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**Research Paper**

# Validation of the Radford Nomogram to Estimate the Minute Volume Required to Attain Normocapnia in Patients Undergoing General Anesthesia: A Single-Center Retrospective Study

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**Objective:** The Radford nomogram, an old mathematical chart device to estimate the required ventilation for maintaining normocapnia, remains unvalidated in patients undergoing modern, balanced anesthesia. This study aims to investigate the performance of the Radford nomogram in patients undergoing general anesthesia and derive a simple equation to estimate the minute volume required to attain normocapnia ($MV_{norm}$).

**Methods:** This single-center retrospective study enrolled 78 patients (age ≥ 18 years) undergoing cerebral revascularization for Moyamoya disease. We defined $MV_{norm}$ as the median of all values of the minute volume during normocapnia (estimated $PaCO_2$: 38–42 mmHg). We examined the agreement level between the estimated minute volume using the Radford nomogram and $MV_{norm}$ using the Bland–Altman analysis. Furthermore, we developed and validated a simple equation predicting $MV_{norm}$ based on gender and a multiple of body weight, using a split-sample validation technique.

**Results:** The Radford nomogram tended to overestimate $MV_{norm}$ with a mean bias of 560 mL/min (95% limits of agreement, -848–1,968 mL/min). The equation developed using data from the development group (n = 52): required minute volume (mL/min) = 85 × body weight (kg) in male patients and 70 × body weight (kg) in female patients. In the validation group (n = 26), the mean bias of this simple equation was 224 mL/min (95% limits of agreement, -1,264–1,712 mL/min).

**Conclusion:** The Radford nomogram overestimates $MV_{norm}$ in modern, balanced anesthesia. The simple equation using gender and a multiple of body weight yields similar predictive performance to the Radford nomogram.

## Introduction

Goal of intraoperative ventilation was to provide normocapnia for patients at risk of cerebral ischemia such as those with Moyamoya disease.[1] Hypocapnia causes cerebral vasoconstriction and could result in cerebral ischemia.[2,3] Alternatively, hypercapnia might cause a decline in the cerebral blood flow by "intracerebral steal" because the collateral network of vessels is in a state of maximal vasodilation.[4-6]

In practice, however, measuring the partial pressure of arterial carbon dioxide ($PaCO_2$) and attaining normocapnia in real time is challenging, especially immediately after anesthesia induction. Repeated assessment of arterial blood gas is difficult immediately after anesthesia induction because anesthesiologists

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are preoccupied with several tasks such as airway management, blood pressure regulation, and patient positioning. Although the partial pressure of end-tidal carbon dioxide ($PetCO_2$) has been used as a noninvasive and real-time estimate of $PaCO_2$, regulating the ventilation using $PetCO_2$ as an indicator might lead to unintended hyperventilation or hypoventilation because of marked variability in the difference between $PaCO_2$ and $PetCO_2$ in mechanically ventilated patients.[7-9] Thus, estimating the required minute ventilation to attain normocapnia would be useful to ascertain the initial ventilator settings, minimizing the risk of hyperventilation or hypoventilation.

The Radford nomogram[10] is an old mathematical chart device to predict necessary tidal volume for mechanical ventilation on the basis of gender, body weight, and respiratory rate. Although the nomogram was validated in patients undergoing general anesthesia in the 1960,[11] the respiratory requirement might be different in patients undergoing modern, balanced anesthesia.

Hence, the primary objective of this study is to investigate the performance of the Radford nomogram in patients undergoing cerebral revascularization for Moyamoya disease, by correlating the minute volume estimated using the Radford nomogram ($MV_{rad}$) with the measured minute volume required to attain normocapnia ($MV_{norm}$). The secondary objective of this study is to derive a simple equation to predict $MV_{norm}$.

# Methods

## Study Design, Setting, and Population

This single-center retrospective study was conducted in Kyoto University Hospital, a teaching hospital in Japan. This study protocol was approved by the Institutional Review Board approved (approval number: R1542, May 17, 2018), which waived the requirement for obtaining informed consent. This study was conducted in accordance with Declaration of Helsinki (2013) and relevant laws in Japan. This study adheres to the Guidelines for Reporting Reliability and Agreement Studies.[12]

In this study, we enrolled adult (age: ≥ 18 years) patients 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 normocapnia was not attained throughout the surgery because $MV_{norm}$ could not be calculated for them. For patients who had > 1 surgery that met the eligibility criteria, we included only the first surgery performed on the patient. All enrolled patients underwent general anesthesia and tracheal intubation. General anesthesia was induced with 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 Fabius GS premium (Dräger Medical, Lübeck, Germany). Furthermore, ventilator setting was adjusted targeting normocapnia ($PaCO_2$ measured by arterial blood gas analysis: 38–42 mmHg).

