



# Effect of Equal Ratio Ventilation on Respiratory Mechanics and Oxygenation During Volume-Controlled Ventilation in Pediatric Patients

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**Purpose:** Children have few small alveoli, which reduce lung compliance; in contrast, their cartilaginous rib cage makes their chest wall highly compliant. This combination promotes lung collapse. Prolonged inspiratory to expiratory (I:E) ratio ventilation is used to optimize gas exchange and respiratory mechanics in surgery. However, the optimal ratio is unclear in children. We hypothesized that, compared to a 1:2 I:E ratio, a 1:1 I:E ratio would improve dynamic compliance and oxygenation, and affect the peak airway pressure in pediatric patients undergoing surgery.

**Materials and Methods:** Forty-eight patients aged  $\leq 6$  years who were scheduled to undergo surgery under general anesthesia with an arterial line were randomly allocated to receive 1:1 (group 1:1) or 1:2 (group 1:2) I:E ratio ventilation. Airway pressure, respiratory system compliance, and arterial blood gas analyses were compared between groups immediately after induction (T0), 30 min after induction (T1), 60 min after induction (T2), immediately after surgery (T3), and on arrival at the post-anesthesia care unit (T4).

**Results:** Peak and plateau airway pressures were significantly lower in group 1:1 than in group 1:2 at T1 ( $p=0.044$  and  $0.048$ , respectively). The dynamic and static compliances were significantly higher in group 1:1 than in group 1:2 at T1 ( $p=0.044$  and  $0.045$ , respectively). However, the partial pressure of oxygen did not significantly differ between groups.

**Conclusion:** Compared to a 1:2 I:E ratio, a 1:1 I:E ratio improved dynamic compliance and lowered the peak airway pressure without complications in pediatric patients. Nevertheless, our results do not support its use solely for improving oxygenation.

**Key Words:** Blood gas analysis, exhalation, inhalation, pediatrics, positive pressure breathing, respiratory mechanics

## INTRODUCTION

Prolonged inspiratory to expiratory (I:E) ratio ventilation is a strategy to improve arterial oxygenation by increasing the mean

airway pressure (Pmean).<sup>1</sup> After it was introduced to treat patients with acute respiratory distress syndrome,<sup>1</sup> its use has been expanded to general anesthesia for surgeries in patients with deteriorated respiratory mechanics and oxygenation.<sup>2-5</sup> Previous studies demonstrated an increase in respiratory system compliance and improved oxygenation in equal I:E ratio ventilation (1:1 I:E ratio) compared to conventional I:E ratio ventilation (1:2 I:E ratio).<sup>4,6,7</sup>

Compared to older children and adults, neonates and younger children have fewer and smaller alveoli, which reduces lung compliance. In contrast, their cartilaginous rib cage makes the chest wall highly compliant; hence, it has no force to oppose the inward elastic recoil of the lungs. This combination promotes lung collapse during inspiration and a relatively low residual lung volume on expiration.<sup>8,9</sup> Due to these respiratory fea-

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tures, a specific ventilator strategy may be needed in children undergoing surgery under general anesthesia.

To improve the compliance of respiratory system and arterial oxygenation, equal I:E ratio ventilation is potentially favorable in pediatric patients relative to conventional I:E ratio ventilation as it resembles normal breathing in infants.<sup>10</sup> However, no studies have evaluated equal I:E ratio ventilation in pediatric patients undergoing surgery under general anesthesia. Therefore, this study aimed to compare the respiratory system and arterial oxygenation during surgery of equal I:E ratio ventilation with conventional I:E ratio ventilation in pediatric patients. The primary objectives included compliances of respiratory system, airway pressures, and arterial partial pressure of oxygen (PaO<sub>2</sub>).

## MATERIALS AND METHODS

### Study population

This was a prospective single-blinded randomized trial. The study was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System, Seoul, Korea (4-2017-0477) and registered at <https://cris.nih.go.kr> (KCT 0005504). Written informed consent was obtained from the guardians of all participants. Pediatric patients aged ≤6 years who were scheduled to undergo surgery with general anesthesia and an arterial line were included in this study. The exclusion criteria comprised patients with pulmonary disease or an anatomical anomaly associated with cardiopulmonary circulation, those who refused to participate in this study, and non-Korean patients.

