**Individual Positive End-expiratory Pressure Settings Optimize Intraoperative Mechanical Ventilation and   
Reduce Postoperative Atelectasis**

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**Supplemental Digital Content**

**Methods**

Between August 2014 and April 2016, forty eligible nonconsecutive patients undergoing elective abdominal surgery were included in the study after giving written informed consent. This study was conducted in Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, city of São Paulo, Brazil. The study was approved by the local ethics committee and was registered at ClinicalTrials.gov (identification number: NCT02314845). Following the study’s plan and design, twenty patients undergoing open abdominal surgery and twenty undergoing laparoscopic surgery were randomized into two treatment arms: in the PEEP-EIT arm, a titrated PEEP was used, and in the PEEP4 arm, a PEEP of 4 cm H2O was used (**Figure 1A**). The inclusion criterion was patient age of at least 18 years. Exclusion criteria, defined *a priori*, were ASA 3 or greater, moderate or severe chronic obstructive pulmonary disease, moderate or severe asthma, moderate or severe restrictive lung disease, or an implanted heart pacemaker.

An EIT belt was placed, and the EIT monitor (Enlight® 1800, Timpel, Sao Paulo, Brazil, approved in Brazil and Europe for the described use but not yet approved by the US Food and Drug Administration) was started, employing continuous recording at 50 Hz. Intraoperative monitoring included an ECG, pulse oximetry, sidestream EtCO2, and invasive arterial pressure measurements.

The anesthesia machines used were Perseus or Primus (Dräger Medical, Lübeck, Germany) or Aestiva/5 (Datex Ohmeda, GE Healthcare, Madison, WI, USA). The integrated and synchronized pressure and flow sensor of the Enlight monitor was connected to the airway proximal to the heat and moisture exchanger.

All patients received total intravenous anesthesia. Anesthesia induction was performed using target control infusions of propofol at 4 mcg/ml and of remifentanil at 1-3 ng/ml. A bolus of cisatracurium (0.2 mg/kg) was also used. To avoid inspiratory efforts, 0.05 mg/kg cisatracurium was administered every 40 minutes. Fluid administration with crystalloids, anesthesia deepness, use of fentanyl or remifentanil for pain management, and use of vasoactive drugs were at the discretion of the attending anesthesiologist. All patients were pre-oxygenated with 100% oxygen before tracheal intubation.

After intubation, mechanical volume-controlled ventilation (VCV) was started at FIO2 = 0.5 with an I:E of 1:2, a PEEP of 4 cm H2O, a tidal volume (VT) of 6 ml/kg predicted body weight (PBW),[1](#_ENREF_1) an inspiratory pause of 30%, and a respiratory rate (RR) that would maintain ETCO2 between 35 and 45 mm Hg. If RR exceeded 24 breaths/minute (bpm), VT could be increased.

After recording a baseline EIT signal, FIO2 was changed to 1, and patients were submitted to a recruitment maneuver in pressure-controlled ventilation (PCV) mode using 20 cm H2O of PEEP and an inspiratory pressure of 40 cm H2O for 2 minutes. At this PEEP level, a decremental PEEP titration maneuver was started in VCV mode, decreasing PEEP by 2 cm H2O at a time for 40 seconds each, keeping VT at 6 ml/kg and RR at 15 bpm. Following the procedure, the EIT monitor automatically calculated and plotted the percentage of overdistended and collapsed lung units (corresponding to the percent mass of overdistended or collapsed lung tissue, respectively) at each PEEP.[2](#_ENREF_2) The titrated PEEP was the PEEP closest to and above the crossing of the curves representing overdistension and collapse (**Figure 1B**), indicating a mechanical compromise where both lung collapse and overdistension were minimized. The PEEP value with best compliance was also noted.

If the patient presented hypotension (mean arterial pressure < 65 mm Hg) during the recruitment maneuver, the attending anesthesiologist interrupted the procedure and administered either ephedrine (5 mg) or metaraminol (0.5 mg) in a bolus according to the patient’s needs. In either case, the dose was repeated until mean arterial pressure reached 65 mm Hg.

After titration, FIO2 was reduced to 0.5, and a new recruitment maneuver was performed followed by VCV using the titrated PEEP for 2 minutes (for monitoring). Randomization to either PEEP-EIT or PEEP4 was performed. If the patient was in the PEEP-EIT arm, PEEP was maintained at the titrated value. If not, it was reduced to 4 cm H2O. All other mechanical ventilation settings were maintained at the values set at the beginning of surgery. Likewise, VT could be increased if RR exceeded 24 bpm, and FIO2 could be increased to maintain SpO2 above 96% or as dictated by blood gas analysis.

