Physiological Effects of Different Recruitment Maneuvers in a Pig Model of ARDS

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Abstract

Background: In acute respiratory distress syndrome (ARDS), lung recruitment maneuvers can recruit collapsed alveoli in gravity-dependent lung regions, improving the homogeneity of ventilation distribution. This study used electrical impedance tomography (EIT) to investigate the physiological effects of different recruitment maneuvers for alveolar recruitment in a pig model of ARDS.

Methods: ARDS was induced in ten healthy male pigs with repeated bronchoalveolar lavage until the arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) (P/F ratio) was < 100 mmHg and remained stable for 30 minutes (T_{ARDS}). ARDS pigs underwent three sequential recruitment maneuvers, including sustained inflation (SI), increments of positive end-expiratory pressure (PEEP) (IP), and pressure-controlled ventilation (PCV) applied in random order, with 30 mins at a PEEP of 5 cmH_2O between maneuvers. Respiratory mechanics, hemodynamics, arterial blood gas, and EIT were recorded at baseline, T_{ARDS}, and before and after each recruitment maneuver.

Results: In all ten pigs, ARDS was successfully induced with a mean 2.8±1.03L (2800±1032.80ml) bronchoalveolar lavages. PaO_2, SO_2, P/F, and compliance were significantly improved after recruitment with SI, IP or PCV (all $p<0.05$), and there were no significant differences between maneuvers. Global inhomogeneity (GI) was significantly decreased after recruitment with SI, IP, or PCV. There were no significant differences in GI before or after recruitment with the different maneuvers. The decrease in GI (ΔGI) was significantly greater after recruitment with IP compared to SI ($p=0.023$), but there was no significant difference in ΔGI between IP and PCV.

Conclusion: SI, IP, and PCV increased oxygenation, and regional and global compliance of the respiratory system, and decreased inhomogeneous gas distribution in ARDS pigs. IP significantly improved inhomogeneity of the lung compared to SI.

Background

Acute respiratory distress syndrome (ARDS) is a clinical syndrome characterized by a decrease in functional lung size[1]. The pathophysiology of ARDS includes diffuse alveolar collapse[3] and acute exudative lesions distributed in a gravitationally dependent gradient[4]. Although this disease was first defined almost 50 years ago, the hospital mortality rate for patients with severe ARDS remains high, estimated at 46%[2].

Lung recruitment maneuvers, including sustained inflation (SI), increments of positive end-expiratory pressure (PEEP) (IP), and pressure-controlled ventilation (PCV), can improve oxygenation and increase respiratory system compliance in patients with ARDS. Recruitment maneuvers can recruit collapsed alveoli in gravity-dependent lung regions and improve the homogeneity of ventilation distribution, but may cause alveolar overdistention and lead to ventilator-associated lung injury in non-dependent regions.[5] A randomized controlled trial showed that SI and PCV improved the arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) (P/F ratio) in 40 patients with ARDS, and the P/F was significantly increased after PCV compared to SI[6]. However, dynamic regional information on changes in lung ventilation after recruitment maneuvers has not been reported.

Recruitment and overdistention during lung recruitment have been evaluated by chest X-ray, computed tomography, and lung ultrasound. Electrical impedance tomography (EIT) is a non-invasive, radiation-free technique that can be used for bedside monitoring of lung tissue aeration during breathing. EIT allows semi-continuous, real-time measurement of changes in electrical resistivity within lung tissue and provides information on regional ventilation distributions [7,8]. Domenighetti[9] reported that EIT can be used to measure impedance changes and assess regional ventilation distribution during tidal breathing. The EIT-based global inhomogeneity (GI) index has been developed as a tool to quantify tidal volume distribution within the lung[10].

Previous research has focused on the effect of recruitment maneuvers on gas exchange and hemodynamics. Literature describing the influence of recruitment maneuvers on global inhomogeneity and regional ventilation distribution is scarce. This study used EIT to investigate the physiological effects of different recruitment maneuvers that achieve the same maximum pressure for alveolar recruitment in a porcine model of ARDS. Findings will inform clinical decision-making around recruitment maneuvers while minimizing the risk of barotrauma in individuals with ARDS.

