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Positive end-expiratory pressure improves elastic working pressure in anesthetized children

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Abstract

Background: Positive end-expiratory pressure (PEEP) has been demonstrated to decrease ventilator-induced lung injury in patients under mechanical ventilation (MV) for acute respiratory failure. Recently, some studies have proposed some beneficial effects of PEEP in ventilated patients without lung injury. The influence of PEEP on respiratory mechanics in children is not well known. Our aim was to determine the effects on respiratory mechanics of setting PEEP at 5 cmH₂O in anesthetized healthy children.

Methods: Patients younger than 15 years old without history of lung injury scheduled for elective surgery gave informed consent and were enrolled in the study. After usual care for general anesthesia, patients were placed on volume controlled MV. Two sets of respiratory mechanics studies were performed using inspiratory and expiratory breath hold, with PEEP 0 and 5 cmH₂O. The maximum inspiratory and expiratory flow (Q_I and Q_E) as well as peak inspiratory pressure (PIP), plateau pressure (P_{PL}) and total PEEP (tPEEP) were measured. Respiratory system compliance (C_{RS}), inspiratory and expiratory resistances (R_{awI} and R_{awE}) and time constants (K_{TI} and K_{TE}) were calculated. Data were expressed as median and interquartile range (IQR). Wilcoxon sign test and Spearman's analysis were used. Significance was set at $P < 0.05$.

Results: We included 30 patients, median age 39 (15–61.3) months old, 60% male. When PEEP increased, PIP increased from 12 (11,14) to 15.5 (14,18), and C_{RS} increased from 0.9 (0.9,1.2) to 1.2 (0.9,1.4) mL·kg⁻¹·cmH₂O⁻¹; additionally, when PEEP increased, driving pressure decreased from 6.8 (5.9,8.1) to 5.8 (4.7,7.1) cmH₂O, and Q_E decreased from 13.8 (11.8,18.7) to 11.7 (9.1,13.5) L·min⁻¹ (all $P < 0.01$). There were no significant changes in resistance and Q_I .

Conclusions: Analysis of respiratory mechanics in anesthetized healthy children shows that PEEP at 5 cmH₂O places the respiratory system in a better position in the P/V curve. A better understanding of lung mechanics may lead to changes in the traditional ventilatory approach, limiting injury associated with MV.

Keywords: Positive end-expiratory pressure, Mechanical ventilation, Respiratory mechanics, Pediatrics

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Background

There are many detrimental effects of positive pressure mechanical ventilation (MV) to the lung parenchyma, giving shape to the entity we know as ventilator induced lung injury (VILI) [1, 2]. Despite that it was initially described for injured lungs [3], VILI has been recognized to affect patients with uninjured lungs, triggering many pathways of local and systemic inflammation [1–4]. Positive pressure MV can cause VILI even when applied for short periods of time, and the role of protective MV during anesthesia has become important for preventing postoperative complications [5–10]. Although the exact incidence of VILI during general anesthesia is unknown, the lungs of patients under general anesthesia are especially vulnerable to VILI, since anesthetic induction reduces the end expiratory lung volume (EELV) by 9–25% in adults and up to 46% in children [11–15]. Cyclic opening and collapsing of alveoli have been indicated as one of the primary mechanisms of VILI during anesthesia. Imaging studies have shown that general anesthesia induces atelectasis of dependent regions and that the use of PEEP prevents its formation [3, 5, 9, 10, 14]. Protective ventilation during general anesthesia [16, 17] to limit tidal volume (6–8 ml/kg) has been widely accepted and incorporated into the operating room (OR), but PEEP use is still not a common practice for patients undergoing general anesthesia [6–10, 17, 18].

In the absence of respiratory muscle activity, working pressure of the respiratory system is the pressure needed to overcome frictional forces, elastic forces and impedance. In this way, an improvement in CRS reflects lower elastic work pressures and, therefore, a pending situation of its more favorable dynamic pressure/volume curve (P/V curve) [19]. These observations also have been described in pediatric animal models [20, 21].