Patients receiving laparoscopic surgery were administered a third recruitment maneuver followed by another PEEP titration procedure, after insufflation of the pneumoperitoneum (data not shown). After this procedure, a fourth recruitment maneuver was performed, and patients were ventilated at the PEEP value used before pneumoperitoneum.

Data collection are shown in **Figures 2A and 2B.** Blood was collected for gas analysis at 3 points in time (**Figures 2A and 2B**). From the pressure, flow, and volumes curves and the recorded EIT signal, the following variables were calculated: plateau pressure (during inspiratory pause), driving pressure (plateau minus PEEP), respiratory system compliance using multiple linear regression, percentage of collapsed lung estimated by EIT,[2](#_ENREF_2) and regional ventilation in dependent regions (the most dependent of four isogravitational regions of interest [ROIs])[3](#_ENREF_3) (**Figure E7**). A software written in LabVIEW (National Instruments, Austin, TX, USA) was used for these analyses.

To guarantee postoperative analgesia, thus reducing influences of pain on postoperative respiratory function, several interventions were used. Intraabdominal injection of local anesthesia was performed at the discretion of the attending surgeon. All patients, whether given epidural or subarachnoid anesthesia, received 2 g endovenous metamizole, 100 mg endovenous tramadol, and 100 mg endovenous cetoprophen. Neuromuscular blocking was reversed in each patient using a 0.03 mg/kg bolus of neostigmine and a 0.015 mg/kg bolus of atropine. Patients were extubated under pressure support ventilation, and FIO2 and PEEP were maintained at values set during surgery. If the patient complained of persistent pain after extubation, 2 to 10 mg morphine could be administered. Once patients were free of pain and nausea and were fit for transportation, recovery ended, and they were transferred to the Radiology Department so that a chest computed tomography (CT) scan could be performed, under low flow (2 L/min) supplemental oxygen through a nasal catheter, if necessary.

***CT image analysis***

All CT images were obtained with the patient in the supine position and during expiratory hold after normal inspiration at functional residual capacity. Low-dose CT, without IV contrast medium, was performed at 120 kVp and 80 mAs.[4](#_ENREF_4) Axial continuous images were reconstructed using the reconstruction algorithm in the CT scanner using a thickness of 5 mm.

Ten slices were selected for each patient so that results could be extrapolated to the whole.[5](#_ENREF_5) The DICOM images were analyzed using Osiris 4.19 (University Hospital of Geneva, Geneva, Switzerland) for manual segmentation of lung parenchyma. The percentage of total lung mass that was nonaerated (densities between -200 and +100 UH) was calculated using Luva 2005 (Nico Heller, 2005).

The primary outcome of this trial was the identification of the PEEP values that produced the best possible compromise between lung collapse and hyperdistention during a PEEP titration procedure using EIT. The secondary endpoint was the amount of atelectasis, in percentage of lung mass, evaluated by a chest CT scan after extubation. Additional exploratory endpoints were the impact of PEEP selection (according to randomization) on pulmonary function and hemodynamics.

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**Table E1.** Baseline Characteristics of the patients

