# Derivation and validation of an equation to determine the optimal ventilator setting in children undergoing intracranial revascularization surgery: A single-center retrospective study

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# Derivation and validation of an equation to determine the optimal ventilator setting in children undergoing intracranial revascularization surgery: a single-center retrospective study

Article category: Research report

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**What is already known**

The aim of intraoperative ventilation is to establish normocapnia in patients with moyamoya disease. If there was a simple equation to predict the optimal ventilator settings required to attain normocapnia in children undergoing general anesthesia, it would be very useful for avoiding unexpected hypocapnia and hypercapnia in children with moyamoya disease; however, such an equation has not yet been reported.

**What this article adds**

We derived and validated a simple equation that predicts the ventilator setting to attain normocapnia in children with moyamoya disease undergoing general anesthesia. These findings can aid anesthesiologists in avoiding unexpected hypo or hypercapnia in children undergoing general anesthesia.

**Abstract**

**Background:** It can be difficult to determine the appropriate ventilator settings to maintain normocapnia in children undergoing general anesthesia for surgery for moyamoya disease, especially immediately following anesthesia induction.

**Aim:** We conducted this study to attempt to derive an equation to predict the appropriate ventilator settings, and subsequently validated the accuracy of the equation.

**Methods:** A retrospective study of 91 pediatric patients less than 18 years of age who underwent cerebral revascularization for moyamoya disease at our institution. 58 patients were used to derive the equation and the subsequent 33 patients were used to validate the equation. We calculated the required respiratory rate to attain normocapnia based on the median of all values of the minute volume during normocapnia (estimated partial pressure of arterial carbon dioxide of 38–42 mmHg) and the assumption that the tidal volume was 8 mL/kg body weight. We derived the regression equation from the derivation data set where the required respiratory rate to attain normocapnia was represented by age. We simplified the equation by rounding coefficients to the nearest integer. The level of agreement between the respiratory rate predicted from the equation and the actual required respiratory rate was assessed in the validation group using Bland–Altman analysis.

**Results:** The derived equation is tidal volume = 8 mL/kg body weight, respiratory rate = 24 - age /min. Bland–Altman analysis in the validation group revealed that the mean bias between the predicted and actual respiratory rate was 0.29 (standard deviation, 3.67). The percentage of cases where the predicted rate was within ±10% and ±20% of the actual rate was 42.4% and 66.7%, respectively.

**Conclusions:** We derived and validated a simple and easily applicable equation to predict the ventilator settings required to attain normocapnia during general anesthesia in children with moyamoya disease.

**Keywords:** ventilators, moyamoya disease, child, infant, hypercapnia, hypocapnia

## Introduction

Moyamoya disease is a disorder caused by either blocked arteries or spontaneous occlusion of the blood vessels of the Circle of Willis.[1-4] During general anesthesia for these patients, hypocapnia, due to hyperventilation, causes cerebral vasoconstriction and may lead to cerebral ischemia.[5, 6] However, hypercapnia may also cause cerebral ischemia by an intracerebral steal effect, as the collateral vessels in patients with moyamoya disease are in a state of maximal vasodilation.[7-9] The aim of intraoperative ventilation is therefore to establish normocapnia in patients with moyamoya disease.[4] However, maintaining a normal partial pressure of carbon dioxide ($PaCO_2$) level continuously in real time is challenging. Arterial blood gas (ABG) analysis, the gold standard for measuring $PaCO_2$, measures $PaCO_2$ only at one point in time, while $PaCO_2$ may fluctuate continuously. Tight control of $PaCO_2$, based on frequent assessment of ABGs, is difficult, especially immediately following anesthesia induction, as anesthesiologists are occupied by a number of tasks such as airway management, blood pressure regulation and patient positioning. The partial pressure of end-tidal carbon dioxide ($PetCO_2$) is commonly used to continuously assess $PaCO_2$, but there can be divergence between $PetCO_2$ and $PaCO_2$,[10-12] and ventilation based on $PetCO_2$ may result in unexpected hypercapnia or hypocapnia.

If there were a simple equation to predict the optimal ventilator settings required to achieve and maintain normocapnia in children undergoing general anesthesia, it would be very useful for avoiding

unexpected hypocapnia and hypercapnia shortly after general anesthesia induction in children with moyamoya disease; however, such an equation has not yet been reported to our knowledge.

We conducted this study to try to derive a simple equation to predict the ventilator settings required to attain normocapnia in children with moyamoya disease, and subsequently validated the accuracy and precision of the equation.

## Methods

### *Study Design, Setting, and Population*

This single-center retrospective study was conducted in Kyoto University Hospital, an 1121 bed teaching hospital in Japan. The study protocol was approved by the Institutional Review Board (approval number: R1542, May 17, 2018), which waived the requirement for obtaining informed consent. This study adheres to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement.[13]

We included pediatric patients less than 18 years of age who underwent cerebral revascularization for moyamoya disease at Kyoto University Hospital from April 2008 to March 2018. We excluded patients if their intraoperative ventilator settings were missing or ABG analysis was not performed during surgery. For patients who had >1 surgery that met the inclusion criteria during the study period, we included only the index case to facilitate data independence. The patient population was divided into two groups: a derivation group of the patients who underwent surgery from 2008 to 2015 and a validation group of the patients who underwent surgery from 2016 to 2018. The time periods for grouping were set such that the number of participants in the derivation group would be approximately twice the number in the validation group. According to the TRIPOD statement,[13] nonrandom split-sample derivation and validation is a stronger design for evaluating model performance than random split-sampling because it allows for nonrandom variation between the two data sets; therefore, we

selected nonrandom split-sampling by year of surgery instead of random split-sampling for model validation.