Methods

The protocol for this study was approved by the Science and Technological Committee and the Animal Use and Care Committee of the University School of Medicine, Nanjing, China. Domestic pigs (Sus scrofa domesticus) were purchased from a local farmer (Qinglongshan animal breeding farm, JiangShu, China). Animal experiments were performed in accordance with the Guidance for the Care and Use of Laboratory Animals[11].

Animal Preparation

Pigs were housed on straw in a cage and fed with a standard diet[12]. Prior to the study, the animals were fasted overnight. Ten healthy male pigs (body weight 50.3±1.5 kg) were anesthetized with an intramuscular injection of ketamine hydrochloride (3 mg/kg), atropine (2 mg/kg) and fentanyl citrate (2 mg/kg) and an intravenous infusion of propofol (1-2 mg/kg·h), fentanyl citrate (0.5-1 μg/kg·h), midazolam (0.1 mg/kg·h), and atracurium (0.4 mg/kg·h) and placed in the supine position on a thermo-regulated operating table. During surgery, pigs received balanced electrolyte solution (5 ml/kg/h), pigs' body temperature was maintained at 37.5°C, and pigs' mean arterial pressure (MAP) was maintained > 60 mmHg with rapid infusions of 0.9% saline (20 ml/kg), as needed.

Following anesthesia, tracheotomy was performed, and pigs were mechanically ventilated (Servo-i ventilator, Solna, Sweden) using volume-control mode at a tidal volume (VT) of 6 mL/kg, a respiratory rate of 30 breaths/min, FiO_2 of 1.0, a inspiration-to-expiration time ratio (I:E) of 1:2, and PEEP of 5 cmH_2O. Arterial blood samples were collected using a thermistor-tipped Pulse Contour Cardiac Output (PiCCO) catheter (Pulsion Medical System, Munich, Germany) inserted in the right femoral artery. Central venous pressure (CVP) and pulmonary arterial wedge pressure (PAWP) were measured using a Swan–Ganz catheter (Arrow International, Reading, PA, USA) inserted in the internal jugular vein. Cardiac output (CO) was measured with the Swan–Ganz catheter, and MAP was monitored with the PiCCO catheter.

Experiment Protocol

Baseline measurements ($T_{Baseline}$) were made after pigs had stabilized for 30 minutes. Subsequently, a pig model of ARDS was established using bilateral lung lavage with isotonic saline (30 ml/kg; 38°C) infused through a funnel. Negative pressure was applied to the proximal portion of an endotracheal tube to remove excessive fluid. Alveolar lavage was repeated every 10 min until the P/F ratio decreased to less than 100 mmHg and remained stable for 30 min (T_{ARDS}); then, FiO_2 was set at 0.4.

ARDS pigs underwent three sequential recruitment maneuvers, including SI, IP and PCV applied in random order according to a random number table, with 30 mins at a PEEP of 5 cmH_2O between maneuvers (Figure 1). Circulatory and lung mechanics recovered in 30 min after recruitment maneuvers[13] and a PEEP of 5 cmH_2O represented physiologic PEEP. SI was performed using continuous positive airway pressure (CPAP) held at 40 cmH_2O for 40 secs[14]. For IP, PEEP was increased from 5 cmH_2O to a maximum of 40 cmH_2O in 5 cmH_2O increments, with each increment lasting 30 secs, and retuned to 5 cmH_2O in the reverse process. For PCV, peak pressure was 40 cmH_2O, inspiratory to expiratory ratio was 1:2, and PEEP was 20 cmH_2O for 2 min. For IP and PCV, respiratory rate was set to 30 breaths/min. Respiratory mechanics, hemodynamic parameters, arterial blood gas, and EIT were recorded at $T_{Baseline}$, T_{ARDS}, and before and after each recruitment maneuver. MAP, CVP, and PAWP were monitored using calibrated pressure transducers. Blood gases were evaluated with an automated blood gas analyser (Nova M; Nova Biomedical, Waltham, MA, USA).

