Influence of Respiratory Gas Density on Tidal Volume During Pressure-Controlled Ventilation: A Laboratory Investigation and Observational Study in Children.

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Influence of Respiratory Gas Density on Tidal Volume during Pressure-Controlled Ventilation: a laboratory investigation and observational study in children.

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Abstract

Fluid mechanics shows that high-density gases need more energy while flowing through a endo-tracheal tube. This means that during general anesthesia, high-density gases left less energy for lung inflation under pressure-controlled ventilation (PCV). However, the impact have not been studied. This study investigated the effects of high-density anesthetic gases on tidal volume (TV) in laboratory and clinical settings.

In laboratory study, a test lung was ventilated at fixed PCV with 22 different gas compositions (density range, 1.22-2.27 kg/m^3) using an Avance® anesthesia machine. The TV of the test lung and the respiratory gas composition were recorded by a pneumotachometer. As a result, the TV of the test lung decreased as the respiratory gas density increased. In clinical study, the change in TV/body weight, accompanied by gas composition change (2% sevoflurane in oxygen and with 0-30-60% of N_2O), was recorded in 30 pediatric patients. Median TV/body weight decreased by 10% when the respiratory gas density increased from 1.41 kg/m^3 to 1.70 kg/m^3, indicating a significant between-group difference ($P<0.0001$). In both laboratory and clinical settings**,** an increase in respiratory gas density decreases the TV during PCV, and it could be well explained by the theory of fluid dynamics.

Keywords: airway resistance, anesthetic gas density, energy of gas, respiratory mechanism, tidal volume

Introduction

Lung compliance and airway resistance are known to affect the tidal volume (TV) during pressure-controlled ventilation (PCV). However, it is not widely understood how respiratory gas composition changes the actual TV of the patient, despite fixed ventilator settings. Thus, it is important for anesthesiologists to understand the factors that can cause actual TV change.

To date, some laboratory studies have shown that the gas density in the breathing system influences airway resistance [1,2]. Recent clinical studies have also found that anesthetic gases, which have higher densities than air and oxygen, increase airway resistance [3,4]. However, this phenomenon has not been well recognized because anesthetic gases have two conflicting characteristics: volatile anesthetics have a physiological bronchodilatory effect that can decrease the resistance of small airway in clinical settings, and anesthetic gases in physical nature have a higher density, which needs higher energy to flow. These characteristics can neutralize each other. To understand the TV change accompanying respiratory gas composition change during PCV, comprehensive studies are required in which the laboratory and clinical data are analyzed based on the laws of physics.

Moreover, some studies have reported that changes in the respiratory gas composition affect the accuracy of respiratory flow measurements [2,5,6], In this regard, with the progress of anesthesia machines, some anesthesia workstations have integrated gas analyzers and use the information of gas compositions to improve flow and volume monitoring so that TV measured by a built-in pneumotachometer is a closer approximation of the delivered TV. External pneumotachometers with gas analyzers have also been widely used. Therefore, to clearify the impact of the respiratory gas compositions on TV during usual PCV settings, precise data using the pneumotachometers with gas analyzers are needed.

In this study, we conducted two laboratory experiments and a clinical study to investigate the impact of respiratory gas density on TV during PCV. In the first stage of the laboratory study, we verified the accuracy of the above-referenced external pneumotachometer using a calibration syringe with various gas mixtures. In the second stage, we ventilated a test lung with the various gas mixtures delivered by an anesthesia machine under a predetermined PCV setting, and recorded the TV of the test lung and the respiratory gas compositions measured by the external pneumotachometer, while simultaneously measuring the TV displayed by the anesthesia machine without the built-in gas analyzer. In the clinical study, we ventilated the pediatric patients with three respiratory gas compositions under fixed PCV setting and measured the TV of the patients for each respiratory gas composition by the pneumotachometer.

Results

Laboratory study

First experiment

The volumes measured by the GF220R tended to decrease with an increase in the density of gas mixtures (Supplementary Table S1). The difference between the maximum and minimum measured volumes was 29.7 mL, equivalent to 2.8% of the 1050 mL syringe. To compensate this trend, the following correcting equation was used for the second experiment:

$$[TV_{actual}] = [\text{TV measured by the GF220R}] \times \frac{1050}{1061.7 - 27.5 \times [\text{density of the gas mixture at 25 °C}]} \cdots$$

equation (1)

Second experiment

Table 1 shows the TV_{actual} and TV_{Avance} with each respiratory gas composition and in each test lung setting. Figure 1 shows a scatter plot of the respiratory gas density versus the TV_{actual} and TV_{Avance}. The TV_{actual} decreased with an increase in the respiratory gas density. When the respiratory gas density was increased from 1.22 kg/m^3 to 2.27 kg/m^3, the TV_{actual} in the R0 setting decreased from 351 ± 0.68 mL to 327 ± 2.3 mL (≑6.8% decrease), and the TV_{actual} in the R50 setting decreased from 260 ± 1.5 mL to 209 ± 2.1 mL (≑20% decrease). There was a significant correlation between the respiratory gas density and TV_{actual} ($P < 0.0001$) in both test lung settings. The Pearson correlation coefficients (r) for this correlation in the R0 and R50 settings were −0.883 and −0.983, respectively.

Contrary to the relationship between the TV_{actual} and the respiratory gas density, the TV_{Avance} increased with an increase in the respiratory gas density (Table 1). When the respiratory gas density increased from 1.22 kg/m^3 to 2.27 kg/m^3, the TV_{Avance} in the R0 setting increased from 296 ± 0.52 mL to 392 ± 0.52 mL (≑32% increase), and the TV_{Avance} in the R50 setting increased from 211 ± 0.42 mL to 242 ± 0.0 mL (≑15% increase). There was also a significant correlation between the respiratory gas density and the TV_{Avance} ($P < 0.0001$). Coefficients (r) of this correlation under the R0 and R50 settings were 0.982 and 0.915, respectively.

The TV_{Avance} agreed with the TV_{actual} only at a respiratory gas density of around 1.7 kg/m^3. Furthermore, the TV_{Avance} was smaller than the TV_{actual} at respiratory gas density < 1.7 kg/m^3, and the TV_{Avance} was larger than the TV_{actual} at respiratory gas density > 1.7 kg/m^3. We found that the ratio of TV_{Avance} to the TV_{actual} increased with an increase in the respiratory gas density regardless of the resistance setting of the test lung (Figure 2). When the respiratory gas density increased from 1.22 kg/m^3 to 2.27 kg/m^3, the ratio of TV_{Avance} to the TV_{actual} at the R0 setting increased from 85 % to 120 %, and the ratio of TV_{Avance} to the TV_{actual} at the R50 setting increased from 81 % to 116 %. Moreover, there was a significant correlation between the respiratory gas density and the ratio of TV_{Avance} to the TV_{actual} ($P <$ 0.0001). Coefficients (r) of this correlation under the R0 and R50 settings were 0.968 and 0.960, respectively.