All enrolled children underwent general anesthesia with tracheal intubation. Anesthesia was induced with thiopental/propofol and remifentanil, while tracheal intubation was facilitated by rocuronium. Anesthesia was maintained with sevoflurane or propofol combined with remifentanil and rocuronium. After tracheal intubation, patients were ventilated using the Fabius GS premium anesthesia machine (Dräger Medical, Lübeck, Germany) with a circle system. Following anesthesia induction, an arterial line was placed and arterial blood sampling was performed as appropriate. Ventilator settings were adjusted to achieve normocapnia ($PaCO_2$ measured by ABG analysis: 38–42 mmHg). $PetCO_2$ was measured throughout the surgery using sidestream capnography through a heat moisture exchange filter with a sampling port and was used to guide the adjustment of ventilator settings. The patients were not routinely warmed or cooled during the procedures.

*Data collection*

Our electronic database contained data on age, gender, height, weight, duration of surgery and intraoperative blood loss. The ventilator settings (expiratory tidal volume, respiratory rate, and expiratory minute volume), $PetCO_2$ values, body temperature measured using a bladder catheter equipped with a temperature probe or a rectal probe, and bispectral index values were recorded automatically every minute directly into an anesthesia information management system (PrimeGaia

PRM-7500, Nihon Kohden, Tokyo, Japan). We also collected data on the existence of chronic pulmonary disease (defined as a previous diagnosis of chronic obstructive pulmonary disease, chronic bronchitis, or emphysema), a history of asthma, side of the surgery, the technique of revascularization, the ventilator parameters and ABG analysis results during the surgery, and perioperative cerebral infarction confirmed by computed tomography or magnetic resonance imaging within 30 days after surgery.

*Calculating the minute volume required to attain normocapnia*

We calculated the estimated $PaCO_2$ as follows: (1) the arterial to end-tidal partial pressure difference of carbon dioxide ($Pa\text{-}etCO_2$) was defined for each individual patient as the median of the differences between $PaCO_2$ and simultaneous $PetCO_2$ readings ($PaCO_2 - PetCO_2$) for all intraoperative ABG measurements; and (2) the estimated $PaCO_2$ was calculated by adding $Pa\text{-}etCO_2$ to the $PetCO_2$ value recorded every minute. Normocapnia was defined as a $PaCO_2$ of 38–42 mmHg. The median of all values of the minute volume during normocapnia was $MV_{norm}$. The respiratory rate during normocapnia ($RR_{norm}$) was calculated from $MV_{norm}$ based on the assumption that the tidal volume was 8 mL/kg body weight. We calculated $RR_{norm}$ based on the assumption that the tidal volume was 8 mL/kg, as this value is close to the physiologic tidal volume[14] with several sources recommending a tidal volume target of 6 to 10 mL/kg.[15, 16]

*Statistical analysis*

In this study, continuous data are presented as the median [interquartile range], while categorical variables are presented as a number (percentage). The correlation between age and $RR_{norm}$ in the derivation data set was evaluated using Pearson's correlation coefficient. We then derived the regression equation by which $RR_{norm}$ is represented by age and also simplified the original equation by rounding coefficients to the nearest integer, so that it can be easily applied in a clinical setting. Additionally, because gender is associated with the minute volume required to attain normocapnia in adults,[17] we examined whether gender was associated with $RR_{norm}$ independent of age and whether the addition of gender to the derived equation improved its predictive performance.

We validated the accuracy and precision of the equations using the validation data set. The correlation between the respiratory rate predicted from the equations and $RR_{norm}$ was assessed using Pearson's correlation coefficient. Agreement between the predicted respiratory rate and $RR_{norm}$ was displayed graphically on the Bland–Altman plots and was presented as the mean difference between the two measurements and the 95% limits of agreement, representing the differences likely to arise between the two measurements with a 95% probability. We also assessed the proportion of patients whose predicted respiratory rate fell within ±10% or ±20% of $RR_{norm}$ to quantify the extent to which the equation either overestimated or underestimated $RR_{norm}$.

We also examined the association between weight (underweight/normal vs. overweight/obese) and the accuracy of the simplified equation using the validation data set. Overweight/obese was defined as

a body mass index at or above the 85th percentile for children of the same age and sex based on recommendations of the Centers for Disease Control and Prevention (CDC).[18] We used the 2000 CDC Growth Charts[19] (for children ≥2 years of age) or The World Health Organization Child Growth Standards[20] (for children <2 years of age) to calculate each child's body mass index, standardized to the reference population for the child's age and sex.

The sample size was determined by including all eligible surgeries in the electronic database to maximize the statistical power. We assumed approximately ten eligible surgeries per year. Assuming that patients were divided into derivation and validation groups at a ratio of 2:1, the sample size of the derivation data set would yield 60–70 patients. On the theoretical grounds, Harrell[21] suggested that the minimum sample size required for linear regression models to ensure accurate prediction was 10–20 subjects per predictor variable. We therefore estimated that we could derive a regression equation with ≤3 predictors using our data set. Statistically significant values were considered to have P values less than 0.05 using two-tailed tests.

**Results**

A review of our database yielded 176 children under 18 years of age with moyamoya disease who underwent cerebral revascularization surgery (Figure 1). Eighty-five patients were excluded: 27 for absent intraoperative ventilator settings, one as no blood gas analysis was performed and 57 for their procedure not being an index case, leaving 91 patients for review. These 91 patients were divided into the derivation group (n = 58) and the validation group (n = 33).

