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Minimizing lung injury during laparoscopy in head-down tilt: a physiological cohort study

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Gregory De Meyer: This author helped to design the trial, to recruit patients, to collect and analyze the data and to write the manuscript.

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Abstract

Background

Increased intra-abdominal pressure during laparoscopy induces atelectasis. Positive end-expiratory pressure (PEEP) can alleviate atelectasis but may cause hyperinflation. Cyclic opening of collapsed alveoli and hyperinflation can lead to ventilator-induced lung injury and postoperative pulmonary complications. We aimed to study the effect of PEEP on atelectasis, lung stress and hyperinflation during laparoscopy in the head-down (Trendelenburg) position.

Methods

An open label, repeated measures, interventional, physiological cohort trial was designed. All participants were recruited from a single tertiary Belgian university hospital. Twenty-three non-obese patients scheduled for laparoscopy in the Trendelenburg position were recruited.

We applied a decremental PEEP protocol (15 - high, 10 and 5 - low cmH_2O). Atelectasis was studied with the lung ultrasound score, the end-expiratory transpulmonary pressure, the P_aO_2/F_IO_2 ratio and the dynamic respiratory system compliance. Global hyperinflation was evaluated by dead space volume, and regional ventilation by lung ultrasound. Lung stress was estimated using the transpulmonary driving pressure and dynamic compliance. Data are reported as medians [25^{th}-75^{th} percentile].

Results

Nineteen patients were analyzed. At 15, 10 and 5 cmH_2O PEEP we measured respectively lung ultrasound scores (%) 11 [0–22]; 27 [11–39]; and 53 [42–61] ($p<0.001$), end-expiratory transpulmonary pressures (cmH_2O) 0.9 [-0.6–1.7]; -0.3 [-2.0–0.7] and -1.9 [-4.6 – -0.9] ($p<0.001$), P_aO2/F_IO_2 ratios (mmHg) 471 [435–538]; 458 [410–537] and 431 [358–492] ($p<0.001$), dynamic respiratory system compliances (ml/cmH_2O^{-1}) 32 [26–36]; 30 [25–34] and 27 [22–30] ($p<0.001$), driving pressures (cmH_2O) 8.2 [7.5–9.5]; 9.3 [8.5–11.1] and 11.0 [10.3–12.2] ($p<0.001$) and alveolar dead space ventilation fractions (%) 10 [9–12]; 10 [9–12] and 9 [8–12] ($p=0.23$). The lung ultrasound score was similar between apical and basal lung regions at each PEEP level ($p=0.76$, 0.37, 0.76 respectively).

Conclusions

Higher PEEP levels during laparoscopy in the head-down position facilitate lung-protective ventilation. Atelectasis and lung stress are reduced in the absence of global alveolar hyperinflation.

Key Points Summary

Question: What is the effect of PEEP on atelectasis, lung stress and hyperinflation during laparoscopy in the head-down position?

Findings: Decremental PEEP resulted in higher lung ultrasound scores, lower end-expiratory transpulmonary pressures, lower P_aO_2/F_IO_2 ratios, higher driving pressures and unchanged alveolar dead space ventilation.

Meaning: High PEEP during laparoscopy in the head down position facilitates lung-protective ventilation by alleviating atelectasis and reducing lung stress, without causing global alveolar hyperinflation.

Glossary of Terms

ARDS: acute respiratory distress syndrome

BMI: Body Mass Index

C_{dyn}: dynamic airway compliance

cmH_2O: centimeters of water pressure

CO_2: carbon dioxide

COPD: Chronic Obstructive Pulmonary Disease

E_{CW}: chest wall elastance

E_L: lung elastance

$ETCO_2$: end-tidal carbon dioxide concentration

F_IO_2: fraction of inspired oxygen concentration

HME: heat and moisture exchanger

I:E ratio: ratio of inspiratory to expiratory time

IBW: Ideal Body Weight

ICP: intracranial pressure

LUS: lung ultrasound

LUSS: lung ultrasound score

MV: minute volume

P_aCO_2: arterial carbon dioxide partial pressure

P_{alv}: alveolar pressure

P_aO_2: arterial oxygen partial pressure

P_aO_2/F_IO_2 ratio: ratio of partial arterial oxygen pressure to fraction of inspired oxygen concentration