## Data Collection

At our institution, the electronic database of surgical patients comprised data on age, gender, height, weight, the American Society of Anesthesiologists Physical Status, duration of surgery, and intraoperative blood loss. Moreover, we collected data on smoking history (ever smoker was defined as smoking ≥ 100 cigarettes during lifetime up to the surgery, as reported previously[13-15]), diagnosis of chronic pulmonary disease (defined as a previous diagnosis of chronic obstructive pulmonary disease, chronic bronchitis, or emphysema), history of asthma, and ventilatory parameters and arterial blood gas results during the surgery from the electronic medical record system.

## Calculating the Minute Volume Required to Attain Normocapnia

The ventilatory settings (tidal volume, respiratory rate, and minute volume) and $PetCO_2$ values were recorded automatically every minute directly into an anesthesia information management system (PrimeGaia PRM-7500, Nihon Kohden, Tokyo, Japan). We calculated the estimated $PaCO_2$ as follows: (1) defining the arterial to end-tidal partial pressure difference of carbon dioxide ($Pa\text{-}etCO_2$) for each individual patient as the median of differences between $PaCO_2$ and simultaneous $PetCO_2$ readings ($PaCO_2$–$PetCO_2$) for all intraoperative arterial blood gas measurements, and (2) calculating the estimated $PaCO_2$ by adding $Pa\text{-}etCO_2$ to $PetCO_2$ value recorded every minute. Then, we defined normocapnia as estimated $PaCO_2$ of 38–42 mmHg. We considered the median of all values of the minute volume during normocapnia as $MV_{norm}$.

### Prediction of the Minute Volume Required to Attain Normocapnia Using the Radford Nomogram

We applied the Radford nomogram, a mathematical chart device to predict necessary tidal volume for mechanical ventilation on the basis of gender, body weight, and respiratory rate, to each patient and estimated the tidal volume required to atttain normocapnia ($TV_{rad}$) for a breathing frequency of 12 breaths/min. Then, we calculated $MV_{rad}$ as 12 × $TV_{rad}$. We also calculated the minute volumes required to attain normocapnia using the Radford nomogram for breathing frequencies of 10 and 14 breaths/min ($MV_{rad10}$ and $MV_{rad14}$, respectively), and assessed the agreement of $MV_{rad10}$ or $MV_{rad14}$ with $MV_{norm}$ using Bland–Altman analysis.

### Statistical Analyses

In this study, continuous data are presented as median [interquartile range], while categorical variables as number (%). We used the linear regression analysis to estimate the correlation between continuous variables. In addition, the agreement between the predicted minute volume and $MV_{norm}$ was displayed graphically on the Bland–Altman plots and was presented by 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 verified the assumption of the normal distribution of the difference using the Kolmogorov–Smirnov normality test. Moreover, we assessed the proportion of patients whose predicted minute volumes were above or below $MV_{norm}$ by, at least, 10% to quantify the extent to which the predicting method was either overestimating or underestimating $MV_{norm}$.

We derived a simple equation to predict MVnorm based on the average values of $MV_{norm}$ per kg body weight for men and women. The estimated minute volume using this simple equation was designated as $MV_{simp}$. We also derived an equation using the ideal body weight rather than actual body weight because, in our opinion, the equation using the actual body weight might overestimate $MV_{norm}$ in obese patients. We determined the ideal body weight using the body mass index method.[16] The estimated minute volume based on gender and ideal body weight was designated as $MV_{simp\text{-}IBW}$. Additionally, we examined whether smoking status and/or history of asthma were associated with $MV_{norm}$ per kg body weight independent of gender, using multivariable linear regression analysis with $MV_{norm}$ per kg body weight as a dependent variable. We used a split-sample validation technique for equation development and validating. We derived equations based on the data obtained from two-thirds of the study population randomly selected using the simple random sampling procedure, and then, verified the equations on the remaining one-third of patients.