Participants were randomly allocated to one of the two following groups in a 1:1 allocation ratio: the equal I:E ratio ventilation group (Group 1:1) and the conventional I:E ratio ventilation group (Group 1:2). Group allocations were generated using R 3.4.0 (Vienna, Austria; <http://www.R-project.org/>) and concealed in a sealed, opaque envelope. The envelope was opened immediately before the induction of anesthesia by HYK. The in-room anesthesiologist was aware of the allocated group, while the participants, guardians, caregivers in the post-anesthesia care unit (PACU) or general ward, and data analysts were blinded to the allocated group.

### Anesthesia and intraoperative monitoring

After participants entered the operating room without premedication, standard monitoring including pulse oximetry, electrocardiography, and non-invasive blood pressure monitoring was performed. After the induction of anesthesia with propofol 2 mg/kg, fentanyl 1 mcg/kg, and rocuronium 0.8 mg/kg, endotracheal intubation was conducted with a cuffed tube of appropriate size. Mechanical ventilation (Primus, Drägerwerk AG & Co., Lübeck, Germany) was started in volume-controlled mode with a fraction of inspired oxygen (FiO<sub>2</sub>) of 0.5, tidal volume of 8 mL/kg based on actual body weight, inspiratory pause of 10%,

and fresh gas flow of 2 L/min. The respiratory rate was initiated at 20–40 breaths/min depending on the patient's age and adjusted to maintain an end-tidal carbon dioxide (ETCO<sub>2</sub>) of 35–40 mm Hg. No external positive end-expiratory pressure (PEEP) was applied. According to the allocated group, a 1:1 or 1:2 I:E ratio was maintained during mechanical ventilation. After intubation, an arterial line was inserted at the radial or femoral artery to monitor continuous blood pressure and to obtain arterial blood gas analysis (ABGA). Depending on the surgery type, a central venous catheter was inserted at the jugular or femoral vein if necessary. The end of anesthesia induction was defined as the time at which all arterial and venous catheterizations were complete.

Anesthesia was maintained using sevoflurane (1.5–2.5 Vol%) and infusions of remifentanyl (0.03–0.1 mcg/kg/min) and rocuronium (5 mcg/kg/min). Body temperature was maintained at >36.0°C using a forced air warming device. Arterial blood pressure was adjusted to remain within 20% of the baseline value. If the arterial blood pressure dropped below 20% of the baseline value, ephedrine (0.1 mg/kg) was injected. If the heart rate dropped to <60 bpm, atropine (0.02 mg/kg) was injected. The intraoperative blood volume was managed with crystalloid (Plasma solution A<sup>®</sup>; CJ, Seoul, Korea) and/or colloid (Volyte<sup>®</sup>, Fresenius Kabi GmbH, Bad Homgurg, Germany) to maintain euolemia. Packed red blood cells, fresh frozen plasma, and platelet concentrations were administered when the haemoglobin level was <8 g/dL, international normalized ratio of prothrombin time was >1.5, and platelet count was <50000 μL, respectively.

After the end of surgery, the patient was extubated and transferred to the PACU. In the PACU, the patient was examined using portable chest radiography and transferred to the general ward when the modified Aldrete score was ≥9 points.<sup>11</sup>

### Data collection

Patient demographics, the type of operation, the durations of anesthesia, the use of ephedrine, desaturation during surgery (peripheral pulse oximetry saturation of <95%), the amount of administered crystalloids, transfusions, bleeding, and urine output, and the duration of PACU stay were recorded and analyzed. The presence of postoperative atelectasis (nonspecific small areas of opacity) and pulmonary edema (appearance of Kerley's B-line) was determined based on chest radiography. During the initial 3 days postoperatively, all respiratory events including dyspnea, pneumonia, and re-intubation were recorded.