P_{aw}: airway pressure

PBW: predicted body weight

P_{drive}: airway driving pressure

PEEP: positive end-expiratory pressure

P_{es}: esophageal pressure

P_L: transpulmonary pressure

P_{Ldrive}: transpulmonary driving pressure

P_{Lee}: end-expiratory transpulmonary pressure

P_{Lpeak}: peak transpulmonary pressure

P_{peak}: peak airway pressure

PPC's: postoperative pulmonary complications

P_{pl}: pleural pressure

REDCap: research electronic data capture

RR: respiratory rate

TREND: transparent reporting of evaluations with nonrandomized designs

VD_{alv}/VT_{alv}: alveolar dead space fraction

VD_{aw}: airway dead space

VT: tidal volume

Introduction

Intra-abdominal surgery is commonly performed by laparoscopy, but increases in abdominal pressure lead to altered respiratory mechanics and potentially excessive lung stress[1]. These effects are exacerbated when combined with head-down (Trendelenburg) positioning.

Induction of general anesthesia reduces respiratory muscle tone and results in cephalad displacement of the diaphragm leading to compression atelectasis, increased pulmonary shunt and decreased oxygenation. This is further associated with an increase in lung stress, through cyclical alveolar recruitment. Changes in ventilation distribution may also lead to regional hyperinflation in non-collapsed lung areas[2, 3]. As atelectasis and regional hyperinflation develop, lung stress increases, promoting both ventilator-induced lung injury and the risk of postoperative pulmonary complications (PPC's)[4]. Furthermore, systemic absorption of CO_2 from the pneumoperitoneum requires increased minute ventilation to maintain normocapnia[5]. Higher driving pressures, tidal volumes and respiratory rates increase the likelihood of cyclical alveolar recruitment, lung stress and ventilator-induced lung injury.

Positive end-expiratory pressure (PEEP) can alleviate atelectasis yet aggravate hyperinflation[2]. Increasing PEEP both enlarges the alveolar dead space, through collapse of peri-alveolar capillaries, and distends the conducting airways, resulting in a higher anatomical dead space[6]. This increase in total dead space ventilation complicates ventilatory management and maintenance of acid-base homeostasis. The ideal PEEP level would optimize alveolar recruitment but avoid excessive hyperinflation[7].

International consensus-based recommendations currently advise PEEP levels of 4-6 cmH_2O during per-operative mechanical ventilation[8]. This is relevant in conventional surgical settings for non-obese patients with healthy lungs, but during laparoscopy with head-down tilt, higher levels may be necessary to reduce atelectasis. Using a PEEP of 4-6 cmH_2O with high plateau pressures results in large driving pressures and may lead to an increased risk of barotrauma. Optimizing PEEP, by titration to the maximum respiratory system compliance, has been proposed[9].

In this physiological study, we investigated the effects of PEEP on atelectasis, lung stress and hyperinflation during laparoscopy in the head-down position. We hypothesized that higher than conventional levels of PEEP (> 5 cmH_2O) would attenuate atelectasis without exacerbating hyperinflation or lung stress.

Methods

The trial was designed as a single-center, open-label, repeated measures physiological cohort study and conducted at the Antwerp University Hospital, Belgium. This study was approved by the Antwerp University Hospital / University of Antwerp Ethics Committee (20/40/516) and written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment at clinicaltrials.gov (NCT04900714, www.clinicaltrials.gov/ct2/show/NCT04900714, Principal investigator: Vera Saldien, Date of registration: May 25th, 2021). Written informed consent was obtained from all study participants before inclusion. The manuscript adheres to the TREND guidelines.

Patients scheduled for elective pelvic laparoscopic surgery in a steep head-down position were screened for inclusion. Exclusion criteria were patient refusal, BMI ≥30 kg.m^{-2}, pregnancy, smoking, an abnormal clinical pulmonary examination, bronchodilator or inhaled corticosteroid therapy, a history of COPD or asthma, and right ventricular failure.