There is little evidence to guide MV during general anesthesia in children [18, 22, 23]. MV parameters are primarily dependent on anesthesiologist preferences and on the characteristics of anesthesia machines [24]. Facing this scenario, many scientific societies have pointed as priority areas of research to the pathophysiology, respiratory mechanics and practice of MV in children for improving outcomes and reducing secondary long-term lung injury [23].

With these facts in mind, we sought to compare respiratory mechanics of setting PEEP at 5 cmH₂O compared to ZEEP (PEEP set at 0 cmH₂O) in anesthetized children without acute pulmonary pathology undergoing elective surgery. We hypothesized that usual respiratory mechanics parameters, measured with a commercial mechanical ventilator, would identify a more protective ventilation with addition of PEEP 5 cmH₂O. Special emphasis was placed on evaluation on respiratory work pressure, flow patterns, resistance and inspiratory and expiratory time constants.

Methods

Study design and setting

This prospective study was conducted at the Surgical Block of Centro Hospitalario Pereira Rossell located in Montevideo, Uruguay. The local ethic committee approved the study and informed consent was obtained for each patient before entering the OR.

Study population

Between February 1, 2015 and April 30, 2016, children younger than 15 years old without preexisting lung injury scheduled for elective surgery were screened for the study. For definitive selection, patients categorized as ASA I or II, requiring orotracheal intubation for the surgery according to the anesthesiologist's criteria, were considered. Patients were excluded if they had any acute condition before or during anesthesia (e.g., laryngospasm, bronchoconstriction, pneumothorax), thoracic surgery, thoracic or airway malformation and chronic lung disease with oxygen dependence. Additionally, patients with endotracheal tube air leak >20% of tidal volume (V_T) were excluded due to possible interference with data acquisition.

Data collection

We registered demographics and clinical information at admission. All procedures before respiratory system mechanics measurements were done according to institutional protocol and anesthesiologist preferences, including anesthesia induction, orotracheal intubation and initial ventilatory settings on the anesthesia machine.

Study protocol

Patients were ventilated on a Galileo Gold® ventilator (Hamilton, Bonaduz, Switzerland) on volume control mode after verification of correct positioning of the endotracheal tube. Baseline settings were as follows: $V_T = 6-8$ mL·kg⁻¹, PEEP = 5 cmH₂O, fraction of inspired oxygen (FiO₂) was adjusted to a target pulse oximetry greater than 95%, inspiratory: expiratory ratio = 1:2, and respiratory rate (RR) was adjusted to achieve an end-tidal carbon dioxide (ETCO₂) 40 ± 5 mmHg. Tracheal tube leak compensation was deactivated through the measurements.

Respiratory mechanics measurements

Two sets of measurements were performed, at ZEEP and PEEP 5 cmH₂O, separated by 5 min of stability, following local protocol for respiratory mechanics measurements. This protocol is summarized in Additional file 1 [19]. All measurements were made in pre-incision surgical time.

Ventilator parameters [peak inspiratory pressure (PIP), plateau pressure (P_{PL}), extrinsic (set) PEEP (PEEP), total PEEP (tPEEP), intrinsic PEEP (iPEEP = tPEEP - PEEP), driving pressure ($\Delta P = P_{PL} - tPEEP$), mean airway pressure expiratory (P_{aw}), V_T , inspiratory time (IT),

respiratory rate (RR), maximum inspiratory and expiratory flow (Q_I and Q_E , $L \cdot \text{min}^{-1}$) were assessed. An inspiratory hold followed by an expiratory hold was performed following the protocol described in Additional file 1. Flow and pressure parameters in these quasi-static conditions at the Y piece (*proximal flow sensor*) were recorded in an ad hoc Microsoft Excel 2010 (Microsoft®, NY, USA) database to calculate respiratory system compliance (C_{RS} , $\text{mL} \cdot \text{cmH}_2\text{O}^{-1} \cdot \text{kg}^{-1}$), inspiratory and expiratory airway resistance (R_{awI} and R_{awE} , $\text{cmH}_2\text{O} \cdot \text{L}^{-1} \cdot \text{s}^{-1}$), and inspiratory and expiratory time constants (K_{TI} and K_{TE} , s) according to formulas described in Additional file 2.