Respiratory mechanics were recorded at four time points during surgery: immediately after induction (T1), 30 min after induction (T2), 60 min after induction (T3), and at the end of surgery (T4). Respiratory mechanics included peak airway pressure (P<sub>peak</sub>), plateau airway pressure (P<sub>plt</sub>), P<sub>mean</sub>, dynamic compliance (C<sub>dyn</sub>), static compliance (C<sub>stat</sub>), ETCO<sub>2</sub>, minute ventilation, and respiratory rate. C<sub>dyn</sub> and C<sub>stat</sub> were calculated using the following formula:

$C_{dyn} \text{ (mL/cmH}_2\text{O/kg)} = \{\text{expiratory tidal volume (mL)} / [\text{P}_{peak} \text{ (cmH}_2\text{O)} - \text{PEEP (cmH}_2\text{O)}]\} / \text{kg}$

$C_{stat} \text{ (mL/cmH}_2\text{O/kg)} = \{\text{expiratory tidal volume (mL)} / [\text{P}_{plt} \text{ (cmH}_2\text{O)} - \text{PEEP (cmH}_2\text{O)}]\} / \text{kg}$

ABGAs, hemodynamics, and body temperature were recorded at five time points: immediately after induction (T1), 30 min after induction (T2), 60 min after induction (T3), at the end of surgery (T4), and at PACU arrival (T5). ABGAs included pH, arterial partial pressure of carbon dioxide ( $\text{PaCO}_2$ ),  $\text{PaO}_2$ , base excess, hemoglobin, and lactic acid. Hemodynamic data included arterial mean blood pressure, heart rate, and pulse pressure variation.

### Statistical analysis

Sample size was calculated using G power 3.1 (Franz Faul, Germany; <http://www.gpower.hhu.de/>). The primary endpoint was  $C_{dyn}$ . A previous study reported that the mean  $\pm$  standard de-

viation of  $C_{dyn}$  was  $0.67 \pm 0.13 \text{ mL/cmH}_2\text{O/kg}$  in 20 mechanically ventilated pediatric patients after cardiac surgery.<sup>12</sup> Assuming that a difference of 0.11 (approximately 10% change) is meaningful, 22 patients were required per group with a type I error of 0.05 (two-tailed) and a power of 0.8. Considering a drop-out rate of 10%, 24 patients were required per group.

All variables are presented as mean  $\pm$  standard deviation, median (interquartile range), or as a number (frequency). Categorical variables were analyzed using the chi-square test or Fisher's exact test. Continuous variables were analyzed using the Mann-Whitney U test or an independent two-sample Student's t test according to normality. Repeated measure variables were corrected by Bonferroni correction to adjust for multiple comparisons.  $p < 0.05$  was considered statistically significant. Statistical analyses were performed using SPSS version 25.0 for Windows (IBM Corp., Armonk, NY, USA).