We did not conduct a formal sample size calculation because this study did not aim to test a certain hypothesis but assess the agreement between the estimated and measured minute volume. Instead, all eligible surgeries performed from the introduction of the current anesthesia information management system (PrimeGaia PRM-7500) at our institution to the conception of this study were included to maximize the reliability of our results. All statistical tests in this study were two-tailed, and we considered $p < 0.05$ as statistically significant. All statistical analyses were performed using the statistical program R (available at http://cran.r-project.org).

## Results

The electronic database search of surgical patients at our institution yielded 134 cerebral revascularization surgeries for Moyamoya disease. After excluding 27 surgeries because of missing intraoperative ventilator settings, 3 for not attaining normocapnia, and 26 for not being the first surgery performed on the patient, we included 78 surgeries in this study.

Table 1 summarizes patients' characteristics and operative variables. Study participants were aged 18–67 years, and 70.5% were females. No patient had chronic pulmonary disease. $MV_{norm}$ ranged 2,640–8,680 (median, 4,100) mL/min, and $MV_{norm}$ per kg body weight ranged 47.7–115.2 (median, 72.7) mL/min. In addition, $MV_{rad}$ ranged 3,840–8,400 (median, 4,560) mL/min. The linear regression analysis revealed a significant and positive correlation between $MV_{rad}$ and MVnorm (Pearson's correlation coefficient: 0.72; $p < 0.001$; Fig. 1). The Bland–Altman analysis revealed that MVrad tends to overestimate $MV_{norm}$ with a mean bias of 560 (standard deviation, 718) mL/min; 95% limits of agreement ranged from -848 to 1,968 mL/min (Fig. 2). The proportion of cases whose prediction fell within ±10% of $MV_{norm}$ was 30.8%; $MV_{rad}$ overestimated $MV_{norm}$ by > 10% in 47 patients (60.3%), and underestimated by > 10% in

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

| Variables | All patients (n = 78) | Development group (n = 52) | Validation group (n = 26) | p |
|---|---|---|---|---|
| Age (years) | 41 [29–47][a] | 41 [31–49] | 37 [26–43] | 0.113 |
| Female gender | 55 (70.5)[a] | 35 (67.3) | 20 (76.9) | 0.380 |
| Height (cm) | 160 [155–167] | 162 [157–167] | 160 [153–167] | 0.465 |
| Weight (kg) | 57 [52–66] | 58 [53–66] | 55 [50–64] | 0.202 |
| BMI (kg/m$^2$) | 21.9 [20.2–24.7] | 22.0 [20.1–25.0] | 21.7 [20.3–24.1] | 0.525 |
| Obese patients (BMI ≥ 30 kg/m$^2$) | 3 (3.9) | 3 (5.8) | 0 (0.0) | 0.212 |
| ASA-PS (1/2/3/missing) | 12/62/1/3 | 5/45/1/1 | 7/17/0/2 | 0.087 |
| Ever smoker | 28 (35.9) | 19 (36.5) | 9 (34.6) | 0.867 |
| Chronic pulmonary disease | 0 (0.0) | 0 (0.0) | 0 (0.0) | — |
| History of asthma | 9 (11.5) | 5 (9.6) | 4 (15.4) | 0.452 |
| Duration of surgery (min) | 300 [247–369] | 308 [261–377] | 274 [224–355] | 0.096 |
| Intraoperative blood loss (mL) | 53 [20–93] | 58 [20–98] | 43 [18–93] | 0.966 |
| The number of arterial blood gas analyses during the surgery | 3 [2–4] | 3 [2–3] | 3 [2–4] | 0.246 |
| Pa-et$CO_2$ (mmHg) | -0.9 [-2.5–0.6] | -1.3 [-2.8–0.6] | -0.7 [-2.1–0.4] | 0.351 |
| Duration of normocapnia (min) | 228 [110–311] | 228 [95–341] | 227 [129–295] | 0.882 |
| $MV_{norm}$ (mL/min) | 4,100 [3,695–4,855] | 4,245 [3,840–4,988] | 3,930 [3,600–4,600] | 0.081 |
| $MV_{norm}$ per kg body weight (mL/min) | 72.7 [63.5–82.5] | 73.0 [63.3–84.6] | 69.0 [64.1–79.3] | 0.421 |
| $MV_{rad}$ (mL/min) | 4,560 [4,320–5,190] | 4,680 [4,440–5,400] | 4,560 [4,200–5,070] | 0.213 |

BMI: body mass index; ASA-PS: the American Society of Anaesthesiologists physical status; Pa-et$CO_2$: arterial to end-tidal partial pressure difference or carbon dioxide; $MV_{norm}$: the measured minute volume required to attain normocapnia; $MV_{rad}$: the minute volume predicted using Radford nomogram.
[a]Continuous data are presented as median [interquartile range], while categorical variables as number (%).

seven patients (9.0%). We also assessed the agreement of $MV_{rad10}$ or $MV_{rad14}$ with $MV_{norm}$ and found that both $MV_{rad10}$ and $MV_{rad\ 14}$ tend to overestimate $MV_{norm}$ (mean bias, 400 and 255 mL; standard deviation, 700 and 707 mL/min; respectively).