EIT Measurements and Analysis

EIT measurements (PulmoVista 500; Dräger Medical GmbH, Lübeck, Germany) were performed for 3 minutes each at $T_{Baseline}$, T_{ARDS}, and before and after each recruitment maneuver as previously described[15]. EIT data were generated by applying small alternate electrical currents through 16 electrodes located equidistant apart on a belt positioned around the pigs' thorax, 5cm above the xyphoid process. A reference electrocardiogram (ECG) electrode was positioned on the abdomen. Current applications and voltage measurements were automatically selected to be compatible with the image reconstruction algorithm. The images were continuously recorded and reconstructed at 40 Hz (Draeger EIT Data Analysis Tool 61).

Four regions of interests (ROI) of the same size and shape consisting of contiguous pixels were identified within EIT images obtained during tidal breathing. A cross section of the lung (ventral to dorsal) was divided into four equal parts, namely ROI1, ROI2, ROI3 and ROI4.[16] Tidal volume distribution within the lung was quantified using the GI, as previously described.[17] For each breathing cycle, the median value of a tidal image, in which each pixel represented the difference in impedance between end-inspiration and end-expiration, was calculated. The absolute difference between the median value and every pixel value was summed to indicate the variation in the tidal volume distribution. EIT- estimated regional compliance for the gravity-dependent and nondependent lung was calculated as Vt_{ROI}/driving pressure[18]. The GI index was adjusted by normalization to the sum of the impedance values. A smaller GI index represented a more homogeneous distribution, and a larger GI index indicated a more inhomogeneous ventilation. The decrease in GI (ΔGI) with each recruitment maneuver was calculated as the difference in GI before and after recruitment.

General anesthesia was maintained throughout the study. After completion of the experiments, the animals were euthanized while in deep anesthesia by an intravenous injection of thiopental.

Statistical Analyses

Statistical analyses were performed using SPSS v20 (Chicago, IL, USA). Differences in global inhomogeneity and changes in global and regional end-expiratory lung impedance among different recruitment maneuvers were investigated. Comparisons were made between values obtained before and after each recruitment maneuver. For non-normally distributed data, results are expressed as median and interquartile range, and comparisons were made with the Wilcoxon rank test. For data that was normally distributed, results are expressed as mean and standard deviation, and comparisons were made with paired samples t tests and Bonferroni correction. $p < 0.05$ was considered statistically significant.

Results

In all ten pigs, ARDS was successfully induced with a mean 2.8±1.03L (2800±1032.80ml) bronchoalveolar lavages. Mean P/F was significantly decreased after the final lavage (81.69±55.79mmHg) compared to baseline (362.48±117.38mmHg).

The recruitment maneuvers did not cause hemodynamic instability, and there were no significant differences in hemodynamic parameters after recruitment with the different maneuvers (Table 1). No animals died during the experiments.

PaO_2, SO_2, and P/F were significantly improved after recruitment with SI, IP or PCV (all $p<0.05$), and there were no significant differences between maneuvers. The recruitment maneuvers had no effect on $PaCO_2$ or pH (Table 1).

Overall respiratory system compliance was significantly increased after recruitment with SI, IP, or PCV ($p< 0.05$) (Table 1). The recruitment maneuvers had no significant effect on compliance in non-gravity-dependent lung regions. Compliance was significantly increased in gravity-dependent lung regions after lung recruitment with IP or PCV, and there were no significant differences between maneuvers (Figure 2).

GI was significantly decreased after recruitment with SI, IP, or PCV (GIpreSI 0.55±0.14u vs. GIpostSI 0.42±0.040; GIpreIP 0.62±0.19u vs. GIpostIP 0.42±0.07u; GIprePCV 0.60±0.09u vs. GIpostPCV 0.4431±0.05u; all $p<0.001$) (Figure 3). There were no significant differences in GI with the different maneuvers. The ΔGI was significantly greater after recruitment with IP compared to SI ($p=0.023$), but there was no significant difference in ΔGI between IP and PCV or between SI and PCV (Figure 4).