Clinical study

During the study period, 30 pediatric patients were included, and respiratory data of three respiratory gas compositions were obtained from all patients. Patient characteristics are summarized in Table 2. Figure 3 shows the mean TV_{actual}/BW of each case. The median value and interquartile range of the 30 cases in three different respiratory gas compositions are also shown in Table 2. When the respiratory gas composition was changed from 2% sevoflurane + O_2 to 2% sevoflurane + 30% N_2O + O_2, and to 2% sevoflurane + 60% N_2O + O_2 (density of 1.41-1.56-1.70 kg/m^3), the median TV_{actual}/BW decreased from 16.0 mL/kg to 15.1 mL/kg (−6%), and to 14.3 mL/kg (−11%), respectively. Wilcoxon signed-rank test showed that there were significant differences in TV_{actual}/BW between each pair of the three respiratory gas compositions ($P < 0.0001$).

Discussion

This study aimed to popularize the physical mechanism that TV of the lung changes in response to the respiratory gas composition change under a constant PCV. This phenomenon is known to medical engineers and certain anesthesiologists, and some anesthesia workstations have integrated gas analyzers to use the gas density for more accurate flow and volume monitoring. However, the degree of the impact of this phenomenon in clinical settings remained unclear. The results of our study were generally consistent with those of previous studies [5,6]. Additionally, our results indicate two important findings: First, the true TV of the lung decreased with an increase in respiratory gas density during PCV as expected, in both laboratory and clinical settings. Second, the TV measured by the flow analyzer without a compensating system (TV_{Avance}) mostly differed from the true TV of the lung (TV_{actual}).

Respiratory gas needs pressure gradient (PG) to flow in a breathing circuit because of friction and turbulence. In the inspiratory phase, a ventilator set in the PCV mode provides flow to the respiratory circuit and increases the airway pressure at the set inspiratory pressure level. When the ventilator observed greater PG during the inspiratory phase, then it regulates flow so as not to exceed the airway pressure beyond the set inspiratory pressure. Therefore, the flow rate is determined by a pressure measured by the ventilator and its feedback control algorithm. Here, the total pressure by the ventilator (P_{vent}) is divided into two portions as follows: the pressure inflating the test lung (P_{lung}) and the pressure used for flowing (ΔE). Based on the Bernoulli's principle, this state is expressed as follows:

$P_{\text{vent}} = \Delta E + P_{\text{lung}}$ ⋯ equation (2)

In the inspiratory phase, this equation can be transcribed as follows:

$P_{\text{vent}} = c_t \frac{1}{2} \rho \bar{Q}_{in}{}^2 + c_p \bar{Q}_{in}$ ⋯ equation (3)

Where c_t indicates the mean dimensionless loss coefficient during the inspiratory phase, c_p indicates the elastance coefficient of the test lung during the inspiratory phase, ρ indicates the respiratory gas density, and $\bar{Q}_{in}$ indicates mean inspiratory volume flow rate (see supplementary equation S2 for more detailed explanation). Since the ventilator of an anesthesia machine with PCV mode regulates inspiratory flow to maintain the airway pressure at the set limit using the built-in pressure sensor, the following equation relating to different gas densities (ρ_1, ρ_2) is established.

$P_{vent} = c_t \frac{1}{2} \rho_1 Q_{1in}{}^2 + c_p Q_{1in} = c_t \frac{1}{2} \rho_2 Q_{2in}{}^2 + c_p Q_{2in}$ ⋯ equation (4)

At densities of 1.21 kg/m^3 (95% air + 5% CO_2) and 2.27 kg/m^3 (30% oxygen + 53% N_2O + 12% desflurane + 5% CO_2), the TV_{actual} in the R0 setting and inspiratory pressure of 15 cmH_2O (= 1471 Pa) are substituted for ρ_1, ρ_2, Q_1, Q_2, and P_{in}, respectively, then c_t and c_p are derived as 1929224441 and 3782709, respectively. Then, ρ and TV (Q) of each respiratory gas composition and the c_t and c_p values obtained above are assigned to equation (3). Therefore, the result of the equation (3) revealed that the total integrated pressure is almost the same regardless of the respiratory gas composition (Figure 4a). In other words, a higher-density respiratory gas can generate more PG in the breathing circuit and have less pressure for inflating the test lung. The same tendency is observed at the R50 setting (Figure 4b).

Furthermore, the effect of the respiratory gas density on Q (= TV) during PCV can be derived from equation (3) as follows:

$$Q = \frac{-c_p + \sqrt{c_p{}^2 + 2c_t \rho \mathrm{P_{vent}}}}{c_t \rho} \quad \cdots \text{ equation (5)}$$

where, c_t and c_p are specific constants and were given as mentioned above.

Figure 5 shows the flow rate, pressure, and volume curves of 95% oxygen and 85% oxygen + 10% desflurane under the R50 setting of our main experiment. The peak flow rate of 95% oxygen was faster than that of 85% oxygen + 10% desflurane, whereas the pressure curves were almost the same. These data agreed with the law of fluid dynamics that flow decreased with an increase in respiratory gas density although, circuit pressure was maintained at the set inspiratory pressure.

Herein, we seek the cause of the difference between $\mathrm{TV_{actual}}$ and $\mathrm{TV_{Avance}}$. Both fixed and variable orifice differential pressure flowmeter measures the volume flow rate (Q) using the following equation:

$$\Delta P = \frac{1}{2}\rho\left(\frac{Q}{A_2}\right)^2 - \frac{1}{2}\rho\left(\frac{Q}{A_1}\right)^2 \quad \cdots \text{ equation (6)}$$

where ΔP is the PG between the upstream and downstream side of the orifice, ρ is the density of the flowing gas, A_1 is the cross-sectional area of the upstream side of the orifice, and A_2 is that of the orifice. In variable orifice differential pressure flowmeter, such as built-in Avance®, equation (6) can be expressed by the following equation (see Supplementary equation S3 for more detailed explanation):

$$Q^2 = C_{(\Delta P)}\frac{\Delta P^2}{\rho},\ Q = \sqrt{\frac{C_{(\Delta P)}}{\rho}} * \Delta P \text{ or } \Delta P = \sqrt{\frac{\rho}{C_{(\Delta P)}}} * Q \quad \cdots \text{ equation (7)}$$

where $C_{(\Delta P)}$ indicates the variable coefficient regulated by ΔP. This equation means ρ is essential to estimate Q. In our experiment, the flowmeter of Avance® cannot use the respiratory gas density (ρ_{dlv}) to correct the measured values, and instead, uses the preset density (ρ_{pst}). Thus, during ventilation with the gas density of ρ_{dlv}, the relationship between delivered flow (Q_{dlv}) and the flow measured by Avance® (Q_A) can be expressed by the following equation:

$$Q_{dlv} = \sqrt{\frac{C_{(\Delta P)}}{\rho_{dlv}}} * \Delta P = \sqrt{\frac{C_{(\Delta P)}}{\rho_{dlv}}} * \sqrt{\frac{\rho_{pst}}{C_{(\Delta P)}}} * Q_A = \sqrt{\frac{\rho_{pst}}{\rho_{dlv}}} * Q_A \cdots \text{ equation (8)}$$

As a result, $TV_{delivered}$ ($= T_{insp} * Q_{dlv}$) and the TV_{Avance} ($= T_{insp} * Q_A$) can be expressed by the following equation:

$$TV_{delivered} = \sqrt{\frac{\rho_{pst}}{\rho_{dlv}}} * TV_{Avance} \cdots \text{ equation (9)}$$

This equation can explain the difference between the TV_{actual} and TV_{Avance} very well, and corresponded to our experimental system in which Avance® did not have a gas sampling module; hence the gas density compensation function did not work, while the compensation function of GF220R is working during laboratory and clinical studies (Figure 2).