Then, we derived a simple equation estimating MVnorm using gender and a multiple of body weight. In the development dataset (n = 52), $MV_{norm}$ per kg body weight was significantly higher in male patients (average: 84.5 vs. 69.7 mL/min per kg body weight; $p < 0.001$, Student's t-test). Based on these findings, we derived following equation: $MV_{simp}$ (mL/min) = 85 × body weight (kg) for males and $MV_{simp}$ (mL/min) = 70 × body weight (kg) for females. The linear regression analysis using the validation dataset (n = 26) revealed a significant and positive correlation between $MV_{simp}$ and $MV_{norm}$ (Pearson's correlation coefficient: 0.71; $p < 0.001$; Fig. 3). The Bland–Altman analysis indicated that $MV_{simp}$ estimates $MV_{norm}$ with a mean bias of 224 (standard deviation, 759) mL/min; 95% limits of agreement ranged from -1,264 to 1,712 mL/min (Fig. 4). The proportion of cases whose prediction fell within ±10% of MVnorm was 50.0%; $MV_{simp}$ overestimated MVnorm by > 10% in eight patients (30.8%) and underestimated by > 10% in five patients (19.2%).

Furthermore, we derived an equation estimating $MV_{norm}$ based on gender and ideal body weight. The mean $MV_{norm}$ per kg ideal body weight was 89.4 mL/min in males and 71.5 mL/min in females in the developing dataset. Thus, we derived following equation: $MV_{simp\text{-}IBW}$ (mL/min) = 90 × ideal body weight (kg) for males and $MV_{simp\text{-}IBW}$ (mL/min) = 70 × ideal body weight (kg) for females. We observed a significant and positive correlation between $MV_{simp\text{-}IBW}$ and $MV_{norm}$ in the validation dataset (Pearson's correlation coefficient: 0.78; $p < 0.001$). The Bland–Altman analysis revealed that $MV_{simp\text{-}IBW}$ estimates $MV_{norm}$ with a mean bias of 269 (standard deviation, 582) mL/min; 95% limits of agreement ranged from -872 to 1,410 mL/min. Using the ideal body weight rather than

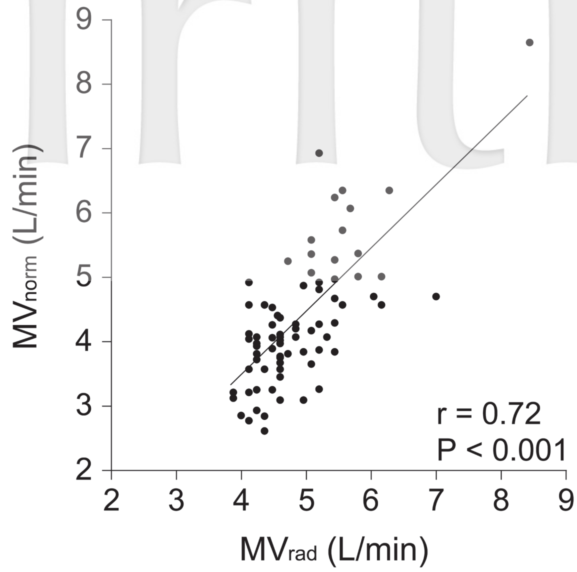


**Fig. 1.** The scatter plot illustrating the correlation between the minute volume estimated using the Radford nomogram ($MV_{rad}$) and the measured minute volume required to attain normocapnia ($MV_{norm}$). Solid line, the linear regression line; r, Pearson's correlation coefficient.