*Characteristics and operative variables*

Demographic data and operative variables are summarized in Table1. Patients were 1–17 years of age, and 60.4% were female. None had a diagnosis of chronic pulmonary disease, four (4.4%) had a history of asthma. The number of ABG measurements during the surgery ranged 1–11 (median, 3) times; 84 patients (92.3%) received ABG measurements twice or more. Median body temperature during normocapnia ranged 35.8°C–37.8°C (median, 36.6°C). $MV_{norm}$ per kg body weight ranged 44.7– 233.3 mL/min (median, 120.5 mL/min) and $RR_{norm}$, calculated from $MV_{norm}$ based on the assumption that tidal volume was 8 mL/kg, was 5.6-29.1 (median, 15.1) /min. Median tidal volume per kg body weight during normocapnia ranged 5.3–15.7 (median, 8.8) mL/kg, and was within the range of 7–9 mL/kg and 6–10 mL/kg in 54.9% and 79.1% of patients, respectively. The derivation and validation groups were similar in terms of demographics or operative variables, except that duration of surgery and duration of normocapnia tended to be longer in validation group.

*Deriving equations to predict the optimal ventilator setting*

The raw values of $RR_{norm}$ as a function of the patient's age in the derivation data set (n = 58) are presented in Figure 2. A strong negative correlation was found between age and $RR_{norm}$ (Pearson's correlation coefficient: −0.76; P <0.001). Based on these data, we derived the following equation using linear regression: predicted respiratory rate = 23.66 − 0.92 × age /min (coefficient of determination = 0.58, P <0.001). Gender was not significantly associated with $RR_{norm}$ after adjusting for age (Table S1). Furthermore, adding gender to the linear regression model did not improve the predictive performance (derived equation: predicted respiratory rate = 23.65 - 0.91 × age - 0.23 (if female); coefficient of determination = 0.58; P <0.001). Similarly, none of the tracheal tube types (cuffed v.s. uncuffed), median body temperature during normocapnia, or median bispectral index values during normocapnia was significantly associated with $RR_{norm}$ after adjusting for age (Table S1). Therefore, we decided to use the equation containing only age as a predictor. Furthermore, the original equation was simplified to: predicted respiratory rate = 24 - age /min (Figure 2).

*Validating the equation*

We verified the accuracy and precision of the original and simplified equations using the validation data set (n=33). The predicted respiratory rate, based on both the original and simplified equations, correlated significantly with $RR_{norm}$ (Pearson's correlation coefficient: 0.61; P <0.001; for both the

original and simplified equations; Figures S1, S2). Bland–Altman analysis revealed that the predicted respiratory rate based on the original equation estimated $RR_{norm}$ with a mean bias of 0.67 /min (95% confidence interval, −0.60–1.94; standard deviation, 3.57; Figure 3A). The mean bias between the predicted respiratory rate based on the simplified equation and $RR_{norm}$ was 0.29 (95% confidence interval, −1.01–1.59; standard deviation, 3.67; Figure 3B). The width of the limits of agreement was 6.99 for the original equation and 7.19 for the simplified equation. When $RR_{norm}$ was predicted using the simplified equation, the percentage of cases whose prediction fell within ±10% and ±20% of $RR_{norm}$ was 42.4% and 66.7%, respectively. The predicted respiratory rate overestimated $RR_{norm}$ by >20% in seven patients (21.2%), and underestimated it by >20% in four patients (12.1%, Figure 4A). A stratified analysis by weight status revealed that the percentage of cases whose prediction fell within ±20% of $RR_{norm}$ was 80.0% in underweight/normal patients, but 25.0% in overweight/obese patients (P = 0.004; Figure 4B). The predicted respiratory rate overestimated $RR_{norm}$ by >20% in four of eight overweight/obese patients (50.0%; Figure 4B).

## Discussion

In this study, we derived and validated a simple equation (tidal volume = 8mL/kg body weight, respiratory rate = 24 - age /min) to predict the ventilator settings required to attain normocapnia in children with moyamoya disease. To the best of our knowledge, this is the first study to derive and validate such an equation during general anesthesia in children. These results can provide a practical guide for determining initial ventilator settings and help avoid unexpected hypo or hypercapnia during general anesthesia in children who require tight control of $PaCO_2$ during surgery as with moyamoya disease.[4] Moreover, the derived equation may serve as a guide to determine settings for children undergoing mechanical ventilation in an environment where it is difficult to monitor $PaCO_2$ or $PetCO_2$, such as on general wards or in emergency rooms.

Ocbo and Terry[22] proposed a simple formula to estimate ventilator requirements in anesthetized adults, in which they estimated minute volume to be 84–88 mL/kg body weight. However, children require a greater minute volume for weight as they have a higher basal metabolic rate than adults. In addition, the lower the child's age, the greater the minute volume for body size is required.[23, 24] In children, anesthesiologists must take into account the fact that ventilator settings required to attain normocapnia change with age. Since the required $RR_{norm}$ linearly decreased as the patient's age increased in this study, we derived an equation by which $RR_{norm}$ was represented by age.