Data analysis

Data are expressed as median and interquartile range (IQR). A previous study found that changing PEEP from 0 to 12 cmH_2O resulted in a decrease in dynamic compliance (C_{dyn}) in 9.4 $\text{ml/cmH}_2\text{O}$ with SD 6.8 [25]. Given the fact that our protocol included a moderate modification of PEEP, from 0 to 5 $\text{ml/cmH}_2\text{O}$, we expected a smaller change of C_{dyn} , 2/3 of previously described [25]. A sample size of 30 patients is needed to determine a variation of C_{dyn} by 6 $\text{ml/cmH}_2\text{O}$, using chi-square test and assuming an α of 0.05 and a power of 90%. Normality was assessed with the Anderson–Darling test. Wilcoxon sign test was performed for comparisons between respiratory mechanics assessments. Spearman's analysis was used to examine correlations between changes in respiratory mechanics and age and ideal body weight. Differences were considered significant if $p < 0.05$. All statistical analyses were performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA). Figures were plotted with GraphPad Prism version 5.0c for Mac (GraphPad Software, La Jolla, CA, USA).

Results

Thirty patients were included in the study. Sixty percent were male, the median age was 39 months (15–61.3), and weight was 15 kg (10.6–21).

Sixty percent of patients received inhaled anesthesia and 40% mixed inhalation and intravenous anesthesia. Abdominal surgery was the most frequent (20 cases), mostly hernioplasty. Malformation of the digestive tract was the most frequent comorbidity, present in 7 patients. Table 1 shows clinical characteristics of included patients.

There were no complications related to the protocol. Table 2 shows ventilatory parameters and respiratory system mechanics for the study population with ZEEP and PEEP of 5 cmH_2O . After setting PEEP at 5 cmH_2O we observed an increase in P_{IP} , P_{PL} and P_{aw} , with a concomitant decrease in $iPEEP$ and ΔP . Figure 1 shows individual changes on ΔP throughout the study. No modifications were done on V_T and thus, changes on ΔP were coupled to variation on C_{RS} .

There was a moderate correlation between age and ideal body weight and changes in Q_E and changes in K_{TE} . Additional file 3 shows the correlation between changes in respiratory parameters and age and ideal body weight. No other correlations with age and weight were found.

Discussion

In this study, we measured pulmonary mechanics in anesthetized healthy children on MV for elective surgery at ZEEP and PEEP 5 cmH_2O using a commercially available mechanical ventilator. Setting PEEP at 5 cmH_2O resulted in a significant decrease in ΔP and $iPEEP$, thereby improving C_{RS} . Changes observed in respiratory mechanics after setting PEEP at 5 cmH_2O are summarized in Fig. 2.

We also found a decrease in Q_E when PEEP was applied. All these findings are indirect signs of lungs in a better position in dynamic P/V curve, suggesting that the addition of a low level of PEEP improves respiratory mechanics.

The effect of PEEP on patients with ARDS was described more than a decade ago, promoting recruitment of non-aerated lung volume and increasing EELV. More recently, many investigators have shown that PEEP should be incorporated to lung protective strategy during the perioperative period in patients at risk for ARDS as well as previously healthy patients [6, 8–10]. In this setting, hypoxemia was not associated with the reduction in EELV, and thus, hypoxemia is thought to be a poor predictor of potential injurious MV. Similar findings have been described in children. Serafini et al. described densities in dependent regions of both lungs on CT scan of 10 infants after induction of anesthesia. They observed reopening of the collapsed lung with addition of 5 cmH_2O of PEEP for 5 min [14]. Kadini et al., in a small study of 8 anesthetized children (range between 2.5 and 6.5 years old), described that 5 cmH_2O resulted in a significant increase of V_T ; thus, C_{RS} improved [24].

