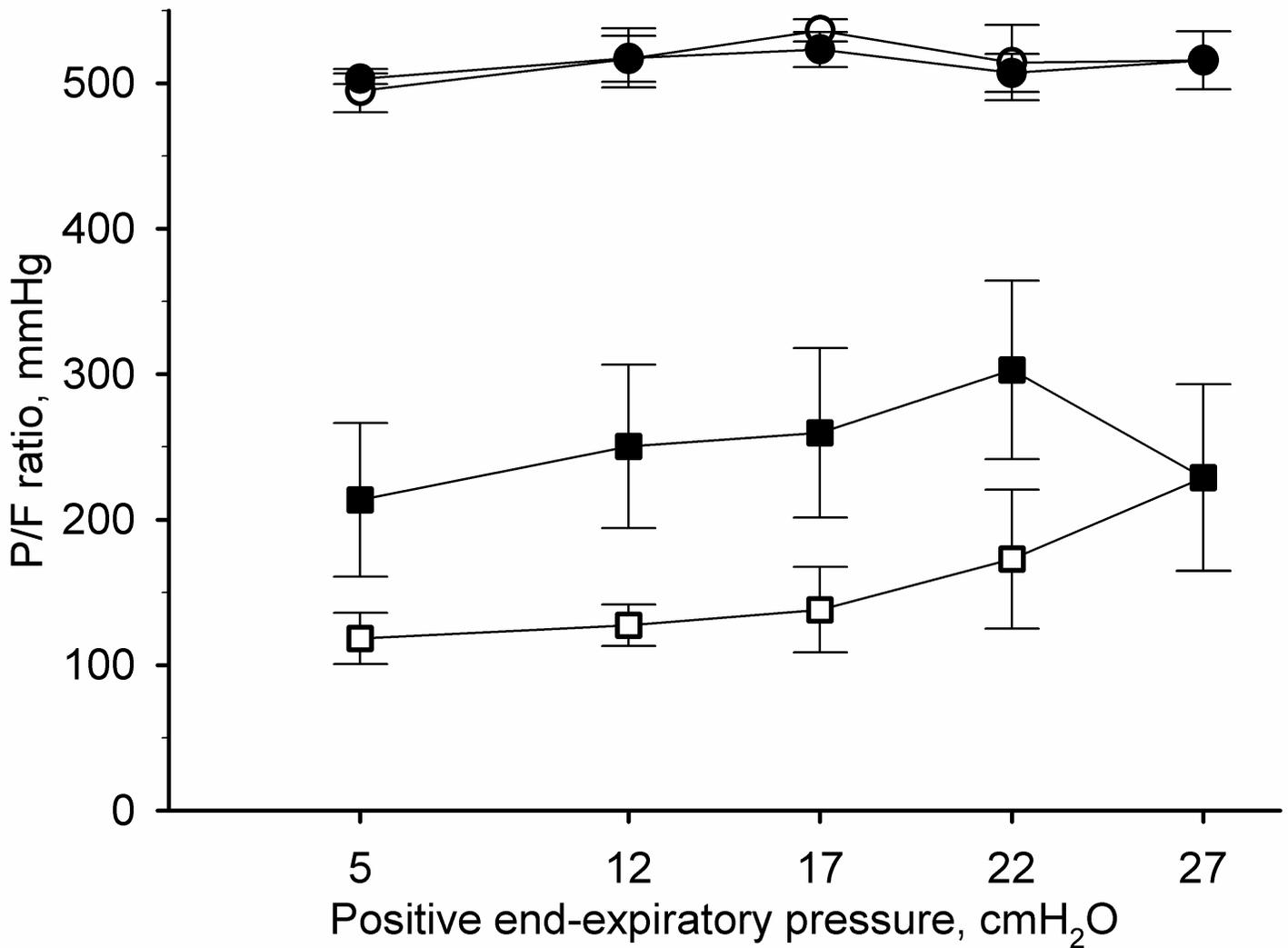
24. Regli A, De Keulenaer BL, Singh B, Hockings LE, Noffsinger B, van Heerden PV (2017) The respiratory pressure-abdominal volume curve in a porcine model. *Intensive Care Med Exp* 5:11
25. Zhou JC, Xu QP, Pan KH, Mao C, Jin CW (2010) Effect of increased intra-abdominal pressure and decompressive laparotomy on aerated lung volume distribution. *J Zhejiang Univ Sci B* 11:378–385
26. Matute-Bello G, Frevert CW, Martin TR (2008) Animal models of acute lung injury. *Am J Physiol Lung Cell Mol Physiol* 295:L379–L399
27. Kuzkov VV, Suborov EV, Kirov MY et al (2010) Radiographic lung density assessed by computed tomography is associated with extravascular lung water content. *Acta Anaesthesiol Scand* 54:1018–1026
28. Rylander C, Högman M, Perchiazzi G, Magnusson A, Hedenstierna G (2004) Oleic acid lung injury: a morphometric analysis using computed tomography. *Acta Anaesthesiol Scand* 48:1123–1129
29. Wiedemann HP, Wheeler AP, Bernard GR et al (2006) Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 354:2564–2575
30. Lattuada M, Hedenstierna G (2006) Abdominal lymph flow in an endotoxin sepsis model: influence of spontaneous breathing and mechanical ventilation. *Crit Care Med* 34:2792–2798
31. De Keulenaer B, Regli A, De Laet I, Roberts D, Malbrain ML (2015) What's new in medical management strategies for raised intra-abdominal pressure: evacuating intra-abdominal contents, improving abdominal wall compliance, pharmacotherapy, and continuous negative extra-abdominal pressure. *Anaesthesiol Intensive Ther* 47:54–62
32. Regli A, De Keulenaer B, De Laet I, Roberts D, Dabrowski W, Malbrain ML (2015) Fluid therapy and perfusional considerations during resuscitation in critically ill patients with intra-abdominal hypertension. *Anaesthesiol Intensive Ther* 47:45–53
33. Regli A, De Keulenaer BL, Palermo A, van Heerden PV (2018) Positive end-expiratory pressure adjusted for intra-abdominal pressure - A pilot study. *J Crit Care* 43:390–394
34. da Silva Almeida JR, Machado FS, Schettino GP, Park M, Azevedo LC (2010) Cardiopulmonary effects of matching positive end-expiratory pressure to abdominal pressure in concomitant abdominal hypertension and acute lung injury. *J Trauma* 69:375–383
35. Krebs J, Pelosi P, Tsagogiorgas C, Alb M, Luecke T (2009) Effects of positive end-expiratory pressure on respiratory function and hemodynamics in patients with acute respiratory failure with and without intra-abdominal hypertension: a pilot study. *Crit Care* 13:R160