The test lung resistance setting of 50 $cmH_2O/L/s$ in our laboratory study was assuming the pediatric patients. Spaeth et al. demonstrated that a 3.5 mm internal diameter (ID) endotracheal tube shows a non-linear relationship between flow rate and pressure gradient at a gas flow of 0.3 L/s, and pressure drop at this flowrate is approximately 17 cmH_2O [8]. This means that a 3.5 mm ID endotracheal tube has the resistance of 57 $cmH_2O/L/s$ at a gas flow of 0.3 L/s, which nearly matches our test lung resistance setting of 50 $cmH_2O/L/s$.

As for the flow state, the flow in a circular tube can be classified into laminar and turbulent. PG is proportional to flow velocity and viscosity in laminar flow, whereas PG is proportional to the square of the flow velocity and density in turbulent flow. Considering the flow state of our experiment from the non-linear relationship, the initial flow of nearly 0.5 L/s observed in our laboratory experiment (Figure 5) indicates that turbulence flow is considered dominant at the initial flow. Therefore, most of the flow in this experiment is considered turbulent; hence, strongly influenced by gas density. Although laminar flow and turbulent flow are co-existing, it is difficult to grasp the character of the flow accurately.

In our laboratory study, the equation (5) indicates that the flow rate (Q) decreased by 6.2%, when the respiratory gas composition is changed from 2% sevoflurane + 93% oxygen + 5% carbon dioxide (mean gas density ρ = 1.472 at 25°C) to 2% sevoflurane + 60% N_2O + 33% oxygen + 5% carbon dioxide (mean gas density ρ = 1.773 at 25°C) under the stable PCV with the test lung resistance setting of 50 $cmH_2O/L/s$. Moreover, most of the patients in our clinical study were intubated with an ID of 3.5 to 4.5 cuffed tubes. Median TV_{actual} decreased by 10%, when the respiratory gas composition was changed from 2% sevoflurane + 93% oxygen to 2% sevoflurane + 60% N_2O + 33% oxygen. Comparing these results, true TV change accompanying the respiratory gas composition change can be attributed to the respiratory gas density change.

Anesthesia machines with uncompensated flow sensors can also cause discrepancies between measured and delivered TV during volume-controlled ventilation (VCV) with higher-density respiratory gas as well as PCV. This is because these anesthesia machines supply reduced inspiratory flow since the inspiratory flow sensor can falsely recognize the reduced inspiratory flow as sufficient due to larger PG caused by higher-density respiratory gas [6]. Then, the expiratory flow sensor can also falsely recognize the reduced expiratory TV as sufficient or that it has reached the target TV.

This study had several limitations. First, to eliminate the bronchodilation effect caused by anesthetic gases, TV data with other than 2% of sevoflurane was excluded. At this point, the bronchodilation effect of anesthetic gases, especially sevoflurane, was thought not to have a significant impact on TV unless when they are significantly narrowed because most of the resistance during typical ventilation conditions is the endotracheal tube. More studies are required to distinguish the density effect from the bronchodilation effect while maintaining constant sedation levels. Second, this study ignored some characteristics of the gas mixture, such as viscosity and interactions of gases, and the respiratory gas density change caused by the compression of the gas associated with airway pressure increase in the inspiratory phase. Further investigations based on the physical principles, which take these factors into account, may demonstrate a more accurate study.

The results of our study indicated two important findings. First, the true TV of the lung decreases with an increase in the respiratory gas density during fixed PCV. In other words, the addition of relatively higher-density anesthetic gases (e.g., N_2O, sevoflurane, and desflurane) can cause a greater pressure gradient, and because of that, the gases have less pressure for lung inflation, which is recognized as decreased TV. Second, if the respiratory gas density increases, the TV displayed on a flow analyzer without a calibrating system (often built-in in anesthesia machines) will increase even though the true TV decreases. Although the respiratory gas density clearly impacts the true TV of a lung, this impact has not been well-popularized. This may be because many anesthesiologists underestimate the impact of gas density, or the external flow analyzer having the gas density calibrating system is not commonly used in clinical settings due to its cumbersome procedure in use.

Methods

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Tohoku University Graduate School of Medicine (November 12, 2020 / 2020-1-727), and Registered at UMIN-CTR (UMIN000042544), November 12, 2020. (https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000048433).

Laboratory study

Anesthesia machine and anesthetic gases

This study was performed at 25 ºC, and the various gas mixtures, composed of oxygen, nitrogen, N_2O, sevoflurane, and/or desflurane, were delivered via an Avance CS® anesthesia machine (GE Healthcare, Chicago, IL) without a built-in gas analyzer. Densities of the gases used in this study at 0 and 25 ºC under atmospheric pressure and dry conditions are shown in Supplementary Table S4. The mean density of the gas mixtures used in this study at 25 ºC under atmospheric pressure and dry conditions (ATPD) is presented in Table 1. During the experiment, the gas flow and a vaporizer were regulated to achieve the target gas compositions.

First experiment

The external flow analyzer GF220R® (Nihon Kohden, Tokyo, Japan) is a fixed orifice differential pressure flowmeter with a side-stream gas analyzer that can measure the flow volume, airway pressure, TV, and respiratory gas compositions at a sampling rate of 125 Hz. Additionally, the GF220R can show TV corrected for the influence of gas density, viscosity, temperature, and pressure under ATPD.

Before the main experiment, we conducted a preliminary experiment to evaluate the accuracy of the GF220R. We manually ventilated the GF220R with 1050 mL of various gas mixtures using a calibration syringe (Minato medical science, Osaka, Japan) at 25 ºC under dry conditions and assessed the potential measurement error of the GF220R. During this experiment, intra-syringe pressure was controlled within the range of 5-20 cmH_2O to accurately simulate the situation in the main experiment. Thereafter, the TV measured by the GF220R in the following experiments were calculated offline using the correction equation derived from this preliminary experiment.

Second experiment

Figure 6 shows the experimental system used in the second experiment. A test lung with adjustable resistance and compliance (Lung simulator, model 0015001, SMS, Harlow, UK) was ventilated by the anesthesia machine at a fixed PCV setting. The GF220R was placed between the Y piece of a breathing circuit and the test lung. Respiratory gas was sampled from the side-stream port between the differential pressure flowmeter and the test lung and returned to the test lung side of the side-stream port so as not to affect the TV measurement. A small amount of CO_2 gas was injected into the test lung, and approximately 38 torr (5%) of $P_{ET}CO_2$ was maintained to recreate clinical gas compositions.