Our results show that the addition of PEEP sets the respiratory system in a better position of the P/V curve, probably related to the reduction of the atelectasis in lung dependent zones after induction of anesthesia and MV with ZEEP. An increase in EELV, maintaining the same V_T , denotes a reduction in global strain and, potentially, VILI [26].

ΔP has taken high priority after the recent pooled data analysis of adult patients with ARDS that showed a significant relationship with mortality [27]. ΔP represents the pressure required for the movement of inspiratory flow and depends on the lung and chest wall viscoelastic resistance [28]. Recently, Neto et al. in a meta-analysis of 2250 patients under general anesthesia found that high ΔP was the only MV parameter associated with postoperative complications [29]. Even more, they found

Table 1 Clinical characteristics of children included in the study

Number	Age (mo)	Weight (kg)	Height (cm)	Surgery	Comorbidities
1	40–50	17.5	105	Inguinal hernia	none
2	40–50	16.7	105	Umbilical hernia	none
3	30–40	13	90	Cryptorchid	none
4	10–20	5.1	67	CVL placement	Short bowel insufficiency
5	30–40	15	94	Anorectoplasty	Partial anomalous venous return
6	40–50	15	94	Inguinal hernia	Asthma
7	20–30	11.2	82	Epigastric hernia	none
8	10–20	9.2	70	Enterostomy closure	Imperforated anus
9	50–60	18	101	Enterostomy closure	Colostomy
10	60–70	14.2	104	Esophageal dilatation	Esofageal coloplasty
11	50–60	26	114	Abdominal tumor	none
12	30–40	22	99	Hidrocele	none
13	50–60	19	90	Fimosis	none
14	30–40	23	103	Cryptorchid	none
15	20–30	11.9	81	Inguinal hernia	none
16	70–80	24.6	120	Cryptorchid	none
17	3–10	7	63	Inguinal hernia	none
18	10–20	10.4	77	Inguinal hernia	none
19	10–20	13.5	80	Cryptorchid	none
20	120–130	25.8	132	Colecystectomy	none
21	3–10	5.7	62	Inguinal hernia	none
22	140–150	40	154.5	Thyroidectomy	none
23	3–10	4.9	N/A	Eventration repair	Traumatic eventration
24	80–90	19.7	116	Enterostomy closure	Hirschprung's Disease
25	80–90	27	118	Enterostomy closure	Hirschprung`s Disease
26	110–120	29	129.5	Anoplasty	Anorectal Malformation
27	100–110	21	116	CVL placement	Astrocytoma
28	10–50	14	103	Anoplasty	Anorectal malformation
29	1–10	4.6	56.5	Exploratory laparoscopy	none
30	10–20	7.3	77	CVL placement	Lymphoblastic leukemia

mo months old, CVL central venous line, N/A non-available

that changes in PEEP that resulted in an increase in ΔP were associated with more postoperative pulmonary complications. It is not surprising that in these studies, ΔP was the best predictor of unfavorable outcomes. We believe that the best performance of this parameter is because it integrates the set tidal volume and the patient's compliance, thus giving a more precise idea of the individual conditions of each patient.

In our patients, we observed a 14.8% (CI95% 9.3,20.3%) reduction of ΔP when PEEP of 5 cmH₂O was applied. The range of improvement was very wide and only one patient had a significant increase in ΔP (greater than 10%). These results are in accordance with a study by Wirth et al. They elegantly showed, with electric impedance tomography in 30 anesthetized children, that changing PEEP from 2

cmH₂O to 5 cmH₂O homogenizes regional lung ventilation [30]. One of our patients had a significant increase of ΔP . This a very good example that ventilatory settings need to be tailored individually, because adding 5 cmH₂O of PEEP probably led to overdistension in this patient. We maintained the set V_T after applying PEEP of 5 cmH₂O; thus, the reduction of ΔP was dependent on the improvement in C_{RS} . The improvement in C_{RS} and EELV may be seen as minor, but we believe that even these small changes may have significant consequences during and after surgery, reducing lung inflammation, alteration of gas exchange, among others. Experimental and clinical data have shown that injurious ventilatory parameters can generate detrimental effects, even when applied for short periods of time [1, 2, 31, 32].