Table 1 Hemodynamic and oxygenation parameters before and after recruitment maneuvers

HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure PAWP, pulmonary artery wedge pressure; CO, cardiac output; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; SaO_2, arterial oxygen saturation; P/F, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; Cr, respiratory system compliance; SI, sustained inflation; IP, increments of PEEP; PCV, pressure-controlled ventilation;

[a]<0.05 versus Before

Discussion

This study used EIT to investigate the physiological effects of different recruitment maneuvers that achieve the same maximum pressure when held for different time spans, including SI, IP and PCV, for alveolar recruitment in

	SI			IP			PCV		
	Before	After	p	Before	After	p	Before	After	p
HR (BPM)	89.1±25.32	97.5±31.17	0.517	90.4±39.40	96.9±46.84	0.950	93.8±38.44	94.1±41.04	0.987
MAP (mmHg)	102.1±23.14	92.7±17.71	0.321	109.2±19.00	96.8±23.93	0.455	109.1±20.26	96.6±23.53	0.219
CVP (mmHg)	7.62±3.37	8.81±3.12	0.420	7.45±2.91	9.10±4.72	0.523	7.42±2.67	9.46±3.41	0.161
PAWP (mmHg)	8.81±4.94	10.72±4.40	0.376	9.34±4.08	11.62±4.88	0.349	9.17±3.67	10.83±4.59	0.372
CO (L/min)	4.74±1.55	4.45±1.35	0.664	4.74±2.11	4.46±1.63	0.733	4.53±1.67	4.48±1.63	0.945
pH	7.28±0.12	7.29±0.12	0.95	7.27±0.13	7.30±0.12	0.627	7.27±0.12	7.31±0.12	0.468
$PaCO_2$ (mmHg)	52.56±13.82	48.24±13.20	0.484	55.82±17.49	45.94±13.82	0.206	56.2±16.15	46.09±13.70	0.568
PaO_2 (mmHg)	81.62±22.36	145.83±26.86[a]	0.000	78.22±24.28	167.98±36.85[a]	0.000	77.54±24.69	155.83±50.85[a]	0.000
SaO_2	86.77±8.28	96.46±2.05[a]	0.002	84.91±8.25	97.57±1.96[a]	0.000	84.63±8.08	94.93±6.52[a]	0.006
P/F (mmHg)	81.62±22.36	145.83±26.86[a]	0.000	78.22±24.28	167.98±36.85[a]	0.000	77.54±24.69	155.83±50.85[a]	0.000
Cr (ml/cmH_2O)	13.34±3.66	24.26±8.00[a]	0.001	12.88±3.20	27.51±7.99[a]	0.000	13.01±3.09	26.67±8.60[a]	0.000
HCO_3^-(mmol/L)	24.13±2.99	23.02±3.25	0.437	24.8±3.73	22.08±3.79	0.144	25.01±3.33	22.54±3.90	0.148

a pig model of ARDS. Findings showed that these recruitment maneuvers increased oxygenation and compliance in overall and gravity-dependent lung regions, and decreased inhomogeneous gas distribution in the ARDS lung, with no adverse effects on hemodynamics immediately after the maneuver. In a previous study[19], CO was monitored during and after recruitment maneuvers in models of ventilator-induced and oleic acid lung injury; findings showed no differences in CO during or after the various recruitment maneuvers.

Patients with ARDS can suffer from inhomogeneous gas distribution, which leads to ventilation–perfusion mismatching, a high dead-space fraction, and the potential for ventilator-induced lung injury (VILI). Recruitment maneuvers aim to open collapsed alveoli and improve oxygenation and respiratory system compliance. However, recruitment maneuvers can over-distend aerated alveoli, and ventilation at high inflation pressures can lead to VILI.

Heterogeneous lung structure (i.e, collapsed and overexpanded contiguous lung regions) is increasingly recognized as a key risk factor for inhomogeneous gas distribution, VILI, and mortality in mechanically ventilated patients[20]. Recent studies showed that the extent of lung inhomogeneities increase with the severity of ARDS[21], and a protective ventilatory strategy may not be sufficient to minimize VILI in patients with ARDS whose disease process is characterized by an inhomogeneous distribution of pulmonary lesions that includes a small, nondependent, normally aerated compartment and a large, dependent, nonaerated compartment[22,23].