We set the following conditions for the test lung: compliance of 50 mL/cmH_2O with resistance of 0 cmH_2O/L/s (R0) and compliance of 50 mL/cmH_2O with resistance of 50 cmH_2O/L/s (R50). The test lung was ventilated by the anesthesia machine with a predetermined PCV setting as follows: a positive end-expiratory pressure (PEEP) of 5 cmH_2O, driving pressure of 15 cmH_2O, respiratory rate of 15 breaths/min, inspiratory time (T_I) of 1 s, and total fresh gas flow of 3 L/min. After attaining a stable respiratory gas composition and the ventilatory status, we simultaneously recorded the respiratory gas composition, the TV of the lung (TV_{actual}), which was measured by the GF220R and then corrected using the correction equation from the first experiment, and the TV displayed by the anesthesia machine (TV_{Avance}). The built-in variable orifice differential pressure flowmeter of the Avance® anesthesia machine without gas module was in a default setting, which used a specific preset gas density for calculating TV values under ATPD. The compliance test for a respiratory circuit used in this study was conducted before the experiments, and the compensation system of the Avance® for the compression volume was active during all the experiments, to minimize the effect of complession volume on TV_{Avance}[7]. Ten consecutive TVs were recorded for each respiratory gas composition at each test lung setting (R0 and R50).

Clinical study

After receiving approval from the Ethics Committee of Tohoku University Graduate School of Medicine, this protocol was registered at UMIN-CTR and implemented from November 2020 to January 2021. Written documentation of informed consent was obtained from the parents of all study participants. This prospective observational study was conducted at Tohoku University Hospital, and patients aged 1-12 years undergoing elective surgery under general anesthesia, with PCV via cuffed endotracheal tube, at the hospital were considered for participation in this study. Exclusion criteria of this study were as follows: presence of respiratory disease, difficult airway, and a risk of malignant hyperthermia.

Ventilatory measurement was performed during the stable period between tracheal intubation and skin incision. During the measurement, anesthesia was maintained with propofol, fentanyl, and remifentanil, and rocuronium was used to eliminate spontaneous breathing. Participants were ventilated by the Avance CS® anesthesia machine. The ventilator settings were as follows: a fixed PEEP of 5 cmH_2O; driving pressure, 10 or 15 cmH_2O; respiratory rate, 15 breaths/min; inspiratory-to-expiratory time ratio, 1:2; and total fresh gas flow, 3 L/min. After attaining a stable target respiratory gas composition and stable ventilatory status, we simultaneously recorded the respiratory gas composition, end-tidal carbon-dioxide tension, and 10 consecutive TV_{actual} and TV_{Avance}. To eliminate the influence of the bronchodilation effect of anesthetic gases on airway resistance, we maintained the end-tidal concentration of sevoflurane at 2% during the measurement periods. The target respiratory gas compositions were as follows: 2% sevoflurane + O_2, 2% sevoflurane + 30% N_2O + O_2, and 2% sevoflurane + 60% N_2O + O_2.

Data analysis

Data analyses were performed using Excel ver. 16 (Microsoft Corp., WA) and JMP Pro 15 (SAS Institute Inc., NC). In the laboratory study, the measured TVs are presented as mean ± standard deviation (SD). The relationships between the respiratory gas density and the two different TVs (TV_{actual} and TV_{Avance}) were analyzed by correlation analysis. In the clinical study, TV_{actual} per body weight (TV_{actual}/BW) data obtained from each participant were presented as mean ± SD. Wilcoxon signed-rank test was used to evaluate a difference of TV_{actual}/BW among the three respiratory gas compositions. $P <$ 0.05 was considered statistically significant.

It was calculated that 24 pairs of data set were needed to demonstrate 6% difference between TV_{actual}/BW of ventilation with 2% sevoflurane + O_2 and with 2% sevoflurane + 60% N_2O + O_2, when mean TV_{actual}/BW, 1 SD, statistical power, and alpha error were set to 10 mL/kg, 10% of TV_{actual}/BW, 80% (0.8), and 5% (0.05), respectively.

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Declarations

Authors' contributions Conceptualization: H.T., Y.F. and S.K.; Methodology: K.T., H.T. and Y.E.; Formal analysis and investigation: K.T., H.T., K.K., and T.I.; Writing - original draft preparation: K.T. and H.T.; Supervision: H.T., Y.E. and M.Y. All authors reviewed the manuscript.

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Consent to participate: Written informed consent was obtained from the parents.

Consent for publication: Written informed consent was obtained from the parents regarding publication of their children’s data and photographs.

Figure legends

Fig. 1 A scatter plot of the respiratory gas density versus the TV of the lung (TV_{actual}) or TV displayed by the anesthesia machine (TV_{Avance}) under two test lung settings during stable pressure-controlled ventilation at predetermined settings. The vertical axis is the TVs and the horizontal axis is the respiratory gas density. Filled circles with black lines and open circles with gray lines indicate TV_{actual} with linear approximation lines in R0 and R50, respectively. Filled triangles with dashed black lines and open triangles with dashed gray lines indicate the TV_{Avance} in R0 and R50, respectively.

Fig. 2 Plot of the ratio of the TV displayed by the anesthesia machine (TV_{Avance}) to the TV of the lung (TV_{actual}) under two test lung settings during pressure-controlled ventilation of the predetermined settings. The vertical axis is the ratio of TV_{Avance} to the TV_{actual} and the horizontal axis is the respiratory gas density. Filled circles with black lines and open circles with gray lines indicate the ratio of TV_{Avance} in the test lung setting at resistance of 0 $cmH_2O/L/s$ (R0) and 50 $cmH_2O/L/s$ (R50), respectively

Fig. 3 Line graph showing the means ± standard division of the TV per body weight (TV/BW) of each clinical case recorded at three respiratory gas compositions. Left, center and right side of line graph indicate respiratory gas composition of 2% sevoflurane + O_2, 2% sevoflurane + 30% N_2O + O_2 and 2% sevoflurane + 60% N_2O + O_2, respectively. Box plot shows the lower quartile, the median (cross marks), and the upper quartile of the 30 cases at each respiratory gas composition. The vertical axis indicates the TV/BW mL/kg, and the horizontal axis indicates the respiratory gas compositions

Fig. 4 The proportion of energy consumed in the inspiratory limb (ΔE) and the energy spent to inflate the test lung (P_{out}) for each respiratory gas composition in the test lung setting at a resistance of (**a**) 0 $cmH_2O/L/s$ and (**b**) 50 $cmH_2O/L/s$. The vertical axis is the percentage of each energy, and the horizontal axis is the respiratory gas density. Black and gray parts of the bar indicate ΔE and P_{out}, respectively

Fig. 5 The flow, pressure, and volume curves obtained in the second experiment of the laboratory study. The three curves on the left were obtained during pressure-controlled ventilation with 95% oxygen, and the three curves on the right were obtained during pressure-controlled ventilation with 85% oxygen + 10% desflurane

Fig. 6 The experimental system. A test lung was ventilated by Avance under stable predetermined pressure-controlled ventilation (PEEP = 5 cmH_2O, driving pressure = 15 cmH_2O, T_I = 1 s, and RR = 15 min^{-1}). The Flow analyzer GF220R was placed between the Y piece of the breathing circuit and the test lung. Carbon dioxide gas was injected into the test lung and was maintained at an end-tidal carbon dioxide tension of approximately 38 Torr (5%)

Table 1 Mean density of each respiratory gas composition at 25 ˚C under atmospheric pressure and dry conditions and the TV of the lung (TV_{actual}) and TV displayed by the anesthesia machine (TV_{Avance}) (mean ± standard division) in the second experiment with each respiratory gas composition and under each test lung setting.