Table 2 Ventilatory parameters and respiratory system mechanics of children under general anesthesia with ZEEP and PEEP of 5 cmH₂O

	ZEEP (n = 30)		PEEP 5 (n = 30)		P value
	MEDIAN	P25, P75	MEDIAN	P25, P75	
FiO ₂	0.40	0.36, 0.50	0.40	0.36, 0.50	1.000
V _{TE}	6.79	6.18, 7.36	6.53	5.97, 7.20	0.290
RR	24	21, 26	24	21, 26	1.0
IT	0.85	0.72, 1.02	0.85	0.72, 1.03	1.00
PIP	12	11, 14	15.5	14.0, 18.5	< 0.01
P _{PL}	7.9	7.2, 9.18	10.95	9.7, 12.6	< 0.01
Paw	4.1	3.6, 4.9	8.5	7.9, 9.8	< 0.01
Q _I	11	8.1, 13.1	11	8.1, 13.1	0.317
Q _E	13.8	11.8, 13.1	11.7	9.1, 13.5	< 0.01
Raw _I	25.7	18.6, 34.3	26.4	20.1, 33.1	0.447
Raw _E	28.9	21.9, 39.4	29.3	22.3, 42.1	0.629
C _{RS}	0.96	0.89, 1.22	1.19	0.94, 1.39	< 0.01
K _{TI}	0.36	0.31, 0.48	0.45	0.38, 0.59	0.004

ZEEP PEEP 0 cmH₂O, FiO₂ fraction of inspired oxygen, V_{TE} expiratory tidal volume (mL·kg⁻¹), RR respiratory rate (breath per minute), IT inspiratory time (s), PIP peak inspiratory pressure (cmH₂O), P_{PL} plateau pressure (cmH₂O), Paw mean airway pressure (cmH₂O), Q_I peak inspiratory flow (L·min⁻¹), Q_E peak expiratory flow, (L·min⁻¹), Raw_I inspiratory airway resistance (cmH₂O·L⁻¹·s⁻¹), Raw_E expiratory airway resistance (cmH₂O·L⁻¹·s⁻¹), C_{RS} static respiratory system compliance (mL·cmH₂O⁻¹·kg⁻¹), K_{TI} inspiratory time constant (s)

The prolongation of K_{TI} and K_{TE} with PEEP of 5 cmH₂O probably reflects mathematical coupling of changes on C_{RS} without modifications on airway resistance. In the same way, the observed lower expiratory flow is related to the lower ΔP. These parameters are indirect markers of improvement on respiratory system mechanics and more protective ventilation.

Our study has some limitations. Respiratory mechanics measurements were done before the surgery, after a short period of applied PEEP; thus, we cannot extrapolate these findings to other surgical timings, e.g., during pneumoperitoneum, when the effect of PEEP preventing lung collapse could be even higher. Due to small size of patients, we did not measure pleural pressure, so we could not determine the contribution of the chest wall to C_{RS}. Included patients were heterogeneous and age range is wide, so in the absence of normal reference data, we cannot generalize these results to all pediatric patients (i.e., younger patients have higher chest compliance, being at higher risk for derecruitment of the lung on ZEEP). Finally, we have to acknowledge that setting of MV parameters can directly modify the component of the equation of motion (i.e., Q_I, RR, I:E ratio), but we tried to standardize the ventilatory setting during measurements. Despite these limitations, we consider our observation of the effect of PEEP in anesthetized