Standard monitors were applied (electrocardiogram, non-invasive blood pressure and peripheral arterial saturation) and all participants were pre-oxygenated before induction of total intravenous anesthesia. This followed a standardized technique using a target-controlled infusion of propofol (Marsh model 3-6 $\mu g.l^{-1}$), sufentanil (0.2 $\mu g.kg^{-1}$) and rocuronium (0.6 $mg.kg^{-1}$). Neuromuscular blockade was maintained with additional boluses of rocuronium to ensure the train of four ratio was ≤ 1 (MechanoSensor, GE healthcare, Chicago, IL, USA). The trachea was intubated with a tracheal tube (7.5mm ID for women, 8.5mm ID for men, Shiley TaperGuard, Covidien, Tullamore, Ireland) and instrumental dead space reduced using an elbow piece and pediatric heat and moisture exchanger (HME; Gibeck Humid-Vent Pedi straight, Teleflex, Wayne, PA, USA). The pressure-and-flow sensor (FluxMed, Buenos-Aires, Argentina) was mounted between the tracheal tube and the HME, and volumetric capnography (Capnostat 5, Philips, Amsterdam, The Netherlands) measured between the HME and the Y-piece. Mechanical ventilation was initiated in volume control mode with a tidal volume of $6ml.kg^{-1}$ of ideal body weight (IBW), an initial PEEP of 5 cmH_2O, a frequency of 15 breaths per minute, an inspiratory:expiratory (I:E) ratio of 1:2, an inspiratory pause of 15% and an F_IO_2 of 0.4. Minimum fresh gas flow was set at or above the minute volume to ensure a consistent F_IO_2 and to prevent rebreathing within the anesthesia circle circuit. End-tidal CO_2 ($ETCO_2$) was maintained between 35–40 mmHg by adjusting the ventilator settings as follows: the respiratory rate was increased to a maximum of 25 breaths per minute, ensuring expiration was complete by reading the expiratory flow curve; if insufficient, the tidal volume was increased to 8 $ml.kg^{-1}$ IBW.

Esophageal pressures (P_{es}) were measured using an 8 French esophageal balloon catheter (AVEA smarthcath adult, Carefusion, CA, USA). Catheter placement and verification of the pressure signal were performed as described by Akoumianaki et al[10]. The balloon was inflated with the minimal volume of air resulting in maximal P_{es} swings[11, 12].

A radial arterial line was sited to perform continuous arterial pressure monitoring and repeated arterial blood gas analysis (Cobas, Roche, Basel, Switzerland). Hemodynamics management was left to the discretion of the attending anesthetist. Fluid management with a balanced crystalloid solution was provided during the study period (<500 ml).

Before inflation of the pneumoperitoneum and head-down positioning, a ventilator-programmed three-step staircase recruitment maneuver, with a default maximum PEEP of 16cmH_2O and a final PEEP of 15cmH_2O, was performed to mitigate post-intubation atelectasis (Aisys CS[2], GE Healthcare, Chicago, IL, USA; Figure 1B). A steady-state period was then maintained for at least 2 minutes before the start of data acquisition. Repeated measurements were recorded intra-operatively during stepwise de-recruitment from 15 (high) to 10 (medium) to 5 (low) cmH_2O PEEP (Figure 1). Airway pressure, airway flow, esophageal pressure and volumetric capnography were recorded continuously (FluxMed GrT, MBMED, Buenos Aires, Argentina, sampling frequency 256Hz). Raw and processed data were exported using the FluxView software (v1.33i, MBMED). At each PEEP level, following a 2-minute equilibration period, 6 lung ultrasound clips were recorded by a single operator (GDM), using a curvilinear 7 Hz probe (BK3500, BK Medical, MA, USA). The transducer was placed perpendicular to the ribs in all accessible lung zones: upper (mid-clavicular line at the level of the clavicula), middle (between the anterior and middle axillary lines high in the axilla) and lower (between the anterior and middle axillary lines close to the diaphragm (supplemental figure SF1). The lungs were scanned bilaterally. Data was collected in REDCap[13, 14] and analyzed using R (v3.6 or higher, R consortium, Vienna, Austria) in the RStudio environment (RStudio PBC, Boston, MA, USA), extended by the tidyverse, rstatix and ggpubr packages (available from https://cran.r-project.org)[15].

Atelectasis was indicated by: (a) increased lung ultrasound scores (LUSS), (b) negative end-expiratory transpulmonary pressures (P_{Lee})[16] (c) low ratios of arterial oxygen tension to inspired oxygen fraction (P_aO_2/F_IO_2 ratios) and (d) low dynamic respiratory system compliances (C_{dyn})[17].