Gas	**Gas composition**																					
N_2 (%)	74	65	45	25	15	5																
O_2 (%)	21	30	50	70	80	90	95	90	80	70	93	50	91	90	30	89	85	30	30	83	30	30
N_2O (%)								5	15	25		45			65			60	59		55	53
S (%)											2		4									
D (%)														5		6	10	5	6	12	10	12
CO_2 (%)	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean density (kg/m^3)	1.216	1.228	1.260	1.293	1.310	1.326	1.334	1.359	1.410	1.460	1.472	1.561	1.609	1.612	1.661	1.668	1.891	1.914	1.965	2.002	2.167	2.268
TV_{actual} in R0 (mL)	351 ±0.68	350 ±1.9	345 ±1.0	342 ±1.7	341 ±1.1	343 ±0.43	345 ±1.5	339 ±1.0	340 ±1.0	339 ±1.1	335 ±2.0	336 ±1.1	338 ±1.7	330 ±1.8	327 ±1.3	330 ±1.4	329 ±0.8	327 ±0.8	324 ±0.9	327 ±2.0	326 ±1.6	327 ±2.3
TV_{Avance} in R0 (mL)	296 ±0.52	295 ±0.74	295 ±0.48	290 ±0.42	288 ±0	300 ±0.47	306 ±0.32	308 ±0.32	300 ±0.52	305 ±0.71	323 ±0	322 ±0	332 ±0.48	334 ±0.42	337 ±0.32	336 ±1.34	350 ±0.48	362 ±0.52	366 ±0.52	355 ±0	384 ±0.52	392 ±0.52
TV_{actual} in R50 (mL)	260 ±1.5	258 ±2.1	259 ±0.9	255 ±1.1	259 ±0.8	257 ±0.7	258 ±1.0	250 ±2.1	252 ±1.9	250 ±0.9	245 ±0.7	239 ±0.7	237 ±0.7	236 ±1.0	230 ±0.3	233 ±0.7	223 ±0.5	219 ±1.0	219 ±0.5	219 ±1.0	211 ±1.3	209 ±2.1
TV_{Avance} in R50 (mL)	211 ±0.42	210 ±0.53	209 ±0.48	205 ±0	206 ±0	215 ±0.48	220 ±0	216 ±0.42	212 ±0.42	212 ±0.42	226 ±0.67	221 ±0	227 ±0.42	228 ±0.52	227 ±0.52	227 ±0	227 ±0.32	234 ±0.42	238 ±0	228 ±0	240 ±0.48	242 ±0

S = sevoflurane; D = desflurane; R0 and R50 = test lung settings with resistance of 0 $cmH_2O/L/s$ and 50 $cmH_2O/L/s$, respectively.

Table 2 Characteristics of patients

Age (y), median [IQR]		1 [1-5]
Sex (male/female)		20/10
Height (cm), median [IQR]		85 [72-110]
Weight (kg), median [IQR]		10.3 [9.1-20.5]
ASA physical status, n (%)	1	28 (93%)
	2	2 (7%)
ETT ID (mm), n (%)	3.0	3 (10%)
	3.5	4 (13%)
	4.0	15 (50%)
	4.5	3 (10%)
	5.0	5 (17%)
Driving pressure (cmH$_2$O)	10	15 (50%)
	15	15 (50%)
Gas composition	**Density (kg/m^3)**	**TV$_{actual}$/BW (mL/kg), median [IQR]**
2% sevoflurane + O$_2$	1.41	16.0 [12.6-20.4]
2% sevoflurane + 30% N$_2$O + O$_2$	1.56	15.1 [11.8-19.5]
2% sevoflurane + 60% N$_2$O + O$_2$	1.70	14.3 [10.7-19.2]

IQR = interquartile range, ASA = American Society of Anesthesiologists, ETT ID = internal diameter of endotracheal tube, TV$_{actual}$/BW = Tidal volume of the lung per body weight

Figures

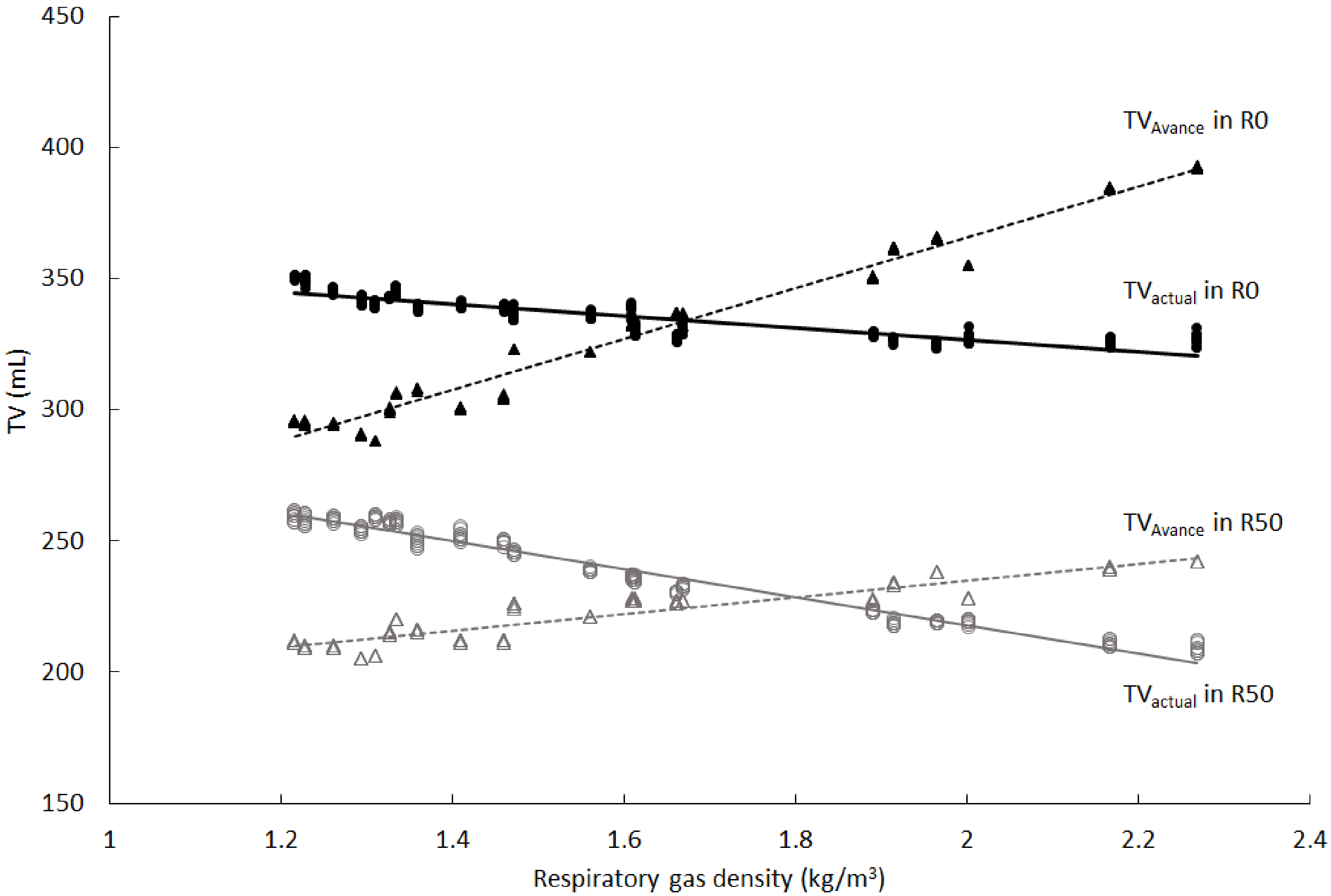


Figure 1

A scatter plot of the respiratory gas density versus the TV of the lung (TVactual) or TV displayed by the anesthesia machine (TVAvance) under two test lung settings during stable pressure-controlled ventilation at predetermined settings. The vertical axis is the TVs and the horizontal axis is the respiratory gas density. Filled circles with black lines and open circles with gray lines indicate TVactual with linear approximation lines in R0 and R50, respectively. Filled triangles with dashed black lines and open triangles with dashed gray lines indicate the TVAvance in R0 and R50, respectively.