Bland–Altman analysis in the validation group showed that estimating $RR_{norm}$ using the simplified equation yielded a small systematic error, which was similar to that when using the original equation;

these data suggest that simplifying the equation by rounding estimates did not substantially reduce the accuracy and justify using the simplified equation as a guide for determining initial ventilator settings. Although the systematic error of the derived equation was shown to be small, the simplified equation overestimated $RR_{norm}$ by >20% in seven patients (21.2%) and underestimated $RR_{norm}$ by >20% in four patients (12.1%). Moreover, the predicted respiratory rate tended to overestimate $RR_{norm}$ in overweight/obese patients. These data suggest that the derived equation is not sufficient in terms of precision (especially in obese patients), and therefore it is necessary to adjust ventilator settings according to measured $PaCO_2$ in patients who require strict control of $PaCO_2$.

To facilitate simplicity, we calculated $RR_{norm}$ from $MV_{norm}$ based on the assumption that the tidal volume was 8 mL/kg body weight, although that did not represent the actual tidal volume. Accurate calculation of $RR_{norm}$ is difficult as minute alveolar ventilation varies depending on tidal volume, even though minute volume is the same.[25] However, the median of tidal volume during normocapnia fell within the range of 7–9 mL/kg body weight in more than half (54.9%) of patients, and therefore we consider that the influence of actual tidal volume variations on the accuracy of $RR_{norm}$ was small.

Because carbon dioxide is an end product of energy production pathways, carbon dioxide production and consequently minute volume required to achieve normocapnia are affected by metabolic rate. Therefore, we examined the effects of body temperature and anesthesia depth (bispectral index), which may change carbon dioxide production by affecting metabolic rate, on $RR_{norm}$. However, we could not determine significant association between these factors and $RR_{norm}$ after adjusting for age.

One possible explanation for the lack of a significant association between body temperature and $RR_{norm}$ was that patients with significant hypo or hyperthermia have not been included in this study. Although there was no significant association between bispectral index and $RR_{norm}$ in this study, the dose of anesthetics or muscle relaxants could still affect required minute volume to attain normocapnia, which needs to be elucidated in the future.

*Strengths and limitations*

A strength of this study included the estimation of minute volume required to attain normocapnia by calculating the estimated $PaCO_2$ on a minute-by-minute basis. This enabled us to precisely determine the ventilator settings required to attain normocapnia. Conversely, this study has several limitations. The single-center design may limit generalizability. However, we validated the accuracy and precision of the equation in a second cohort of patients, different from those used to derive the equation. Our data set did not include patients with chronic pulmonary disease, in whom the optimal ventilator settings to attain normocapnia may be different. Similarly, our data set did not include infants under 1 year of age, and therefore the proposed equation should not be extrapolated to these populations. We could not assess whether ventilation mode (e.g. pressure v.s. volume controlled) affected the required minute volume because data on ventilation mode was not recorded. Finally, small sample size was also a limitation of this study. However, the sample size of the derivation group fulfilled the rule of 20 subjects per predictor variable.[21] As for validation group, because the width of the 95% confidence

intervals for the mean bias of the derived equations was less than three /min, we consider that the sample size was acceptable to assess the accuracy of the derived equation.

*Conclusions*

In conclusion, we derived and validated a simple and easily applicable equation (tidal volume = 8mL/kg body weight, respiratory rate = 24 - age /min) to predict the ventilator setting required to attain normocapnia during general anesthesia in children with moyamoya disease. This equation may serve as a practical guide for determining initial ventilator settings and may help to prevent unexpected hypocapnia or hypercapnia during general anesthesia in children < 18 years of age.

**Ethical approval:** Kyoto University Hospital Ethics Committee; Date of approval 5/17/2018; Approval number: R1542

**Conflicts of interest:** No conflicts of interest to declare.

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**Table 1.** Patients' characteristics and operative variables

| Variables | All patients (n=91) | Derivation group (*n* = 58) | Validation group (n=33) |
|---|---|---|---|
| Age (years) | 8 [5–11] | 8 [6–11] | 9 [5–12] |
| Female gender | 55 (60.4%) | 34 (58.6%) | 21 (63.4%) |
| Height (cm) | 128 [111–147] | 126 [111–143] | 134 [110–149] |
| Weight (kg) | 28 [20–37] | 27 [20–36] | 28 [19–49] |
| Overweight/obese | 17 (18.7%) | 9 (15.5%) | 8 (24.2%) |
| History of asthma | 4 (4.4%) | 2 (3.5%) | 2(6.1%) |
| Side of the surgery (right/left/bilateral) | 44/46/1 | 30/28/0 | 14/18/1 |
| The technique of revascularization (direct/indirect/combination) | 27/1/63 | 15/0/43 | 12/1/20 |

| | | | |
|---|---|---|---|
| Duration of surgery (min) | 293[253–329] | 260[238–305] | 326[293–345] |
| Intraoperative blood loss (mL) | 30 [10–55] | 35 [10–66] | 30 [5–43] |
| Use of cuffed tracheal tube | 80 (87.9%) | 51 (87.9%) | 29 (87.9%) |
| Pa-et$CO_2$ (mmHg) | 0.9 [−0.5–2] | 0.8 [−1.1–2] | 1.1 [0.2–1.9] |
| Duration of normocapnia (min) | 182 [65–274] | 164 [56–248] | 226 [90–329] |
| Median body temperature during normocapnia (°C) | 36.6 [36.3–36.9] | 36.7 [36.4–37.0] | 36.6 [36.2–36.8] |
| Median bispectral index during normocapnia | 59 [52–63] | 59 [54–65] | 59 [51–62] |
| $MV_{norm}$ (mL/min) | 3330 [2800–4000] | 3300 [2800–3970] | 3360 [2535–4130] |
| $MV_{norm}$ per kg body weight (mL/min) | 120.5 [98.1–148.8] | 123.4 [100.5–161.1] | 118.3 [85.7–144.7] |
| Perioperative cerebral infarction | 5 (5.5%) | 4 (6.9%) | 1 (3.0%) |

Overweight/obese was defined as a body mass index at or above the 85$^{th}$ percentile for children of the same age and sex. Body temperature was not recorded in 24 patients and bispectral index was not recorded in 35 patients. Pa-et$CO_2$, arterial to end-tidal partial pressure difference of carbon dioxide; $MV_{norm}$, measured minute volume required to achieve normocapnia.