## CONSORT

TRANSPARENT REPORTING of TRIALS

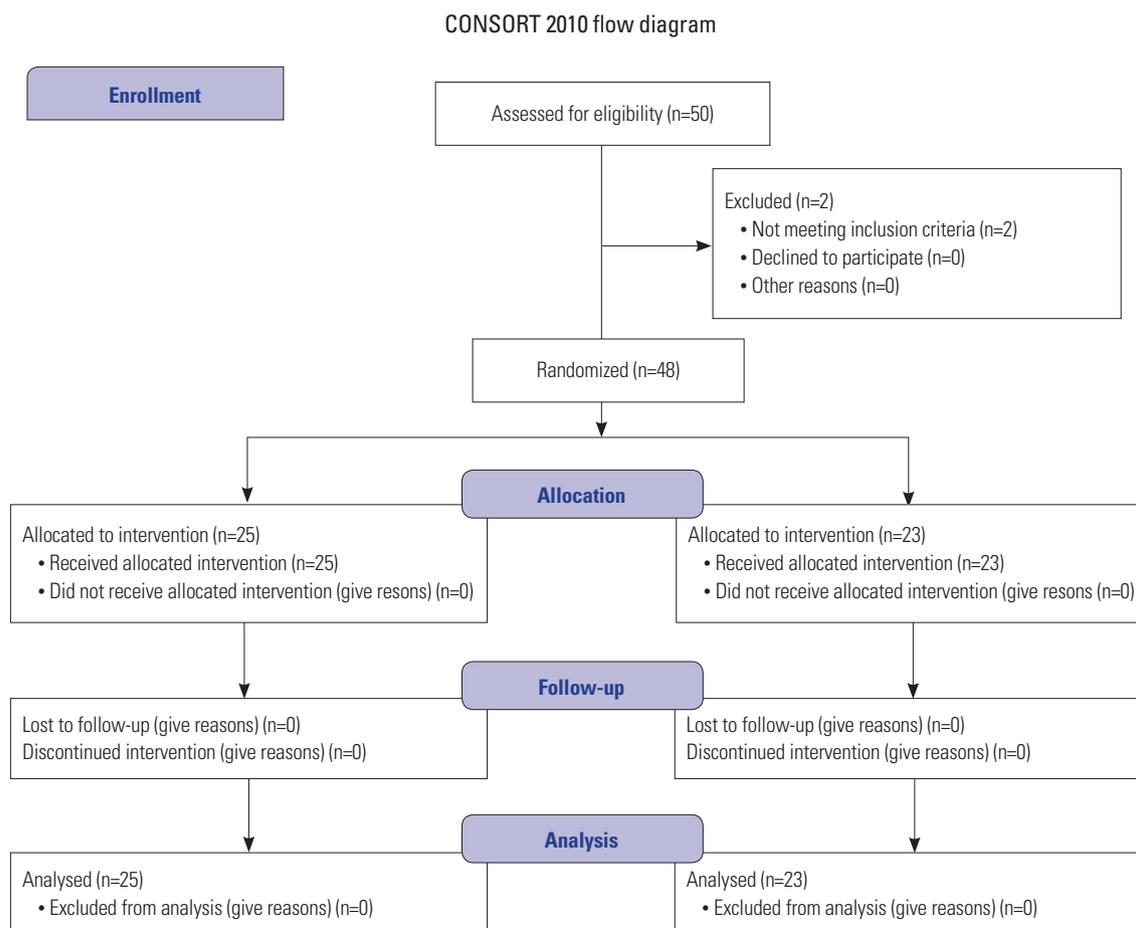


Fig. 1. CONSORT flowchart.

## RESULTS

Of 50 eligible patients, two were excluded as one had a double outlet right ventricle and the other was non-Korean. Finally, a total of 48 patients were randomly assigned to the equal and conventional ratio groups and analyzed without follow-up loss. The CONSORT flowchart is shown in Fig. 1. All patients underwent surgery in a supine position. The preoperative patient demographics and perioperative details were comparable between the two groups (Table 1).

Respiratory mechanics and ABGAs are presented in Fig. 2 and Table 2. Ppeak and Pplt were significantly lower in Group 1:1 than in Group 1:2 at 30 min after anesthetic induction (Ppeak: 14.1±2 cmH<sub>2</sub>O vs. 16.9±4.8 cmH<sub>2</sub>O, adjusted *p*=0.044; Pplt: 13.4±2 cmH<sub>2</sub>O vs. 16.4±4.9 cmH<sub>2</sub>O, adjusted *p*=0.048, respectively) (Fig. 2A and B). Pmean was higher in Group 1:1 than in Group 1:2 at all-time points, although not significantly (Fig. 2C). Cdyn and Cstat were significantly higher in Group 1:1 than in Group 1:2 at 30 min after anesthetic induction (Cdyn: 0.62±0.12 mL/cmH<sub>2</sub>O/kg vs. 0.54±0.14 mL/cmH<sub>2</sub>O/kg, adjusted *p*=0.044; Cstat: 0.65±0.13 mL/cmH<sub>2</sub>O/kg vs. 0.56±0.15 mL/cmH<sub>2</sub>O/kg, adjusted *p*=0.045, respectively). However, there were no significant differences in PaO<sub>2</sub> between the two groups at any time point. In addition, other ABGAs including ETCO<sub>2</sub>, minute ventilation, respiratory rate, pH, PaCO<sub>2</sub>, base excess, hemoglobin, and lactic acid did not significantly differ between the groups. Hemodynamic data, including arterial mean blood pressure and heart rate, and pulse pressure variation, also did not signifi-

cantly differ between groups at any time point. No patient exhibited hypothermia (body temperature <36°C).

No significant atelectasis or pulmonary edema was noted on chest-radiographs acquired immediately after surgery. However, at 1 day after surgery, cardiac arrest occurred in one patient of Group 1:2 due to suspected signs of pulmonary aspiration. The patient regained spontaneous circulation after cardiopulmonary resuscitation. The remaining patients were discharged after an uneventful postoperative course.