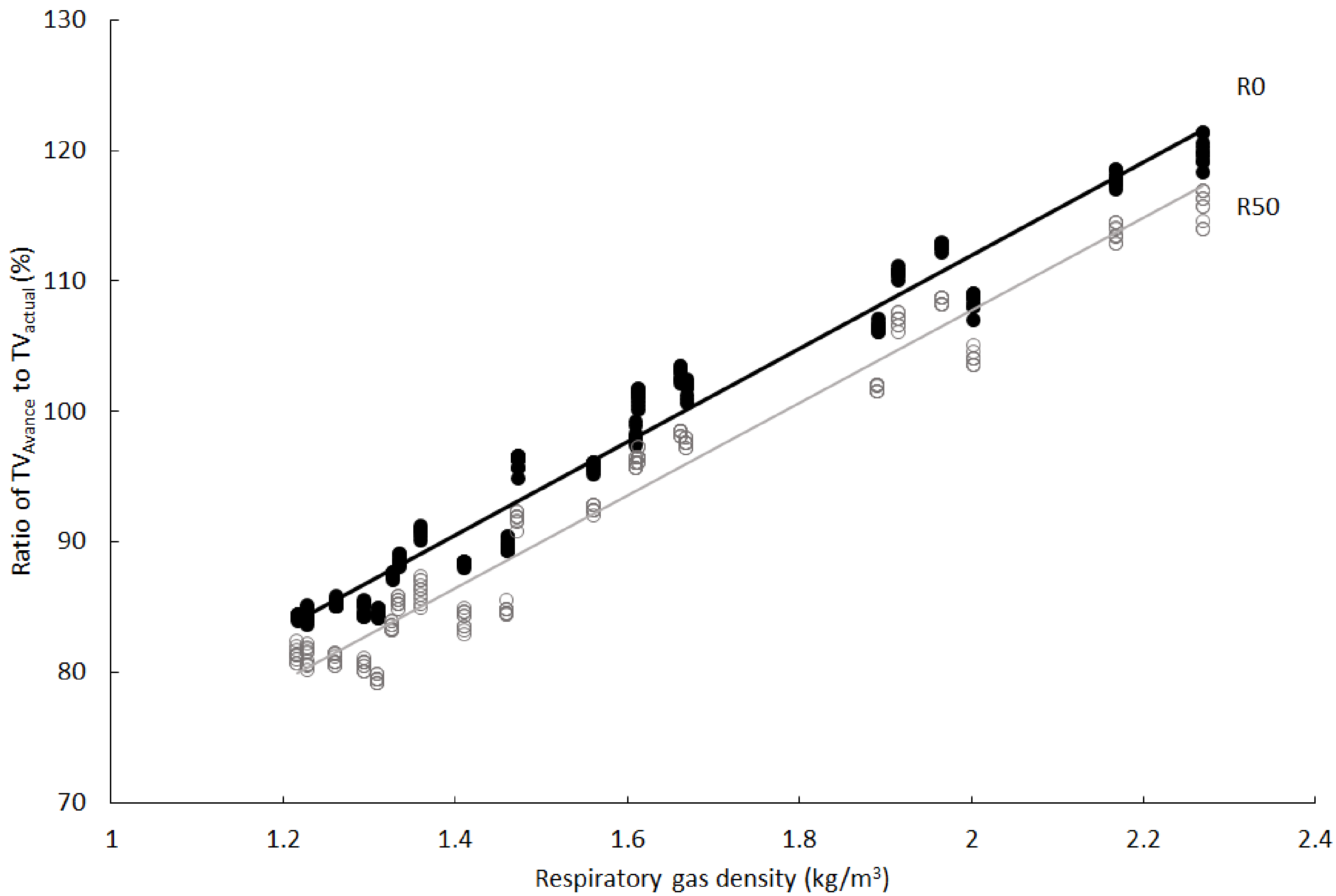
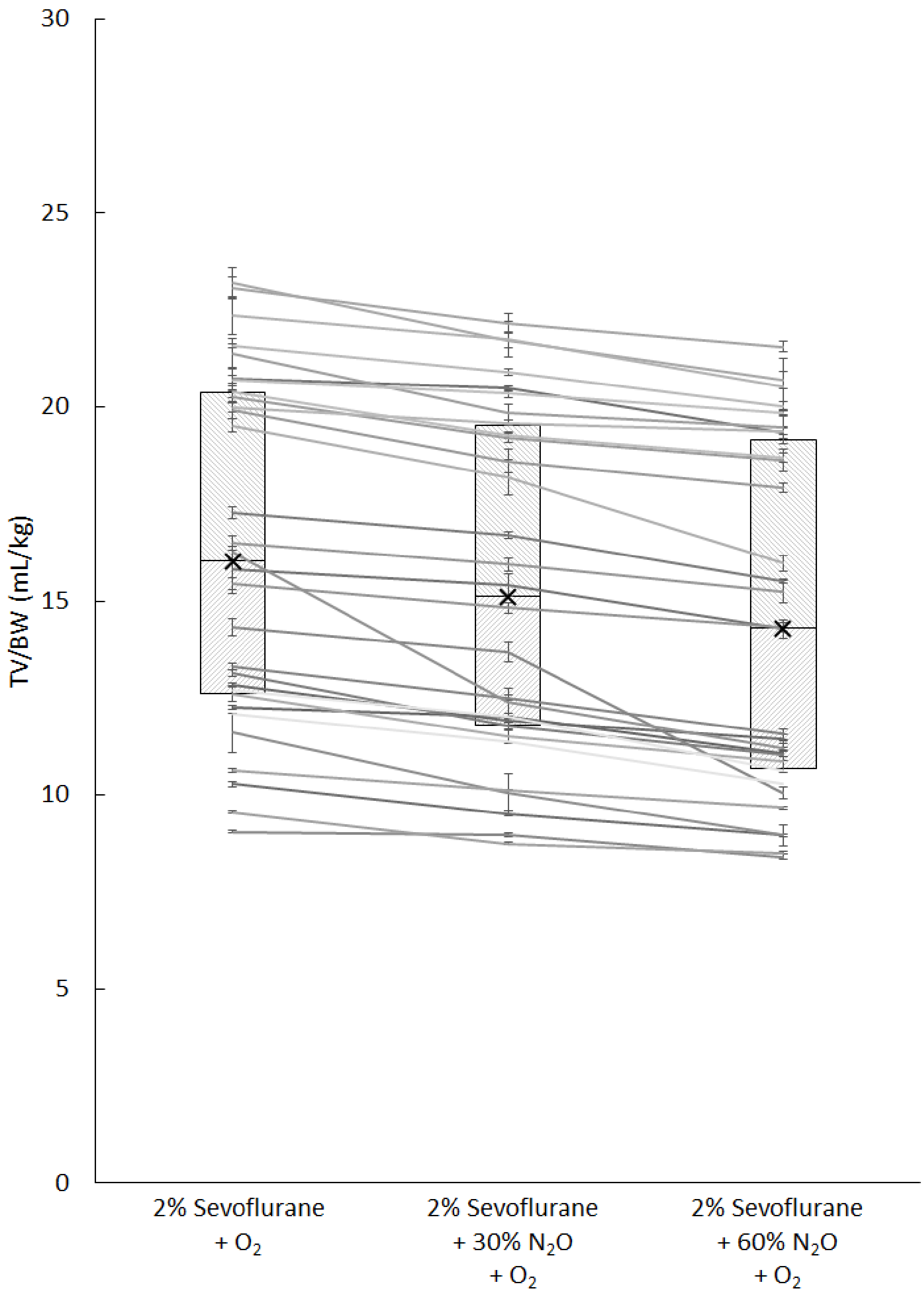