Ultrasound clips were scored *post-hoc* by a clinical expert (TS), blinded for the lung zone and level of PEEP. The LUSS, based on B-line patterns (indicative of subpleural atelectasis, supplemental figure SF2, supplemental table ST1)[18], was calculated for each PEEP level by adding the scores of the 6 scanned lung zones and expressing this as a % of the maximum value. Thus, a high LUSS is associated with increased atelectasis. In case of an ambiguous recording, the score was omitted, and the maximal score adjusted. A minimum of 4 clips per PEEP level were scored to avoid bias from potential regional differences in aeration. Scores from the upper and lower lung zones were compared using an analogous calculation performed on scores from both upper clips and both lower clips at each level of PEEP.

The transpulmonary pressure (P_L) was defined as *alveolar pressure – pleural pressure*, and calculated by FluxView as airway pressure *(P_{aw}) – esophageal pressure (P_{es}*, supplemental figure SF3*)*[19]. The median P_{Lee} was determined as the median P_L at end-expiration using validated custom software[20].

Lung stress

Lung stress was quantified as a low C_{dyn}, a high airway driving pressure

(P_{drive}) or high transpulmonary (P_{Ldrive}) driving pressure.

P_{drive}, reflecting the stress over the entire respiratory system (lung + chest wall), was defined as *plateau airway pressure (P_{plat}) – PEEP*. P_{Ldrive}, reflecting the driving pressure over the lung[19, 21], was calculated as *median peak transpulmonary pressure (P_{Lpeak}) – P_{Lee}*. C_{dyn} was calculated by the FluxView software, as *tidal volume divided by P_{drive}.*

Hyperinflation was assessed by: (a) the physiological (VD_{alv}) and anatomical dead space volume (VD_{aw}), (b) the alveolar dead space fraction (VD_{alv}/VT_{alv}), all deduced from the volumetric capnography signal[22] and (c) the P_{Lee} where positive values suggest hyperinflation[16].

The primary outcome variable was the LUSS. Secondary outcomes were: P_{Lee}, P_{drive}, C_{dyn}, P_aO_2/F_IO_2 ratio and VD_{alv}/VT_{alv}.

Statistical analysis

A sample size calculation was performed in G*Power (v3.1, Heinrich Heine Universität, Düsseldorf, Germany)[23]. The alpha error of 0.02 was Bonferroni-corrected for the three repeated measurements. Considering a dropout rate of 15%, a total of 23 study subjects were required to provide 80% power at an estimated effect size of 0.8. During recruitment, the sample size was updated from 15 to 23 participants following approval by the ethics committee.

Data are presented as proportions or medians with 25th to 75th percentiles. Normality was assessed with the Shapiro-Wilk test. Paired data were compared using the Friedman test, with *post-hoc* analysis for between-group differences assessed by the two-sided paired Wilcoxon signed-rank test. P-values were adjusted with the Bonferroni-Holm correction for multiple testing. Apical and basal LUSS were compared using the two-sided Wilcoxon signed-rank test with Bonferroni-Holm correction.

Results

Twenty-three patients were recruited between June 21st and September 23rd, 2021. Four patients were excluded, 1 due to a protocol violation and 3 because of insufficient quality of the esophageal pressure recordings. Nineteen patients were retained for analysis (supplemental figure SF4). Volumetric capnography was missing in 4 patients and blood gas analysis for one. As this conformed with 'missing completely at random', a complete case analysis was performed.

The population characteristics are presented in Table 1. Mean arterial pressure increased significantly with increasing PEEP ($p<0.001$). The operating table angulation remained unchanged throughout the study protocol (22°, IQR 22-25).

High PEEP resulted in a lower LUSS ($p<0.001$), a less negative P_{Lee} ($p<0.001$), a higher C_{dyn} ($p<0.001$) and a higher P_aO_2/F_IO_2 ratio ($p<0.001$, Figure 2). In 7 of the 19 patients (37%), P_{Lee} remained negative at high PEEP. Also, high PEEP resulted in a lower P_{drive} and P_{Ldrive} (both $p<0.001$, Figure 3). VD_{alv}/VT_{alv} did not change with decremental PEEP ($p=0.23$). However, VD_{aw} increased with higher PEEP ($p<0.001$). Dynamic intrinsic PEEP was lower at PEEP 15 compared to PEEP 5 ($p=0.049$) or PEEP 10 ($p=0.023$, Figure 4). As

PEEP decreased from 15 to 10 to 5 cmH_2O, P_{Lee} remained positive in 12 (63%), 7 (37%) and 1 (5%) participant(s) respectively (Figure 2B).