## DISCUSSION

In this study, we evaluated the respiratory mechanics and arterial oxygenation in equal I:E ratio ventilation compared to conventional I:E ratio ventilation in pediatric patients aged ≤6 years. We found that equal I:E ratio ventilation reduced Ppeak and Pplt and increased respiratory system compliance at 30 min after anesthetic induction compared to the conventional I:E ratio ventilation. However, equal I:E ratio ventilation did not improve arterial oxygenation compared to conventional I:E ratio ventilation.

A typical I:E ratio for mechanical ventilation has a longer expiratory phase than inspiratory phase, such as 1:2, 1:2.5, or 1:3, as these ratios resemble normal physiologic breathing.<sup>13</sup> Prolonged I:E ratio ventilation, such as 1:1, 1.5:1, or 2:1, was introduced in the critical care field,<sup>1</sup> and has expanded to the surgical field in patients with reduced oxygenation such as those undergoing one-lung ventilation,<sup>2,6,14</sup> laparoscopic surgery,<sup>3,4</sup> and cardiac surgery.<sup>5</sup> The main mechanism of prolonged I:E ratio ventilation is to increase Pmean by increasing the time spent at high inspiratory airway pressure on the respiratory cycle.<sup>13</sup> Pmean correlates with mean alveolar pressure, which acts by inflating the alveoli to oppose the inward elastic recoil of the lungs. Therefore, a higher Pmean could improve lung compliance and arterial oxygenation via recruitment of collapsed lung tissue.

Infants and children are vulnerable to lung collapse and have reduced respiratory system compliance.<sup>8,9</sup> Therefore, specific ventilation strategies have been introduced in the treatment of pediatric patients to protect the lungs and improve arterial oxygenation.<sup>12,15,16</sup> These strategies aim to reduce lung injury caused by high Ppeak and prevent repetitive opening and closing of the alveoli.<sup>10</sup> Equal I:E ratio ventilation may be a good strategy in pediatric patients in terms of reducing Ppeak and increasing Pmean while minimizing lung injury, compared to other aggressive oxygenation strategies such as high PEEP or inspiratory pressure. In addition, equal I:E ratio ventilation resembles normal breathing in infants with a high respiratory rate and short expiratory times.<sup>10</sup>

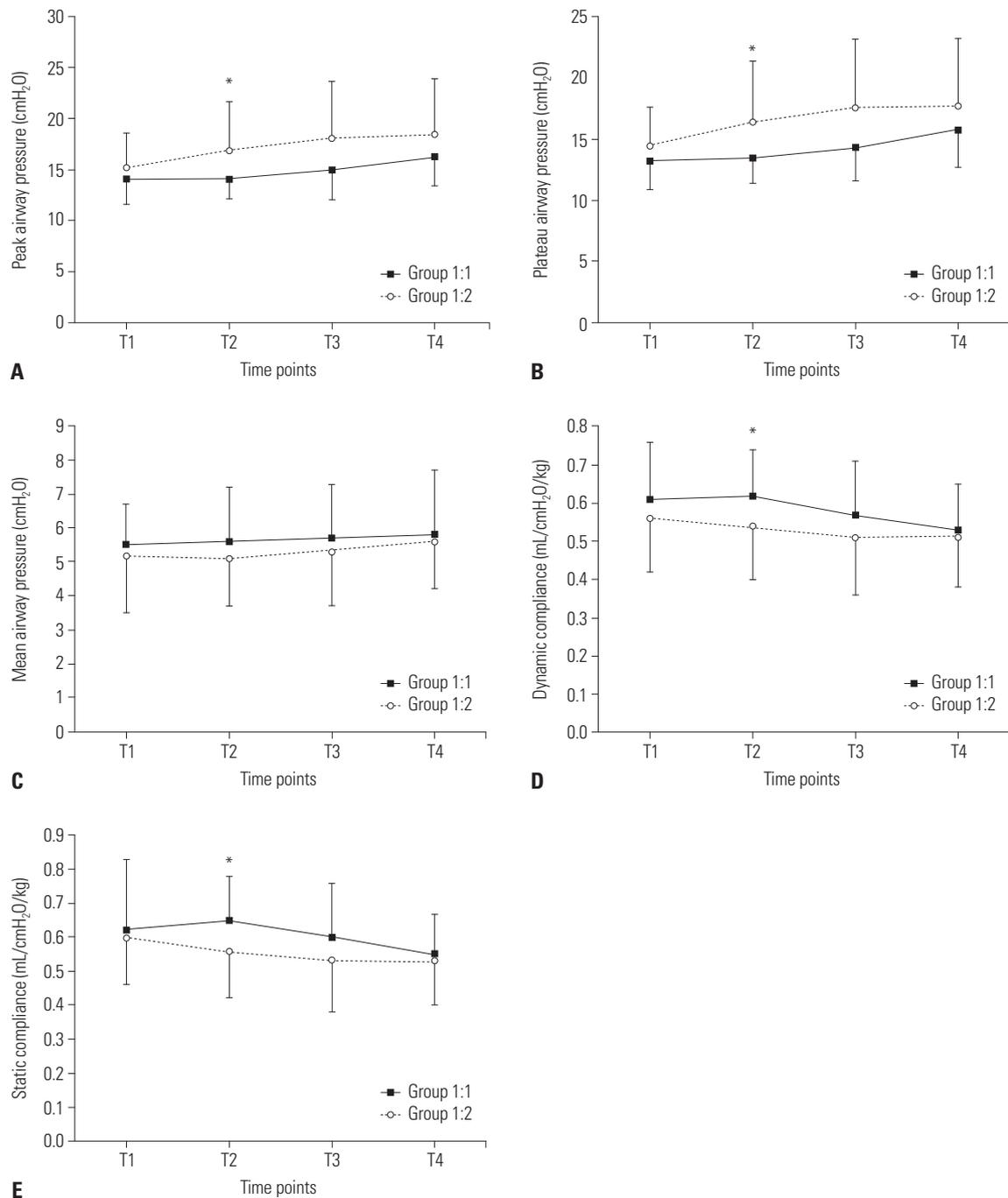
The current study revealed that equal I:E ratio ventilation improved respiratory system compliance while lowering Ppeak and Pplt at 30 min after anesthesia induction. However, the im-