Figure 2

Plot of the ratio of the TV displayed by the anesthesia machine (TVAvance) to the TV of the lung (TVactual) under two test lung settings during pressure-controlled ventilation of the predetermined settings. The vertical axis is the ratio of TVAvance to the TVactual and the horizontal axis is the respiratory gas density. Filled circles with black lines and open circles with gray lines indicate the ratio of TVAvance in the test lung setting at resistance of 0 cmH2O/L/s (R0) and 50 cmH2O/L/s (R50), respectively



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Line graph showing the means ± standard division of the TV per body weight (TV/BW) of each clinical case recorded at three respiratory gas compositions. Left, center and right side of line graph indicate respiratory gas composition of 2% sevoflurane + O2, 2% sevoflurane + 30% N2O + O2 and 2% sevoflurane + 60% N2O + O2, respectively. Box plot shows the lower quartile, the median (cross marks), and the upper quartile of the 30 cases at each respiratory gas composition. The vertical axis indicates the TV/BW mL/kg, and the horizontal axis indicates the respiratory gas compositions

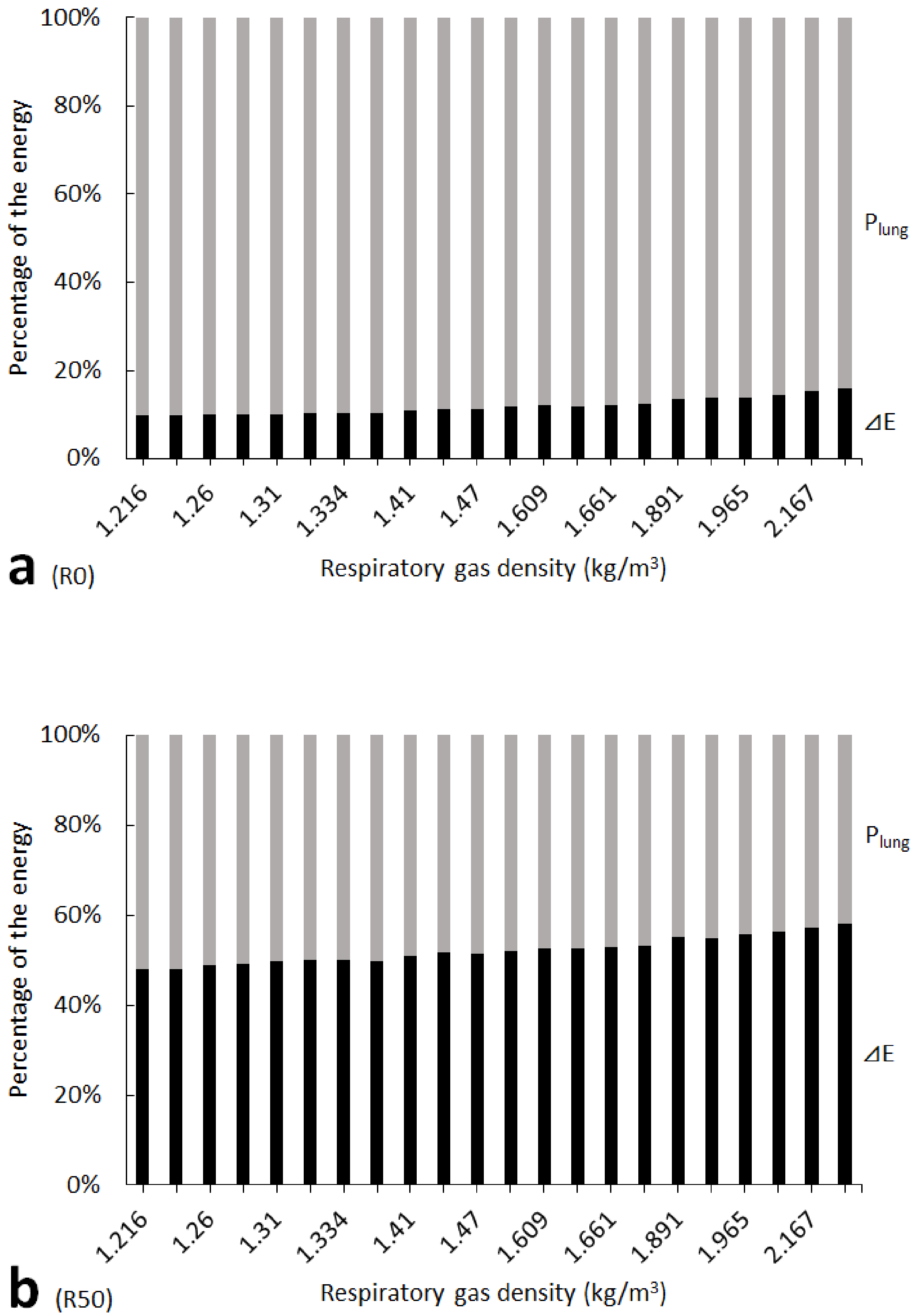


Figure 4

The proportion of energy consumed in the inspiratory limb (ΔE) and the energy spent to inflate the test lung (Pout) for each respiratory gas composition in the test lung setting at a resistance of (a) 0 cmH2O/L/s and (b) 50 cmH2O/L/s. The vertical axis is the percentage of each energy, and the horizontal axis is the respiratory gas density. Black and gray parts of the bar indicate ΔE and Pout, respectively