In the present study, the inhomogeneous distribution of lung alterations in the pig model of ARDS was directly assessed using EIT. EIT has several advantages compared to established imaging techniques such as CT as it is radiation free and applicable at the bedside. In previous studies, Zhao[17] et al developed the GI index to quantify the spatial extent and dispersion in the distribution of tidal breath, reporting that a larger GI index reflected more inhomogeneity between lung units. A tidal EIT image is generated and variations in pixel values are used as an indicator of the inhomogeneity of air distribution during tidal ventilation[17]. In the present study, we used the GI index as a direct representation of global inhomogeneity in tidal ventilation in ARDS pigs. As the GI index is 0.40 ± 0.05 in patients under anesthesia without pulmonary disease[17], the GI index was expected to be > 0.45 in our experimental animals. We assessed the change in inhomogeneity with various recruitment maneuvers. Our results showed that recruitment maneuvers were able to decrease the inhomogeneity of the lung, possibly because of their ability to couple regional recruitment with partially preserved diaphragm activity, both of which were able to increase homogeneity of the lung[16,24,25]. Previous studies have shown different recruitment maneuvers are associated with differences in oxygenation, respiratory system compliance, hyperinflation, and hemodynamics[13,26,27,28]. However, a ventilation strategy with aggressive lung recruitment may increase mortality in patients with ARDS[29]. The present study showed that IP significantly improved inhomogeneity of the lung compared to SI in ARDS pigs. These data suggest that evaluating the effect of recruitment maneuvers with EIT could play a role in minimizing VILI. Results of this study should be extrapolated to the clinical setting with caution, considering the differences in the shape of the thorax between pigs and humans. Clinical trials are required to evaluate the efficacy and safety of recruitment maneuvers in patients with ARDS, and current evidence does not support the use of recruitment maneuvers in clinical practice.

Our study was associated with several limitations. First, we measured hemodynamic parameters after not during recruitment maneuvers. A previous study[19] recorded hemodynamic parameters during and after recruitment maneuvers. Cardiac output was transiently decreased during recruitment maneuvers, there were no sustained hemodynamic effects following recruitment maneuvers, and no difference was found among recruitment maneuvers, which was consistent with our research. Second, the relative impedance changes monitored by EIT may have been affected by cardiac movement. Errors in the reconstruction algorithm and resorption atelectasis could not be measured as EIT was used for monitoring dynamic ventilation distribution. Third, the decrease in GI in the different ROIs would be very informative. Unfortunately, our analytical software can only generate a global value. Last, maximal recruitment of the lung was not achieved with any maneuver. Failure to achieve maximal recruitment of the lung would affect monitoring of end-expiratory lung impedance. A peek pressure of 40 cmH_2O may not have been sufficient for opening certain alveoli in ARDS pigs. Borges[30] et al. reported that when PEEP was set to 25 cm H_2O in patients with ARDS, producing peak airway pressures of 40 cm H_2O, lung recruitment was approximately 67%. When peak airway pressures of 60 cm H_2O were reached, lung recruitment was approximately 87%. Maximal recruitment would further improve the heterogeneity of the lung, but with a concrete risk of damaging the nondependent normally aerated compartments.

Conclusions

This study used EIT to show that different recruitment maneuvers that achieve the same maximum pressure, including SI, IP, and PCV, increased oxygenation and overall and EIT- estimated regional compliance, and decreased inhomogeneous gas distribution with no adverse effects on hemodynamics in ARDS pigs. IP significantly improved inhomogeneity of the lung compared to SI and PCV. Further studies are needed to confirm the clinical significance of these findings.

Abbreviations

ARDS: acute respiratory distress syndrome; EIT: electrical impedance tomography; PaO2: arterial partial pressure of oxygen; FiO2: fraction of inspired oxygen; P/F ratio: arterial partial pressure of oxygen /fraction of inspired oxygen; SI: sustained inflation; PEEP: positive end-expiratory pressure; IP: increments of positive end-expiratory pressure; PCV: pressure-controlled ventilation; GI: global inhomogeneity; ΔGI: decrease in GI; MAP: mean arterial pressure; V_T: tidal volume; I:E: inspiration-to-expiration time ratio; CO: cardiac output; CVP: central venous pressure; PAWP: pulmonary arterial wedge pressure; PiCCO: pulse contour cardiac output; $T_{Baseline}$: time of baseline; T_{ARDS}: time of the ARDS model remained stable for 30 min; CPAP: continuous positive airway pressure; ECG: electrocardiogram; ROI: regions of interests; VILI: ventilator-induced lung injury