**Figure Legends**

**Figure 1.** Flow chart of the study participants.

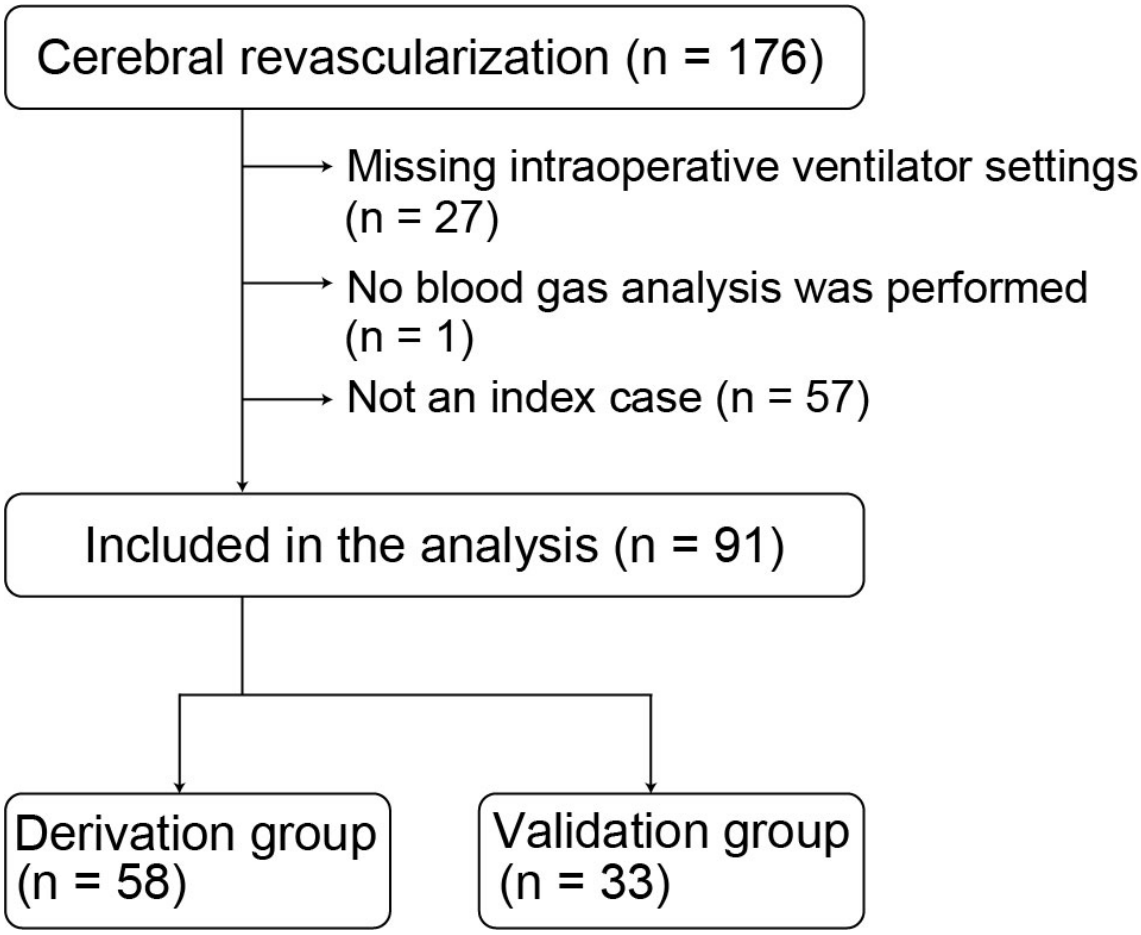


**Figure 2.** Scatter plot illustrating the correlation between age and $RR_{norm}$ in derivation group. Dashed line, the linear regression line; solid line, the line representing the simplified equation obtained by rounding coefficients to the nearest integer; $RR_{norm}$, respiratory rate during normocapnia when tidal volume was assumed to be 8 mL/kg body weight.