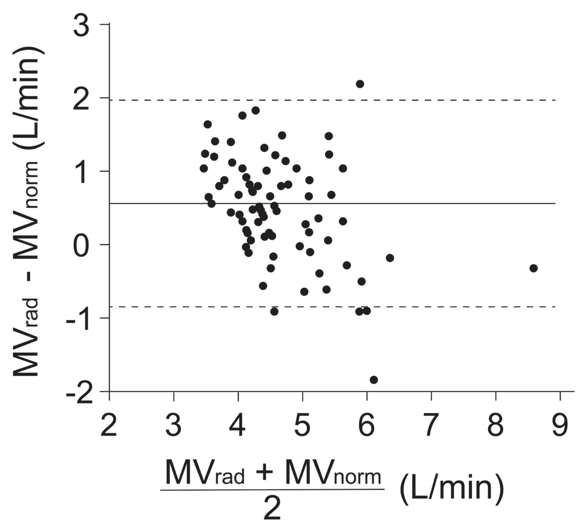


**Fig. 2.** The Bland–Altman plots illustrating the agreement between the minute volume estimated using the Radford nomogram ($MV_{rad}$) and the measured minute volume required to attain normocapnia ($MV_{norm}$). The y-axis represents the difference between $MV_{rad}$ and $MV_{norm}$, and the x-axis represents the mean of $MV_{rad}$ and $MV_{norm}$. Solid line, the mean bias between $MV_{rad}$ and $MV_{norm}$; dashed lines, 95% limits of agreement.

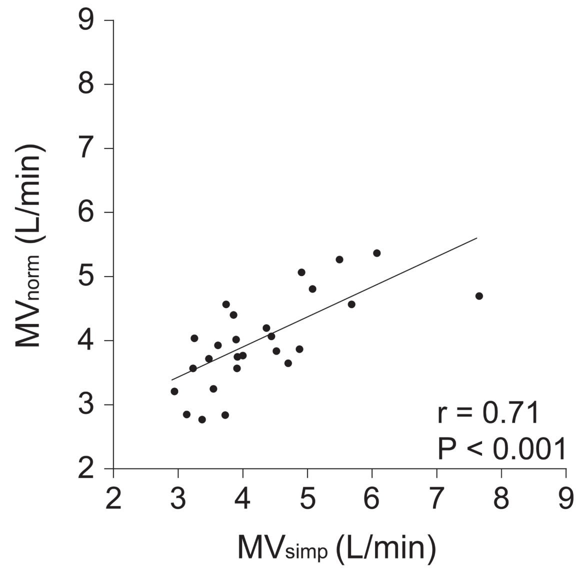


**Fig. 3.** The scatter plot illustrating the correlation between the minute volume estimated using the simple equation based on gender and a multiple of body weight ($MV_{simp}$) and the measured minute volume required to attain normocapnia ($MV_{norm}$). Solid line, the linear regression line; r, Pearson's correlation coefficient.

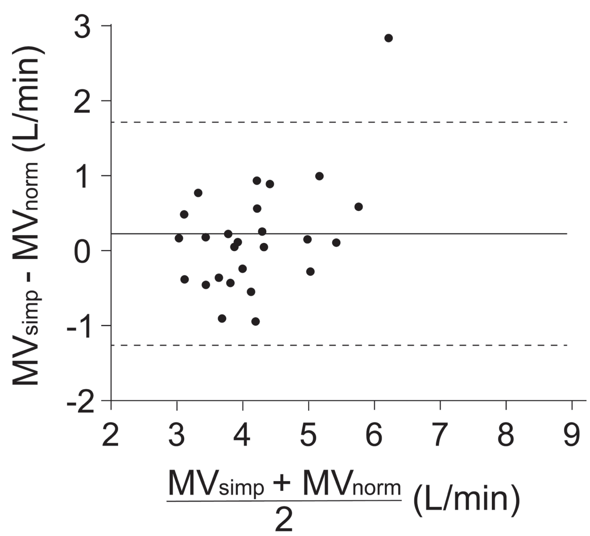


**Fig. 4.** The Bland–Altman plots illustrating the agreement between the minute volume estimated using the simple equation based on gender and a multiple of body weight ($MV_{simp}$) and the measured minute volume required to attain normocapnia ($MV_{norm}$). The y-axis represents the difference between $MV_{simp}$ and $MV_{norm}$, and the x-axis represents the mean of $MV_{simp}$ and $MV_{norm}$. Solid line, the mean bias between $MV_{simp}$ and $MV_{norm}$; dashed lines, 95% limits of agreement.

the actual body weight did not significantly increase the percentage of cases whose prediction fell within ±10% of MVnorm (50% vs. 50%; p = 1.000).