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Demographic and ClinicalVariables** | | **Laparoscopic (n=20)** | | | | **OpenSurgery (n=20)** | | | |
| **PEEP4  (n=10)** | | **PEEP-EIT (n=10)** | | **PEEP4 (n=10)** | | **PEEP-EIT (n=10)** | |
| **Age, median, (IQR), yr** |  | 52.1 | (41-60) | 45.1 | (28-65) | 56.4 | (33-68) | 56.4 | (26-74) |
| **Male sex, n (%)** |  | 3 | (30) | 2 | (20) | 5 | (50) | 8 | (80) |
| **Weight, mean± SD, kg** |  | 86.5 | ± 15.8 | 78.5 | ± 17.1 | 71.5 | ± 12.8 | 75.1 | ± 14.6 |
| **PBW, mean± SD, kg** |  | 54.1 | ± 12.5 | 54.7 | ± 7.9 | 54.4 | ± 7.2 | 62.4 | ± 8.4 |
| **BMI, mean ± SD, kg/m2** |  | 33.3 | ± 2.4 | 30.0 | ± 4.7 | 27.9 | ± 3.9 | 26.7 | ± 3.1 |
| **Thoracic perimeter, mean ± SD, cm** |  | 106.5 | ± 7.2 | 100.9 | ± 8.4 | 97.1 | ± 8.3 | 97 | ± 7.9 |
| **Type of Surgery** |  |  |  |  |  |  |  |  |  |
|  | **Urology, n (%)** | 0 | (0) | 0 | (0) | 5 | (50) | 8 | (80) |
|  | **Gastric, n (%)** | 10 | (100) | 9 | (90) | 0 | (0) | 0 | (0) |
|  | **Gynecology, n(%)** | 0 | (0) | 1 | (10) | 5 | (50) | 2 | (20) |
| **ASA 1, n (%)** |  | 1 | (0) | 3 | (30) | 5 | (50) | 3 | (30) |
| **ASA 2, n (%)** |  | 9 | (90) | 7 | (70) | 5 | (50) | 7 | (70) |
| **Hypertension, n (%)** |  | 4 | (40) | 7 | (70) | 4 | (40) | 3 | (30) |
| **Hypothyreoidism, n (%)** |  | 1 | (10) | 2 | (20) | 0 | (0) | 0 | (0) |
| **Diabetes, n (%)** |  | 1 | (10) | 3 | (30) | 1 | (10) | 2 | (20) |
| **CKD, n (%)** |  | 0 | (0) | 1 | (10) | 0 | (0) | 0 | (0) |
| **Smoking Status** |  |  |  |  |  |  |  |  |  |
|  | **Never, (%)** | 7 | (70) | 7 | (70) | 9 | (90) | 4 | (40) |
|  | **Former (%)** | 1 | (10) | 1 | (10) | 1 | (10) | 2 | (20) |
|  | **Current (%)** | 2 | (20) | 2 | (20) | 0 | (0) | 4 | (40) |
| **Active Cancer, n (%)** |  | 0 | (0) | 1 | (10) | 5 | (50) | 8 | (80) |
| **Chemotherapy, n (%)** |  | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) |

PBW = Predicted Body Weight; BMI = body mass index; ASA = American Society of Anesthesiology status classification system; CKD = Chronic Kidney Disease. CKD as defined according to KDIGO.