**Table 1.** Patients Characteristics and Perioperative Details

	Group 1:1 (n=25)	Group 1:2 (n=23)	<i>p</i> value
Age, month	14.9 (10.8–42.7)	13.2 (7.0–26.0)	0.194
Sex (male)	15 (60)	12 (52)	0.585
Height, cm	86±15	81±16	0.255
Weight, kg	11 (9–15)	10 (8–14)	0.160
Operation name			0.716
Cranioplasty	15 (60)	14 (61)	
Brain tumor removal	8 (32)	7 (30)	
Distraction device removal	2 (8)	1 (4)	
Third ventriculotomy	0	1 (4)	
Anesthesia time, min	310±89	309±114	0.958
Ephedrine	2 (8)	0	0.490
Desaturation (SpO <sub>2</sub> <95%)	0	1 (4)	0.479
Crystalloid, mL	522±215	466±275	0.431
Packed RBC, mL	338±191	282±117	0.302
Urine output, mL	110±72	144±113	0.237
Blood loss, mL	528±319	481±349	0.632
PACU stay, min	77 (46–102)	60 (48–106)	0.733

SpO<sub>2</sub>, peripheral pulse oximetry saturation; PACU, post-anesthesia care unit; RBC, red blood cell.

Continuous variables are presented as mean±SD or median (interquartile range). Nominal variable are presented number (frequency).



**Fig. 2.** Intraoperative respiratory mechanics. (A) Peak airway pressure. (B) Plateau airway pressure. (C) Mean airway pressure. (D) Dynamic compliance. (E) Static compliance. \* $p < 0.05$ . T1, after induction; T2, 30 minutes after induction; T3, 60 minutes after induction; T4, end of surgery.