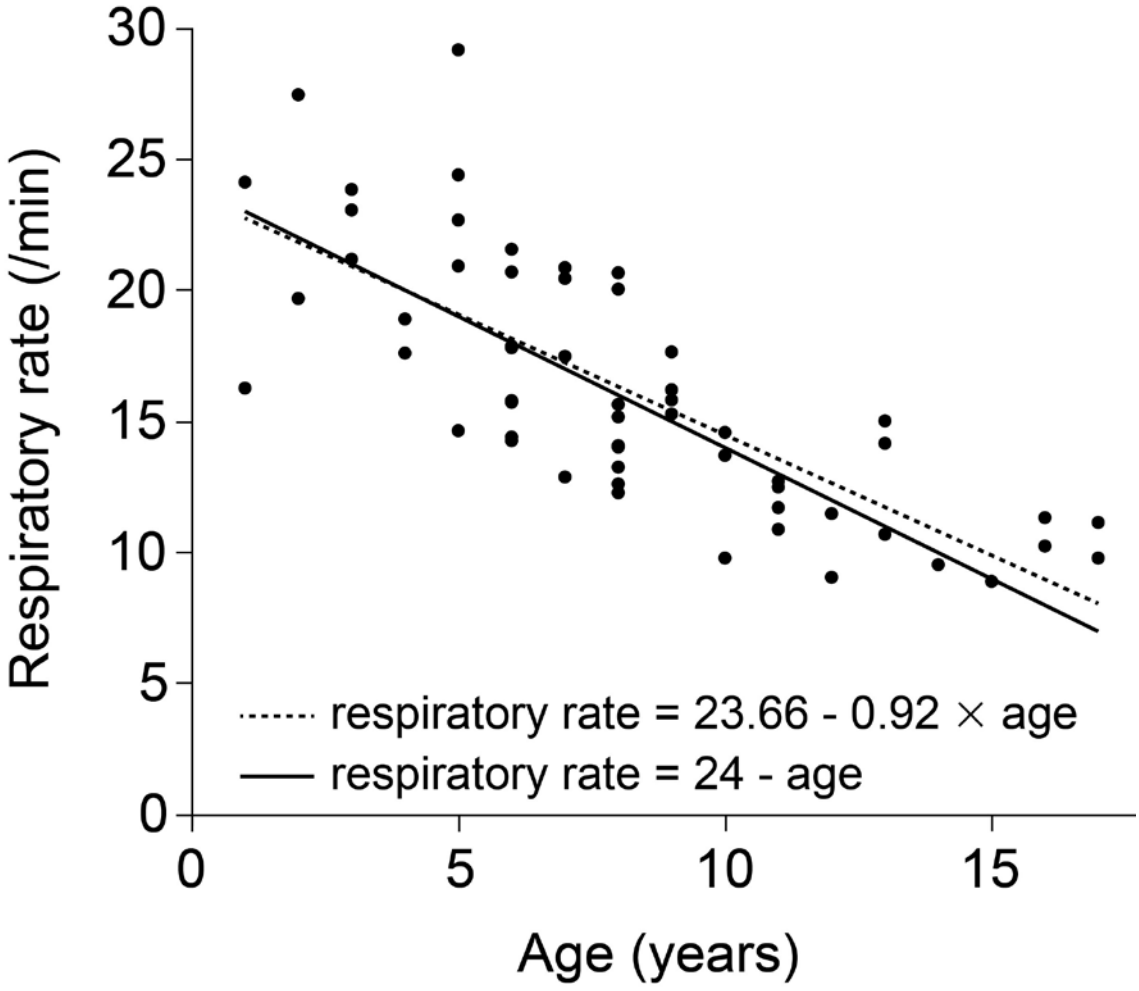


**Figure 3.** Bland–Altman plots illustrating the agreement between predicted respiratory rate based on the original (A) and simplified (B) equations and $RR_{norm}$ in validation group. The *y*-axis represents the difference between the predicted respiratory rate based on the equations and $RR_{norm}$, and the *x*-axis represents the mean of the predicted respiratory rate based on equations and $RR_{norm}$. Solid line, mean bias between the predicted respiratory rate based on equations and $RR_{norm}$; dashed lines, 95% limits of agreement; $RR_{norm}$, respiratory rate during normocapnia when tidal volume was assumed to be 8 mL/kg body weight.