In multivariable linear regression analysis with $MV_{norm}$ per kg body weight as a dependent variable, neither smoking status nor history of asthma was significantly associated with $MV_{norm}$ per kg body weight (Table 2).

## Discussion

This study investigated the performance of the Radford nomogram to estimate the minute volume required to attain normocapnia in patients undergoing cerebral revascularization for Moyamoya disease. The findings revealed that the Radford nomogram overestimated the required minute volume with a mean bias of 560 mL/min. In addition, we derived and validated a simple equation using gender and a multiple of body weight to estimate the required minute volume.

Nunn[11] reported that the Radford nomogram displayed little systematic error in patients undergoing general anesthesia. In this study, however, the Radford nomogram overestimated $MV_{norm}$ by 560 mL/min on average, and overestimation exceeded 10% in 60.3% of patients. These findings suggest that patients are prone to be hyperventilated when determining the ventilator setting based on the Radford nomogram. Several possible descriptions exist for the discrepancy in the findings of Nunn[11] and this study. First, drugs used for anesthesia in this study (propofol/sevoflurane and remifentanil) are, perhaps, markedly different from those when Nunn[11] conducted their study. The difference in anesthetic drugs could have accounted for the differences in the metabolic activity and carbon dioxide production. Second, the difference in the ventilators used could have led to the difference in the size of dead space or the efficiency of ventilation. Third, the validation methods for the Radford nomogram varied between studies. Nunn11 obtained data from anesthetized patients with various $PaCO_2$ values and used the scatter plot of $PaCO_2$ against the minute volume. Conversely, we used data from patients who attained normocapnia. To the best of our knowledge, this is the first study to investigate the performance of the Radford nomogram using data from anesthetized patients who attained normocapnia.

We derived the simple equation using gender and a multiple of body weight as a practical equation to estimate the required minute volume; it had smaller mean bias and the similar width of limits of agreement compared with the Radford nomogram. Moreover, it offers an advantage of being easy to remember, which is essential for practical use. Ascertaining the initial ventilator setting using our simple equation and then adjusting it per the blood gas results could effectively minimize the risk of hypercapnia or hypocapnia.

Ocbo and Terry[17] proposed a simple formula to estimate the ventilatory requirement in anesthetized patients—a minute volume of 84–88 mL/min per kg body weight. However, in our dataset, $MV_{norm}$ per kg body weight was significantly higher in male patients than that in female patients. Thus, we derived the equation separately for male and female patients.

In our dataset, using the ideal body weight rather than the actual body weight did not markedly improve the agreement between the predicted minute volume and $MV_{norm}$. However, our dataset comprised only three (3.8%) obese patients (body mass index ≥ 30 kg/m$^2$). Hence, we could not determine which one of the equations based on the actual or ideal body weight precisely predicts the required minute volume in obese patients, thereby necessitating future studies.

### Strengths and Limitations

The strengths of this study included the precise estimation of the minute volume required to attain normocapnia by calculating the estimated $PaCO_2$ on the minute-by-minute basis. Conversely, this study

**Table 2.** Multivariable linear regression analysis assessing the association of smoking status and history of asthma with $MV_{norm}$ per kg body weight independent of gender

| | β (95% confidence interval) | p value |
|---|---|---|
| Intercept | 74.9 (70.3–79.5) | |
| Female gender | -6.27 (-9.75– -2.79) | < 0.001 |
| Ever smoker | 1.03 (-2.22–4.28) | 0.529 |
| History of asthma | -1.74 (-6.65–3.16) | 0.481 |

$MV_{norm}$, the measured minute volume required to attain normocapnia.

has several limitations that merit consideration when interpreting the results. First, we enrolled only relatively young patients (all patients were aged < 70 years) and did not include patients with chronic pulmonary diseases. The minute volume required to attain normocapnia might be different in older patients or those with chronic pulmonary diseases. Hence, future studies are warranted to ascertain the optimal initial ventilator settings in these patients. Second, ventilatory strategies to attain normocapnia were not standardized, and the variation in the ventilatory strategies might have affected our results. Finally, the small sample size might have reduced the reliability of our results.

### Conclusion

This study reveals that the Radford nomogram overestimates the minute volume required to attain normocapnia with a mean bias of 560 mL/min in modern, balanced anesthesia. We propose the following simple equation to estimate the required minute volume: required minute volume (mL/min) = 85 × body weight (kg) in male patients and 70 × body weight (kg) in female patients.

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