**Table E2.** Ventilation Parameters of all acquired times

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Time of Acquisition** | **Parameters** | **Laparoscopic (n=20)** | | | | | **Open Surgery (n=20)** | | | | |
| **Randomized Group** | | | | | **Randomized Group** | | | | |
| **PEEP4  (n=10)** | | **PEEP-EIT (n=10)** | | **P** | **PEEP4 (n=10)** | | **PEEP-EIT (n=10)** | | **P** |
| **Baseline**  **(before recruitment maneuver)** | VT/Kg (ml/kg) | 7 | ± 0.7 | 6.4 | ± 0.5 | 0.073 | 6.6 | ± 0.5 | 6.2 | ± 0.7 | 0.144 |
| PEEP (cmH2O) | 4.2 | ± 0.3 | 4.1 | ± 0.4 |  | 4.1 | ± 0.1 | 4.4 | ± 0.4 |  |
| Plateau pres.(cmH2O) | 15.7 | ± 2.4 | 13.9 | ± 3.3 | 0.195 | 13.3 | ± 2.5 | 13.4 | ± 1.9 | 0.883 |
| CRS (cmH2O/ml) | 33.5 | ± 8.1 | 37.7 | ± 9.7 | 0.317 | 42.1 | ± 15.7 | 43.5 | ± 7.9 | 0.807 |
| DP (cmH2O) | 11.6 | ± 2.5 | 9.8 | ± 3.1 | 0.188 | 9.3 | ± 2.5 | 9.1 | ± 1.7 | 0.869 |
| Collapse on EIT (%) | 44.6 | ± 15.4 | 41.7 | ± 18.0 | 0.711 | 35 | ± 16.1 | 31.3 | ± 9.2 | 0.530 |
| **During Titration**  **(At PEEP-EIT)** | VT/Kg (ml/kg) | 7.1 | ± 0.5 | 6.7 | ± 0.5 | 0.086 | 6.8 | ± 0.5 | 6.5 | ± 0.6 | 0.125 |
| PEEP (cmH2O) | 14.3 | ± 1.5 | 12.9 | ± 1.6 |  | 10.2 | ± 2.3 | 10.3 | ± 2.3 |  |
| Plateau pres.(cmH2O) | 19.5 | ± 2.0 | 18.1 | ± 1.9 | 0.130 | 16.1 | ± 3.1 | 16.8 | ± 3.3 | 0.660 |
| CRS (cmH2O/ml) | 77.1 | ± 14.0 | 75.3 | ± 8.6 | 0.742 | 75.9 | ± 18.0 | 71.9 | ± 15.7 | 0.601 |
| DP (cmH2O) | 5.3 | ± 0.7 | 5.2 | ± 0.7 | 0.796 | 6.0 | ± 1.3 | 6.5 | ± 1.1 | 0.336 |
| Collapse on EIT (%) | 6.5 | ± 5.6 | 4.5 | ± 3.9 | 0.375 | 3.6 | ± 1.8 | 5.4 | ± 2.8 | 0.097 |
| **During Titration**  **(at PEEP 4)** | VT/Kg (ml/kg) | 7.2 | ± 0.5 | 6.7 | ± 0.5 | 0.05 | 6.6 | ± 0.4 | 6.4 | ± 0.5 | 0.339 |
| PEEP (cmH2O) | 3.7 | ± 0.3 | 3.8 | ± 0.4 |  | 4.0 | ± 0.3 | 4.2 | ± 0.4 |  |
| Plateau pres.(cmH2O) | 12.7 | ± 1.4 | 11.7 | ± 1.2 | 0.121 | 11.8 | ± 1.4 | 11.7 | ± 2.0 | 0.913 |
| CRS (cmH2O/ml) | 44.9 | ± 8.8 | 48.8 | ± 7.7 | 0.301 | 49.3 | ± 12.6 | 52.6 | ± 13.4 | 0.319 |
| DP (cmH2O) | 8.9 | ± 1.5 | 8.0 | ± 1.3 | 0.138 | 7.8 | ± 1.5 | 7.5 | ± 1.9 | 0.735 |
| Collapse on EIT (%) | 39.2 | ± 12.5 | 36.4 | ± 11.8 | 0.622 | 21.4 | ± 13.7 | 22.0 | ± 9.4 | 0.913 |
| **After randomization**  **(selected PEEP)** | VT/Kg (ml/kg) | 7.1 | ± 0.7 | 6.5 | ± 0.8 | 0.071 | 6.6 | ± 0.4 | 6.3 | ± 0.6 | 0.206 |
| PEEP (cmH2O) | 3.8 | ± 0.3 | 13.2 | ± 1.4 | <0.001 | 3.9 | ± 0.3 | 10.1 | ± 2.0 | <0.001 |
| Plateau pres.(cmH2O) | 13.7 | ± 1.4 | 18.7 | ± 2.0 | <0.001 | 11.7 | ± 1.4 | 16.6 | ± 3.1 | <0.001 |
| CRS (cmH2O/ml) | 39.6 | ± 7.2 | 67.6 | ± 6.7 | <0.001 | 48.8 | ± 13.2 | 66.2 | ± 14.2 | 0.011 |
| DP (cmH2O) | 9.8 | ± 1.4 | 5.5 | ± 0.8 | <0.001 | 7.7 | ± 1.5 | 6.5 | ± 1.3 | 0.070 |
| Collapse on EIT (%) | 42.5 | ± 12.6 | 10.3 | ± 10.2 | <0.001 | 29.8 | ± 14.2 | 8.5 | ± 5.1 | <0.001 |
| **1h of Surgery** | VT/Kg (ml/kg) | 7.0 | ± 0.6 | 6.5 | ± 0.7 | 0.088 | 6.6 | ± 0.4 | 6.3 | ± 0.6 | 0.139 |
| PEEP (cmH2O) | 4.0 | ± 0.2 | 13.3 | ± 1.4 | <0.001 | 4.0 | ± 0.3 | 10.1 | ± 2.1 | <0.001 |
| Plateau pres.(cmH2O) | 18.4 | ± 2.4 | 22.0 | ± 2.9 | 0.06 | 13.6 | ± 2.4 | 18.3 | ± 3.8 | 0.003 |
| CRS (cmH2O/ml) | 26.4 | ± 5.7 | 42.5 | ± 9.1 | <0.001 | 39.3 | ± 10.4 | 51.6 | ± 10.4 | 0.016 |
| DP (cmH2O) | 14.4 | ± 2.5 | 8.7 | ± 1.8 | <0.001 | 9.6 | ± 2.4 | 8.2 | ± 1.8 | 0.142 |
| Collapse on EIT (%) | 55.4 | ± 10.6 | 36.7 | ± 17.3 | 0.028 | 39.3 | ± 17.0 | 28.1 | ± 9.2 | 0.085 |
| **Before extubation** | VT/Kg (ml/kg) | 7.2 | ± 0.6 | 6.6 | ± 0.6 | 0.056 | 6.8 | ± 0.4 | 6.5 | ± 0.6 | 0.290 |
| PEEP (cmH2O) | 4.0 | ± 0.2 | 13.3 | ± 1.5 | <0.001 | 4.0 | ± 0.3 | 10.2 | ± 2.0 | <0.001 |
| Plateau pres.(cmH2O) | 15.7 | ± 1.9 | 20.3 | ± 2.2 | <0.001 | 13.1 | ± 2.1 | 18.0 | ± 3.3 | 0.001 |
| CRS (cmH2O/ml) | 33.3 | ± 6.8 | 53.2 | ± 4.3 | <0.001 | 43.0 | ± 14.6 | 54.8 | ± 10.2 | 0.052 |
| DP (cmH2O) | 11.8 | ± 1.8 | 7.1 | ± 0.9 | <0.001 | 9.2 | ± 2.1 | 7.8 | ± 1.4 | 0.105 |
| Collapse on EIT (%) | 58.1 | ± 7.3 | 25.3 | ± 13.8 | <0.001 | 38.4 | ± 17.3 | 27.4 | ± 7.9 | 0.084 |