**Table 2.** Arterial Blood Gas Analyses

	T1		T2		T3		T4		T5	
	Group 1:1	Group 1:2								
pH	7.4 (0.1)	7.4 (0.0)	7.4 (0.1)	7.4 (0.1)	7.4 (0.0)	7.4 (0.0)	7.4 (0.0)	7.4 (0.0)	7.4 (0.0)	7.4 (0.1)
PaO <sub>2</sub> , mm Hg	220 (49)	215 (37)	223 (45)	215 (40)	228 (36)	218 (44)	238 (32)	231 (32)	160 (68)	172 (84)
PaCO <sub>2</sub> , mm Hg	36 (7)	34 (5)	34 (4)	35 (5)	36 (3)	36 (4)	36 (4)	37 (4)	33 (5)	31 (6)
Lactate, mmol/L	1.4 (1.0)	1.3 (0.3)	1.3 (0.7)	1.3 (0.4)	1.5 (0.8)	2.3 (4.4)	1.5 (0.7)	1.6 (0.7)	2.0 (0.5)	2.2 (1.5)
P/F ratio	450 (80)	431 (75)	452 (89)	430 (74)	454 (73)	423 (88)	476 (64)	450 (70)	359 (150)	360 (105)

T1, after induction; T2, 30 minutes after induction; T3, 60 minutes after induction; T4, the end of surgery; T5, the arrival of post-anesthesia care unit; PaO<sub>2</sub>, arterial partial pressure of oxygen; PaCO<sub>2</sub>, arterial partial pressure of carbon dioxide; P/F ratio, PaO<sub>2</sub> to fraction of inspired oxygen ratio.

Data are presented as mean (standard deviation).

proved respiratory mechanics were not maintained until the end of surgery. In addition, arterial oxygenation did not significantly differ between groups, although the equal I:E ratio group had consistently higher PaO<sub>2</sub> than did the conventional I:E ratio group. There are several possible explanations for these results. First, the relatively small sample size could have led to an underestimation of the differences between the two groups. Second, we did not apply adequate alveolar recruitment manoeuvres and PEEP. Since general anesthesia promotes atelectasis formation, adequate alveolar recruitment manoeuvres and PEEP are needed to improve lung compliance and arterial oxygenation.<sup>17</sup> Although we did not find significant atelectasis on postoperative chest radiographs, micro-atelectasis occurred during surgery. It is possible that the progression of micro-atelectasis offset the beneficial effects of equal I:E ratio ventilation. Third, FiO<sub>2</sub> and PaO<sub>2</sub> showed no linear correlation with one another, and the rate of PaO<sub>2</sub> increase was slowed by the increase in FiO<sub>2</sub>.<sup>18</sup> Therefore, it is possible that the relatively high PaO<sub>2</sub> level at an FiO<sub>2</sub> of 0.5 offset the further improvement in arterial oxygenation by improved respiratory mechanics compared to the lower FiO<sub>2</sub>.

This study had several limitations. First, the sample size was relatively small. As a result, it was likely to be underpowered for several variables. Second, we did not measure other respiratory mechanics, such as transpulmonary pressure, lung compliance, and chest wall compliance, as these measures require esophageal pressure monitoring via an esophageal balloon catheter. Third, we initiated data collection for respiratory mechanics and ABGAs after all lines were assessed in consideration of patient safety. Therefore, a considerable amount of time was required to record the data from intubation. Since we could not measure the true baseline values, we did not use statistical methods to evaluate interactions between the groups and times, such as a repeated measure analysis of variance or linear mixed model. Fourth, children's lung compliance and stiffness of rib cage increase rapidly with age.<sup>19</sup> Although there was no statistical difference in age between the two groups, even a small difference in age can affect the respiratory mechanics.

In conclusion, equal I:E ratio ventilation could be applied as an alternative ventilator strategy for pediatric patients to reduce P<sub>peak</sub> and to improve respiratory system compliance without complications, although this study did not reveal an improvement in arterial oxygenation compared to conventional I:E ratio ventilation. Further study is required to establish the beneficial effects of equal I:E ratio ventilation in vulnerable children.

## AUTHOR CONTRIBUTIONS

**Conceptualization:** Bon-Nyeo Koo. **Data curation:** Seung Yeon Choi. **Formal analysis:** Sung-Yeon Ham. **Investigation:** Hei Jin Yoon. **Methodology:** Ha Yeon Kim and Bon-Nyeo Koo. **Project administration:** Ha Yeon Kim. **Supervision:** Bon-Nyeo Koo. **Validation:** Eun Jung Kim. **Visualization:** Sung-Yeon Ham. **Writing—original draft:** Ha Yeon Kim. **Writing—review & editing:** Eun Jung Kim and Bon-Nyeo Koo. **Ap-**

**proval of final manuscript:** all authors.

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