Atelectasis and de-recruitment were similar across different lung zones: LUSS were comparable between lower and upper lung regions at each level of PEEP (Supplemental figure SF5). At low PEEP, B-lines, indicative of decreased aeration, or areas of consolidation were present in both basal as well as apical lung zones. In contrast, there was an absence of atelectasis in both dependent and non-dependent lung zones at high PEEP.

Discussion

We report the effects of decremental PEEP during volume-controlled mechanical ventilation for laparoscopic surgery in the head-down position. Patients were recruited according to strict criteria for physiological study, which allowed for a large effect size with sufficient statistical power. Four independent measures (LUSS, P_{Lee}, P_aO_2/F_IO_2 ratio and C_{dyn}), indicate the degree of atelectasis, which was present in all lung zones. High PEEP attenuated atelectasis, resulted in homogeneous alveolar recruitment and reduced lung stress without hyperinflation.

Individualization of PEEP

Atelectasis and cyclical alveolar recruitment (atelectrauma) increase the risk of PPC's, and prolonged hospital stay[24].

Lung protective ventilation guidelines in the surgical patient currently advocate tidal volumes of 6-8 $ml.kg^{-1}$ predicted body weight (PBW) and an initial PEEP of 5cmH_2O. PEEP should be individually adapted thereafter[8]. In clinical practice, this means adjusting PEEP to obtain the highest C_{dyn}, lowest P_{drive} or a P_{Lee} of zero[16, 25].

Our results indicate that C_{dyn} was highest, and that P_{drive} and P_{Ldrive} were lowest at high PEEP, suggesting alveolar recruitment.

Titrating PEEP using P_{Lee} is less straightforward, as P_{Lee} values can be affected by technical issues[10]. Tidal pressure differences, such as P_{Ldrive}, seem less sensitive to error than absolute pressures, even if P_{Lee} and P_{Lplat} increase equally with a higher balloon filling volume. PEEP titration to the lowest P_{drive} or highest C_{dyn} may be more accurate.

Seven participants (37%) had a negative P_{Lee} at high PEEP, suggesting alveolar collapse. These patients might have benefited from higher PEEP, if using P_{Lee} for PEEP titration[16]. Further increases may have been limited by hyperinflation, dead space ventilation and respiratory acidosis.

Three fixed PEEP levels were studied. Consequently, some subjects may have benefited from higher or lower individually optimized PEEP. According to Tharp et al., *calculated* optimal PEEP during laparoscopy with head-down tilt ranges from 0 to 36.6 cmH_2O[26].

Effect of PEEP on lung stress

P_{drive} and P_{Ldrive} increased with decreasing PEEP, implying higher lung stress through alveolar derecruitment. In ARDS patients, lowering P_{drive} was associated with decreased mortality[27]. In surgical patients, titrating PEEP to reduce P_{drive} lowered the incidence of postoperative atelectasis[7, 28].

Attenuating lung stress by reducing P_{drive} may therefore be important in avoiding ventilator-induced lung injury.

Measuring P_{es} and calculating P_{Ldrive} helps differentiating ventilatory stress on the lung from that on the chest wall. In the head-down position, E_{CW} increases to a greater extent than E_L[29]. Therefore, a high P_{drive} as read from the ventilator does not necessarily imply an increased P_{Ldrive}. This observation has been confirmed by others[21].

At high PEEP, P_{Ldrive} showed lower variability compared to P_{drive} (Figure 3), suggesting that the relation between P_{drive} and P_{Ldrive} varies with PEEP. In a *post-hoc* analysis using a mixed effects model, we explored the effect of PEEP on the relationship between P_{drive} and P_{Ldrive} (figure 5, supplemental text file 1). The significant interaction between PEEP and P_{drive} ($p<0.001$) implies that, for a constant P_{drive}, increasing PEEP is associated with a lower P_{Ldrive}. Studies measuring only P_{drive} may, therefore, be confounded by PEEP[30, 31].

Our results demonstrate a lower P_{Ldrive} with higher mean airway pressures. Increased PEEP reduces lung stress only if zones of atelectasis are recruited without increasing regional hyperinflation. P_{drive} was lower after alveolar recruitment (high PEEP). As only PEEP, not mean airway pressure, prevents expiratory alveolar collapse, limiting P_{plat} to a fixed cut-off would not have avoided atelectasis. Minimizing P_{drive} by titrating PEEP independent of P_{plat}, therefore, best attenuates atelectrauma.