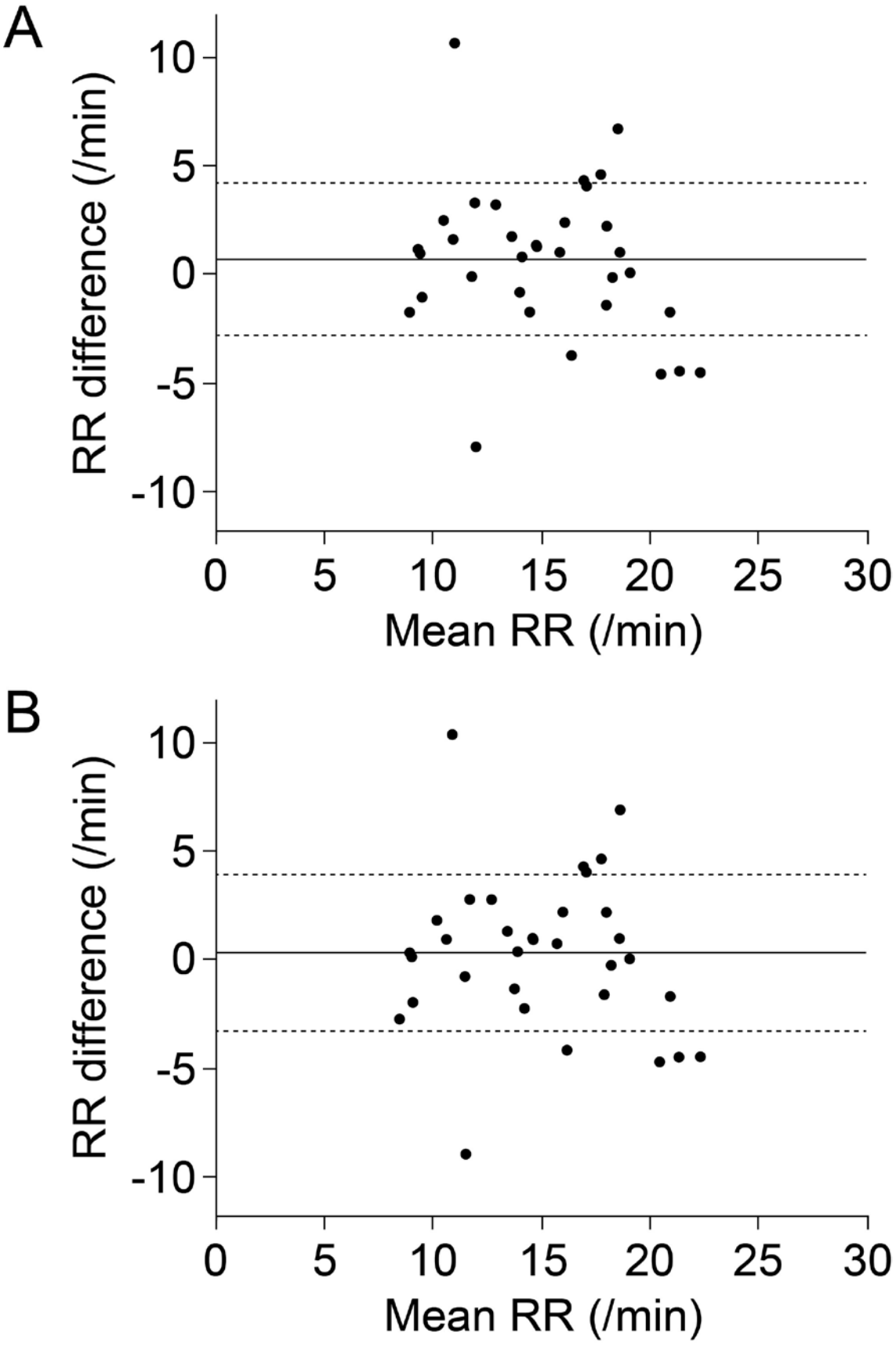
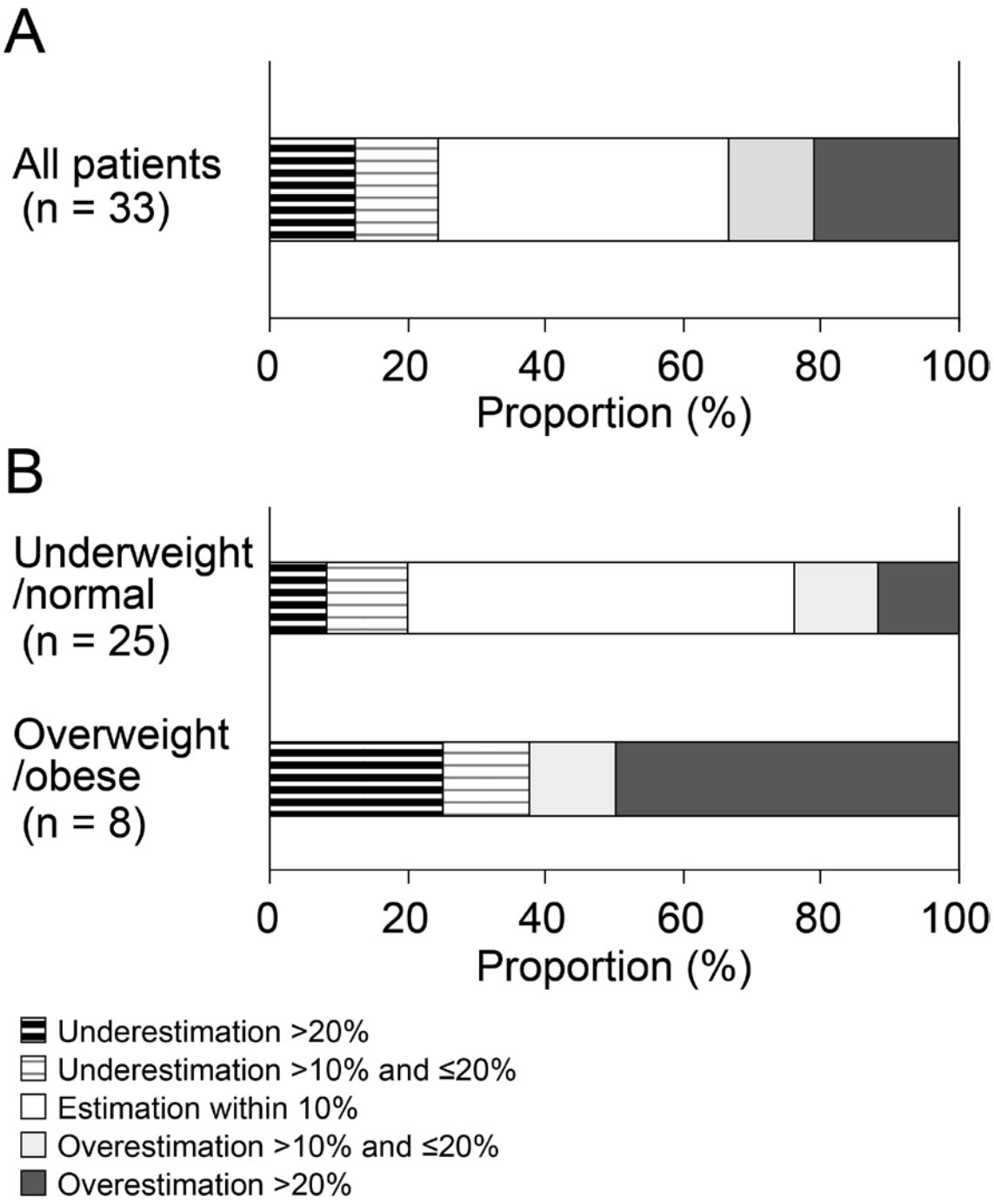


**Figure 4.** (A) Accuracy of prediction of $RR_{norm}$ by the simplified equation in (A), all patients in the validation group, and (B), patients in the validation group stratified by weight. $RR_{norm}$, respiratory rate during normocapnia when tidal volume was assumed to be 8 mL/kg body weight.