## Figures



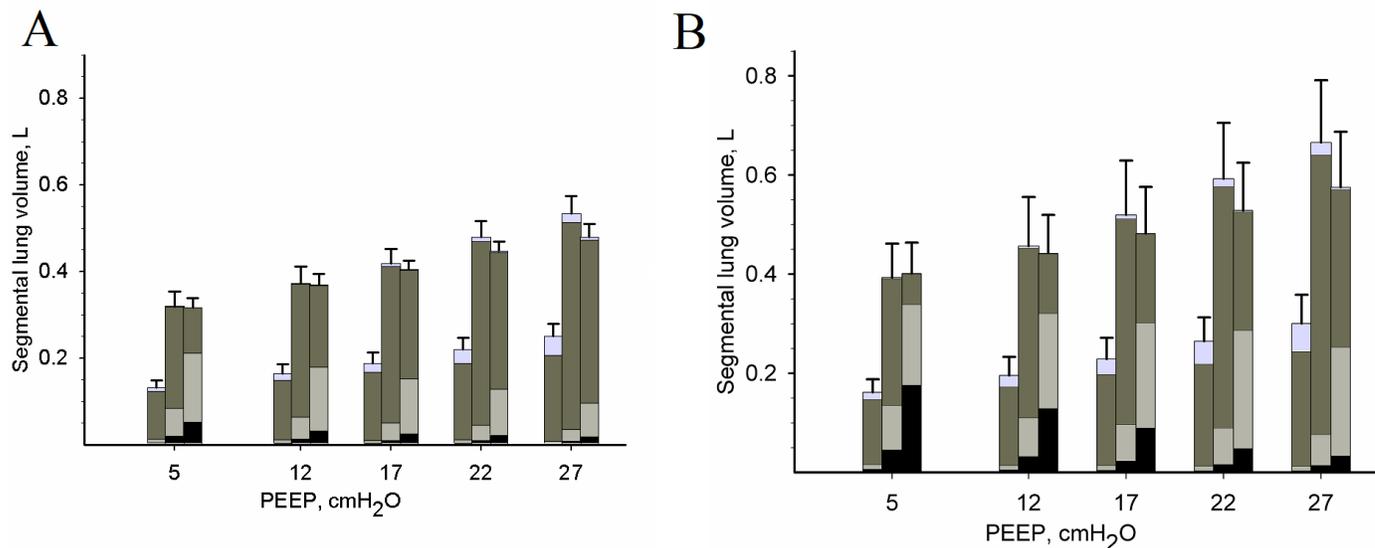
**Figure 1**

Segmental end-expiratory lung volumes measured by computed tomography during different conditions being: healthy lungs and not inflated abdomen (baseline), healthy lungs and intra-abdominal hypertension (IAH), injured lungs and not inflated abdomen (baseline), and injured lungs and IAH. Three lung segments are depicted at each condition with left to right representing ventral, medial and dorsal lung segment respectively. Segmental lung volumes are a composite of overdistended (light grey on the top, -1,000 to -901 HU), normally aerated (dark grey, -900 to -501 HU), poorly aerated (light grey third from top, -500 to -101 HU) and non-aerated atelectatic lung (black, -100 to 200 HU). Mean and SE are shown.



**Figure 2**

Arterial oxygen tension/fractional inspiratory concentration of oxygen (P/F ratio) in mmHg in function of different levels of positive end-expiratory pressures (PEEP). Abdomen was inflated to an intra-abdominal pressure of 27cmH<sub>2</sub>O (20mmHg). PEEP was stepwise increased (white circles, “healthy ascending”) and then decreased (black circles, “healthy descending”) in healthy lungs before creation of lung injury with oleic acid. Thereafter PEEP was increased stepwise (unfilled square symbols, “sick ascending”) and then decreased (black square symbols, “sick descending”). Mean and SE are shown. Mixed linear model was applied. Overall oleic acid ( $p < 0.01$ ) decreased, PEEP increased ( $p = 0.03$ ) oxygenation. Descending as opposed to ascending PEEP was associated with increased oxygenation only in injured lungs ( $p < 0.01$ ).



**Figure 3**

Effect of descending positive end expiratory pressure (PEEP) level on end-expiratory segmental lung volumes measured by computed tomography with healthy lungs (panel A) and after creating lung injury (panel B). Abdomen was inflated to an intra-abdominal pressure of 27 cmH<sub>2</sub>O (20 mmHg). Three lung segments are depicted at each condition with left to right representing ventral, medial and dorsal lung segment respectively. Segmental lung volumes are a composite of overdistended (light grey, -1,000 to -901 HU), normally aerated (dark grey, -900 to -501 HU), poorly aerated (light grey third from top, -500 to -101 HU) and non-aerated atelectatic lung (black, -100 to 200 HU). Mean and SE are shown.

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