Declarations

Ethics approval and consent to participate

The study was approved by the Science and Technological Committee and the Animal Use and Care Committee of the Southeast University School of Medicine, Nanjing, China.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used during the current study are 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

XFP was responsible for conception and design of the study; acquisition, analysis and interpretation of data; and drafting and revising the article for final approval before publication. PC and WLH was responsible for design of the study; acquisition and analysis of data; and revising the article. LL and LSQ participated in data analysis and interpretation of the results. GFM participated in interpretation of the results and writing the article. YY participated in data analysis; interpretation of the results; and writing the article. HYZ was responsible for the conception and design of the study; analysis and interpretation of data; drafting and revising the article, providing important intellectual content; and final approval before publication. All authors read and approved the manuscript.

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Figures

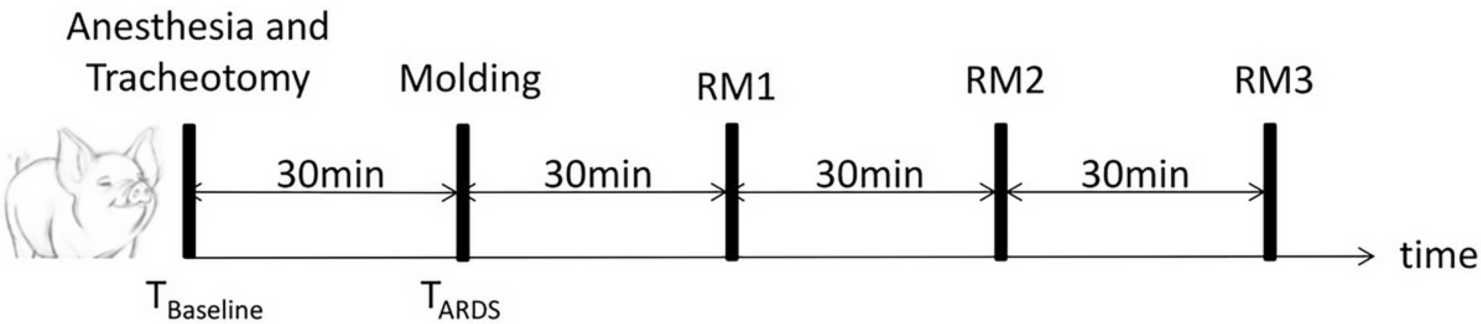

Figure 1

Flowchart of study design. ARDS pigs underwent three sequential recruitment maneuvers applied in random order according to a random number table, with 30 mins at a PEEP of 5 cmH2O between maneuvers. Respiratory mechanics, hemodynamic parameters, arterial blood gas and EIT were recorded at TBaseline, TARDS, and before and after each recruitment maneuver