Supporting data

Table S1. Association between patient/operative variables and the respiratory rate during normocapnia after adjusting for age.

| Variables | Regression coefficient (95% confidence interval) | *P* value |
|---|---|---|
| Female gender | −0.23 (−1.08–0.61) | 0.586 |
| Use of cuffed tracheal tube | −0.69 (−1.96–0.59) | 0.283 |
| Median body temperature during normocapnia (°C) | 1.59 (−0.26–3.44) | 0.09 |
| Median bispectral index during normocapnia | 0.03 (−0.06–0.12) | 0.468 |

Figure S1. Scatter plot illustrating the correlation between the predicted respiratory rate based on the original equation and $RR_{norm}$ in validation group. Solid line, the linear regression line; *r*, Pearson's correlation coefficient; $RR_{norm}$, respiratory rate during normocapnia when tidal volume was assumed to be 8 mL/kg body weight.

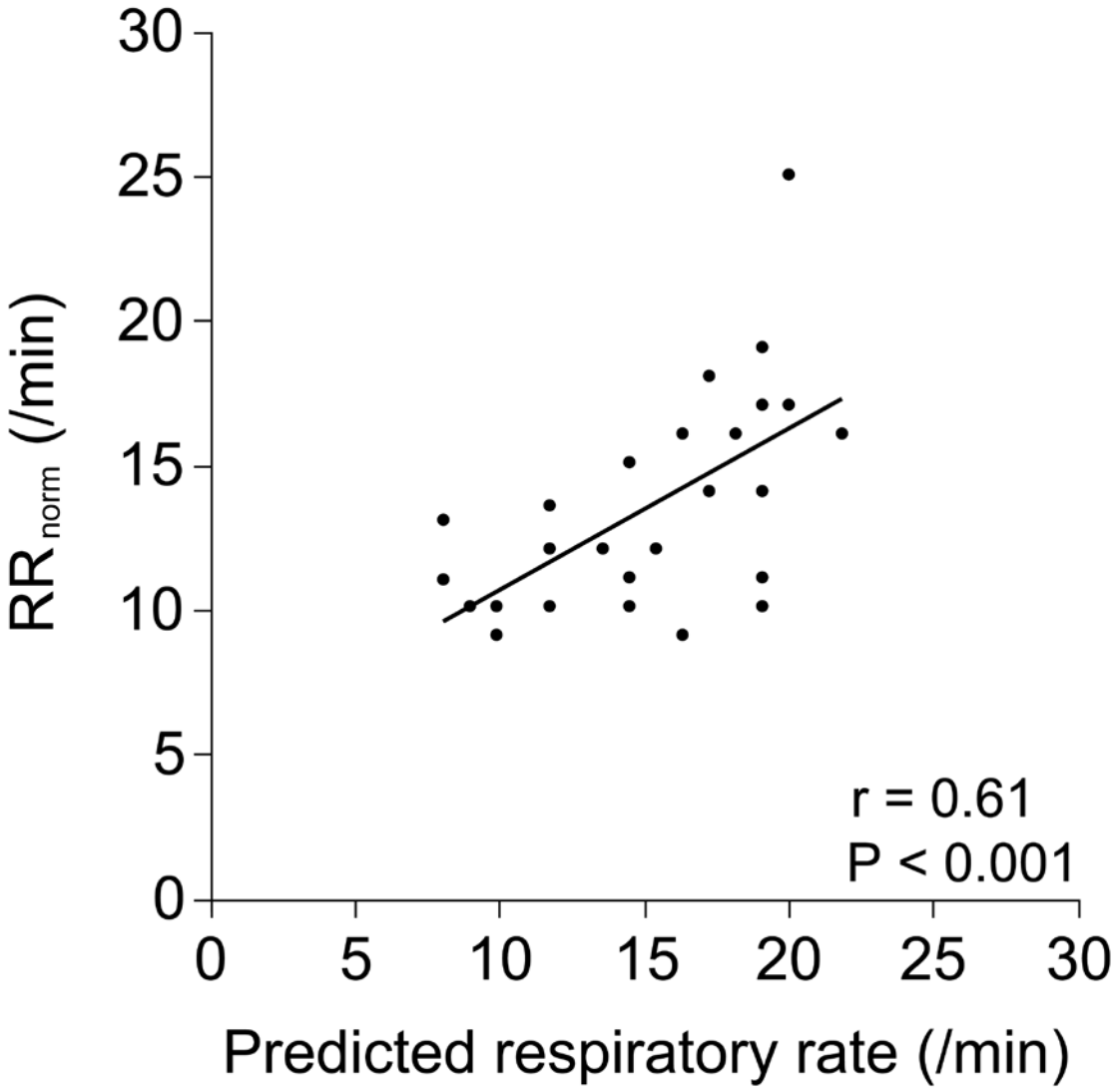


Figure S2. Scatter plot illustrating the correlation between the predicted respiratory rate based on the simplified equation and $RR_{norm}$ in validation group. Solid line, the linear regression line; *r*, Pearson's correlation coefficient; $RR_{norm}$, respiratory rate during normocapnia when tidal volume was assumed to be 8 mL/kg body weight.