Intraoperative P_{es} monitoring

P_{es} represents intra-pleural pressure in the dorso-basal lung zones[10]. Pleural pressure in other areas may differ slightly due to gravity[32]. Our ultrasound data demonstrates that atelectasis was equally present in upper and lower lung regions, so the observed P_{es} values are most likely representative of the entire dorsal lung.

P_{es} monitoring has been adopted in acute lung injury[33], but could also help individualize lung protective ventilation in selected surgical cases.

P_{es} measurements are, however, prone to error and should be interpreted carefully[34]. Positioning of the catheter must be critically assessed[10] and the balloon volume should be adjusted to maximize the tidal P_{es} swing[12].

Regional distribution of atelectasis

LUSS did not differ between apical (lower) and basal (upper) lung zones, implying homogeneous atelectasis. This may have occurred due to similar compressive forces at the apex (gravity) and base (pneumoperitoneum).

Ultrasound may lack sensitivity in detecting small differences in atelectasis, especially when the observed effect size is small. Furthermore, ultrasonography cannot easily differentiate normal aeration from hyperinflation. Volumetric capnography distinguishes global VD_{aw} from VD_{alv}[22]. VD_{aw} increased at high PEEP, while the VD_{alv}/VT_{alv} remained constant. This may be attributed to bronchial distension at elevated airway pressures[6]. The unchanged VD_{alv} suggests global alveolar hyperinflation was absent.

Hemodynamic effects

Mean arterial pressure decreased with decreasing PEEP. Further hemodynamic investigation is merited to explain this unexpected finding.

Limitations

Previous studies have determined the LUSS from 6 zones per lung field[35], but we used 1 ventral and 2 ventrolateral zones from lung apex to base purely for technical reasons. PEEP levels were not allocated randomly, because de-recruitment occurs practically instantaneously, whereas recruitment is time dependent. Optimum PEEP for each patient could not be determined as the protocol prohibited individualization of PEEP settings. Only low levels of dynamic intrinsic PEEP were observed (0.5-0.8 cmH_2O) and no significant change occurred during derecruitment. Increased abdominal pressures during laparoscopy aid passive expiration, which was judged for completeness from the ventilator flow curve. An expiratory hold was not performed. Finally, volumetric capnography was recorded in only 15 patients.

This study confirms that high PEEP (15 cmH_2O) results in homogeneous recruitment of atelectasis during laparoscopic surgery in the head-down position. This benefit occurs without increases in physiological dead space or hyperinflation. The increased end-tidal CO_2, often observed in this clinical setting, is partly due to increased anatomical dead space, presumably through bronchial distention. Higher PEEP also resulted in both increased C_{dyn} and lower P_{Ldrive}. These data suggest that higher PEEP is associated with reduced lung stress during laparoscopy with head down tilt.

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Figure legends

Figure 1 Temporal sequence of the study protocol events (A) with description of the recruitment manoeuvre performed on the Aisys CS^2 ventilator (B).

Figure 2 Atelectasis as measured by the lung ultrasound score (A, n=19), the end-expiratory transpulmonary pressure (B, n=19), dynamic respiratory system compliance (C, n=19) and the P_aO_2/F_IO_2 ratio (D, n=18). Grey lines connect identical participants. Paired Wilcoxon signed-rank test with Bonferroni-Holm correction. *F_IO_2: fraction of inspiratory oxygen; P_aO_2: arterial oxygen tension; PEEP: positive end-expiratory pressure*

Figure 3 Lung stress as measured with the airway driving pressure (A, n=19) and the transpulmonary driving pressure (B, n=19). Grey lines connect identical participants. Paired Wilcoxon signed-rank test with Bonferroni-Holm correction. *PEEP: positive end-expiratory pressure*

Figure 4 Global hyperinflation as represented by the physiological dead space ratio (A, n=15), anatomical dead space volume (B, n=15) as measured with volumetric capnography and dynamic intrinsic PEEP (C, n=19). Grey lines connect identical participants. Paired Wilcoxon signed-rank test with Bonferroni-Holm correction. *PEEP: positive end-expiratory pressure*

Figure 5 Relationship between airway driving pressure (P_{drive}) and transpulmonary driving pressure (P_{Ldrive}) per level of PEEP. A linear regression line per PEEP level, with standard error in gray, is included. Each dot represents one breath. *PEEP: positive end-expiratory pressure*