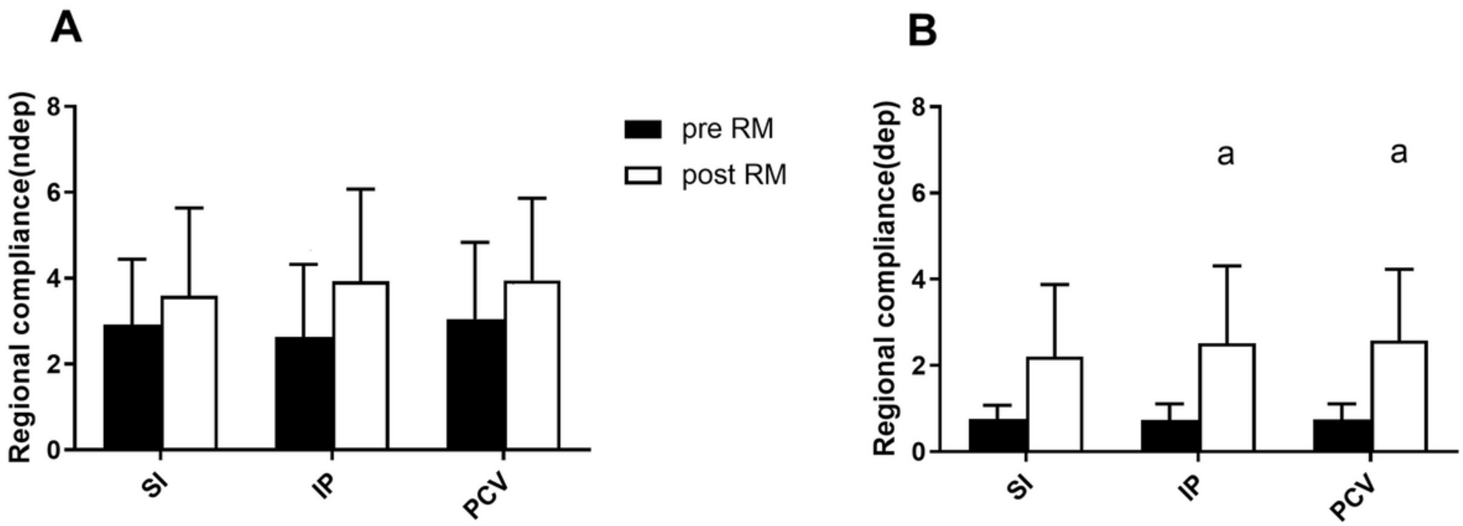

Figure 2

Compliance in non-gravity-dependent (A) and gravity-dependent (B) lung regions. Compliance in different regions was calculated by dividing VtROI by tracheal pressure changes assuming no flow at the end of inspiration and expiration. VtROI = (Δ ZROI/ Δ ZGLOB) × Vt. ap<0.05, comparison between before and after recruitment maneuver SI, sustained inflation; IP, increments of PEEP; PCV, pressure-controlled ventilation; RM, recruitment maneuvers; ROI, four regions of interest; VtROI, regional Vt values; Δ ZROI, the regional impedance change for a ROI; Δ ZGLOB, the sum of all impedance changes in the ROIs

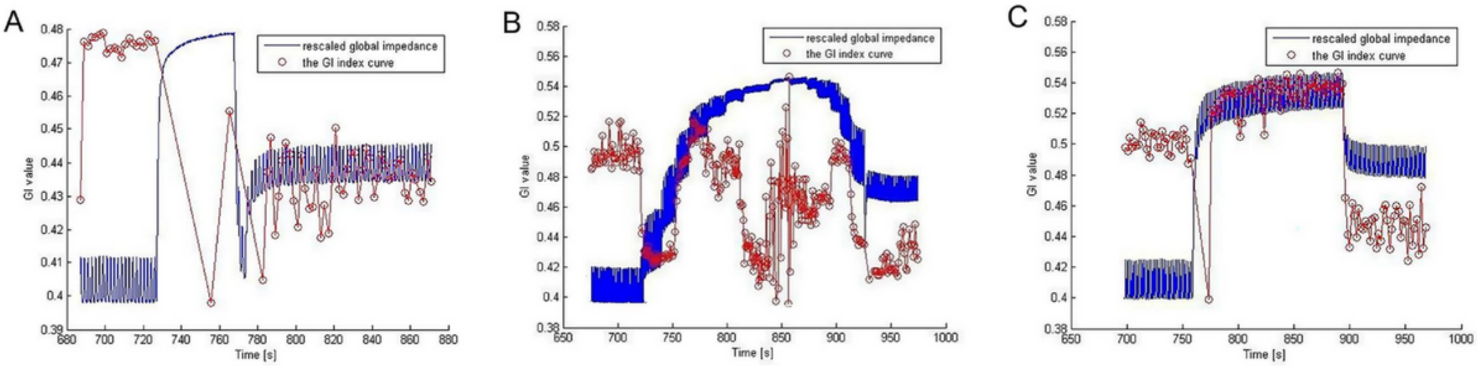

Figure 3

EIT-based global inhomogeneity (GI) index with recruitment A: SI; B: IP; C: PCV. Recruitment maneuvers were performed in the same pig. The figure was exported by a data analysis tool, and the scales cannot be adjusted. Blue lines indicate rescaled global impedance, and red circles indicate the GI index. The GI index increased during recruitment with PCV, and varied during recruitment with SI and IP. The GI index was significantly decreased after recruitment with SI, IP, or PCV. SI, sustained inflation; IP, increments of PEEP; PCV, pressure-controlled ventilation