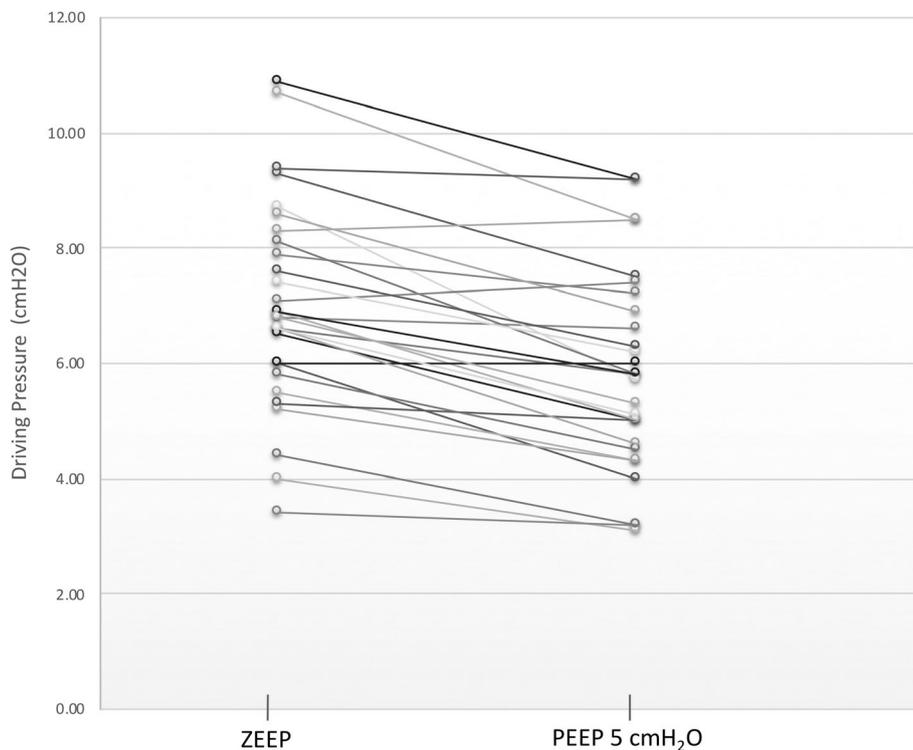
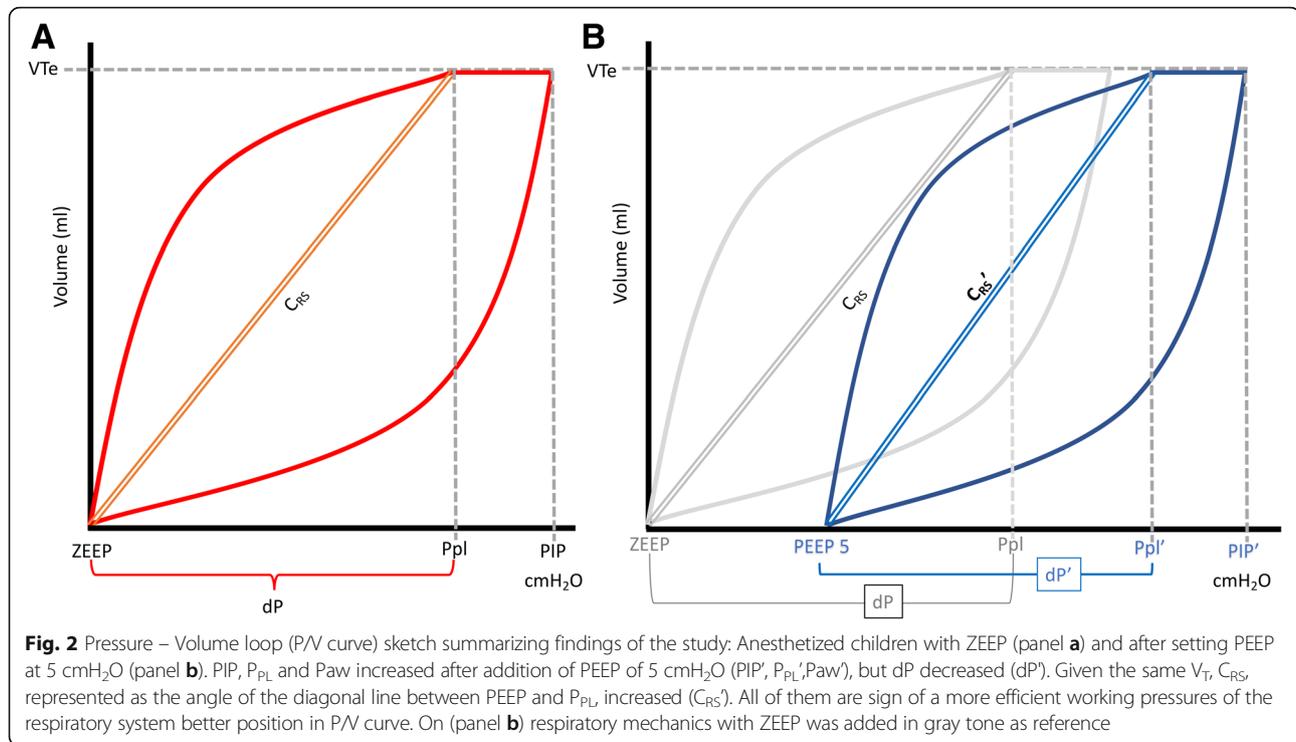