Data are expressed as mean ± SD. Plateau pres.: Plateau Pressure; DP: Driving pressure; CRS: Compliance of the respiratory system. Collapse on electrical impedance tomography is expressed as percentage of total lung mass; PEEP 4: group randomized to PEEP of 4cmH2O; PEEP-EIT: group randomized to PEEP titrated by EIT; P (t-test) for the difference between PEEP 4 and PEEP-EIT arms in the same type of surgery (laparoscopic or open surgery).

**Figures**

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**Figure E1.** Correlation of titrated PEEP according to EIT (PEEP-EIT) and by an alternative method (best respiratory system compliance), using as criterion the PEEP value with best compliance. PEEP-EIT was chosen during decremental PEEP titration by EIT and was considered as the nearest PEEP above the crossing of the curves representing overdistension and collapse, indicating a mechanical compromise where both, lung collapse and overdistension were minimized. Solid line is the identity line. Dashed line is the regression line.



**Figure E2.** Mean respiratory system compliance during intraoperative period in open surgery (A) and laparoscopic surgery (B). Shaded areas represent standard error mean (SEM). Closed circles represent PEEP-EIT arm and open circles represent PEEP4 arm. In both types of surgery, CRS was higher in PEEP-EIT arm after randomization.



**Figure E3.** Mean ventilation estimated by EIT on dorsal region (ROI 4) during intraoperative period in open abdominal surgery (A) and laparoscopic surgery (B).Shaded areas represent standard error mean (SEM). Closed circles represent PEEP-EIT arm and open circles represent PEEP4 arm. In both types of surgery, percentage of ventilation in ROI 4 was higher in PEEP-EIT arm after randomization.



**Figure E4.** PaCO2 medians and interquartile ranges (IQ) during intraoperative period in open surgery (A) and laparoscopic surgery (B). Grey boxes represent PEEP-EIT arm and white boxes represent PEEP4 arm. There was no significant difference between the two arms.

\* P<0.05 – difference from time “after randomization”



**Figure E5**. Individual length of stay (LOS) in the hospital and group median and interquartile range (IQ). Closed circles represent PEEP-EIT arm and open circle represent PEEP4 arm. There was no significant difference between the two arms.



**Figure E6**. Correlation between driving pressure (measured at PEEP-EIT, tested for all patients before randomization) and BMI. Closed circles represent individual patient data. Patients in both arms were submitted to a recruitment maneuver and to a decremental PEEP titration. PEEP-EIT was chosen during decremental PEEP titration by EIT and was considered as the nearest PEEP above the crossing of the curves representing overdistension and collapse, indicating a mechanical compromise where both, lung collapse and overdistension were minimized.



**Figure E7**. Functional lung image obtained by Electrical impedance tomography (EIT) divided into four regions of interest (ROI). The regional ventilation (ΔZ) in ROI-4 (dorsal) was analyzed during intraoperative period: decrease in ventilation in this area suggests lung collapse.