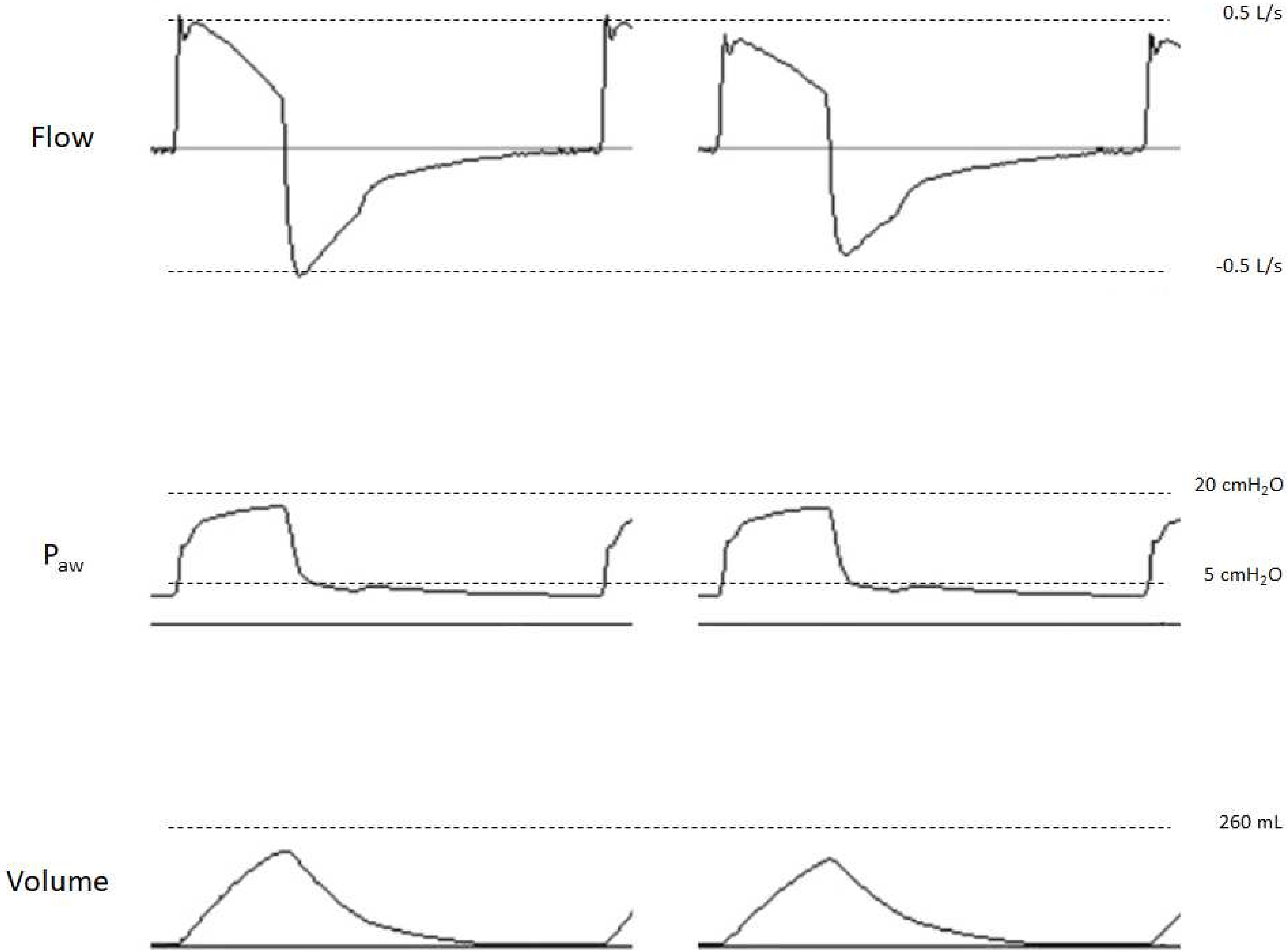
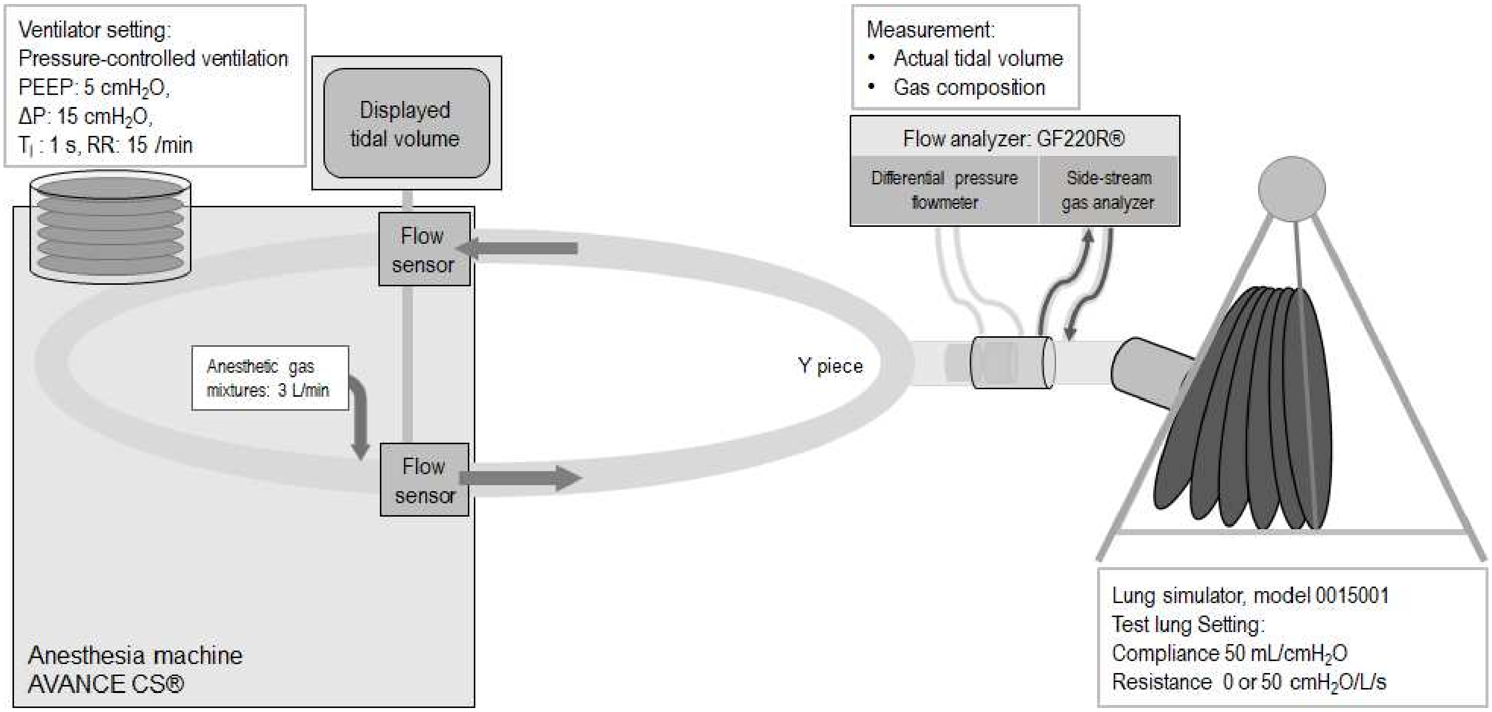


Figure 5

The flow, pressure, and volume curves obtained in the second experiment of the laboratory study. The three curves on the left were obtained during pressure-controlled ventilation with 95% oxygen, and the three curves on the right were obtained during pressure-controlled ventilation with 85% oxygen + 10% desflurane



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The experimental system. A test lung was ventilated by Avance under stable predetermined pressure-controlled ventilation (PEEP = 5 cmH2O, driving pressure = 15 cmH2O, TI = 1 s, and RR = 15 min-1). The Flow analyzer GF220R was placed between the Y piece of the breathing circuit and the test lung. Carbon dioxide gas was injected into the test lung and was maintained at an end-tidal carbon dioxide tension of approximately 38 Torr (5%)

Supplementary Files

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