Fig. 1 Individual value plot of driving pressure (cmH₂O) with ZEEP and PEEP at 5 cmH₂O in anesthetized healthy children



children under mechanical ventilation important in terms of a pathophysiological approach to reduce VILI.

Conclusion

Setting PEEP at 5 cmH₂O in children during general anesthesia improved elastic working pressure of the respiratory system, decreasing driving pressure and intrinsic PEEP. These findings are indirect signs of lungs in a better position in pressure/volume curve, suggesting that the addition of a low level of PEEP improves respiratory mechanics. These findings may be measured with usual mechanical ventilators and anesthesia machines, analyzing respiratory system mechanics after an inspiratory and expiratory hold. Future studies in infants are needed to address respiratory mechanics during anesthesia, ideally in a specific age group and pathologies with high-risk postoperative complications. A better understanding of respiratory system mechanics in children during general anesthesia may lead to a better titration of mechanical ventilation, preventing VILI.

Additional files

Additional file 1: Respiratory mechanics measurements. Panel A shows Respiratory mechanics measurement protocol. Panel B shows and illustration of Airway Pressure versus time and flow versus time curves during inspiratory and expiratory breathhold. The components of work of breathing, elastic and threshold are represented. (JPG 2451 kb)

Additional file 2: Formulas for estimation of lung mechanics in quasi - static conditions. (DOCX 15 kb)

Additional file 3: Correlations between changes in respiratory parameters and age and ideal body weight. (DOCX 15 kb)

Abbreviations

ARDS: Acute respiratory distress syndrome; C_{RS}: Compliance respiratory system; CT: Computed tomography; EELV: End expiratory lung volume; iPEEP: Intrinsic positive pressure at the end of exhalation; K_{TE}: Expiratory time constant; K_{TI}: Inspiratory time constant; MV: Mechanical ventilation; P_{aw}: Airway pressure; PEEP: Positive pressure at the end of exhalation; PIP: Peak inspiratory pressure; P_{PL}: Plateau pressure; Q_E: Maximum expiratory flow; Q_I: Maximum inspiratory flow; RawE: Resistance expiratory airway; RawI: Resistance inspiratory airway; RR: Respiratory rate; tPEEP: Total positive pressure at the end of exhalation; VILI: Ventilator induced lung injury; V_T: Tidal volume; ZEEP: Positive pressure at the end of exhalation set at 0 cmH₂O; ΔP: Driving pressure

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Availability of data and materials

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials. Raw data generated cannot be publicly available due to concerns of privacy of research participants, but may be available from the corresponding author FD on request.

Authors' contributions

Study design: PC, SG, FC, JM, RH, FD; Measurements of respiratory mechanics: SG, FC, JM, RH; Statistic analysis: PC, BE, FD, SG; Writing the manuscript: PC,

SG, BE, FD; Review of the manuscript: All authors. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Institutional Review Board at Centro Hospitalario Pereira Rossell approved the study (#2852015).

Written informed consent to participate was obtained from the parents/guardians after preanesthetic interview by the PI of the study.

Consent for publication

Written consent was obtained from caregivers of included patients.

Competing interests

The authors declare that they have no competing interests.

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