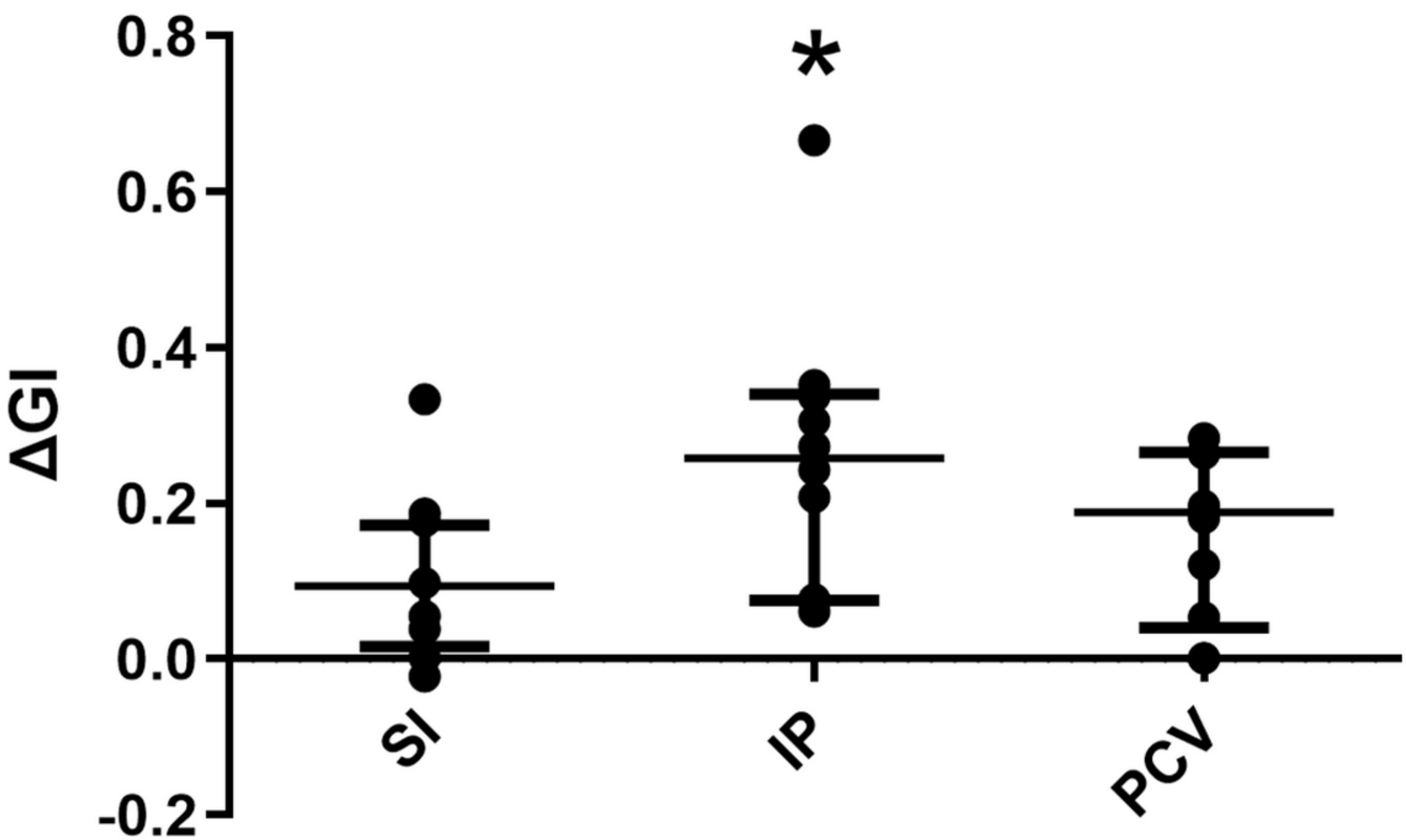

Figure 4

Decrease in EIT-based global inhomogeneity (ΔGI) index after recruitment *p<0.05 SI vs. IP

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- NC3RsARRIVEGuidelinesChecklist2014.docx