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Attaining Low Tidal Volume Ventilation During Patient Triggered Ventilation in Sedated Subjects

Moe Koide, Akinori Uchiyama, Tomonori Yamashita, Takeshi Yoshida, and Yuji Fujino

BACKGROUND: Low tidal volume (V_T) ventilation has become the preferred approach in patients in the ICU. Sedation reduces V_T by attenuating respiratory drive. Even in deep sedation, some patients exhibit high V_T. We aimed to determine factors associated with low V_T ventilation in deeply sedated subjects who exhibited an inspiratory effort by examination of the acid/base balance using the Stewart model. METHODS: The medical records of 630 consecutive subjects admitted to the ICU over 1 y were reviewed retrospectively, and daily data sets of patients with a persistent inspiratory effort, P_{aO_2}/F_{IO_2} < 300 mm Hg, PEEP > 5 cm H_2O, and a Richmond Agitation Sedation Scale score of −4 or −5 who received assisted pressure-regulated ventilation were collected. The data sets were stratified into high V_T (≥ 8 mL/kg predicted body weight [PBW]) and low V_T (> 8 mL/kg PBW) groups. RESULTS: Among 235 matched data sets from 100 subjects, 101 and 134 data sets were in the low V_T and high V_T groups, respectively. Set pressure was not different between the groups. PEEP was lower in the low V_T group, and opioids were more frequently used in the high V_T group. Strong ion difference (SID) was higher in the low V_T group. Multivariate analysis revealed that higher SID, lower total nonvolatile weak anion (A_{TOT}), and absence of opioid administration were associated with attaining low V_T ventilation. Furthermore, V_T/PBW and SID demonstrated a weak inverse correlation, whereas V_T/PBW and A_{TOT} exhibited a weak correlation. V_T/PBW was lower in the group with higher SID and lower A_{TOT}, indicating a tendency of metabolic alkalosis. CONCLUSIONS: Despite weak effects of high SID and low A_{TOT}, efficient management of the buffering function might be a feasible strategy to achieve low V_T ventilation. *Key words: acid/base balance; patient triggered ventilation; deep sedation; low tidal volume; Stewart model.* [Respir Care 0;0(0):1–•. © 0 Daedalus Enterprises]

Introduction

Low tidal volume (V_T) ventilation is essential for ensuring lung protection during mechanical ventilation in patients with ARDS.[1-4] Low V_T ventilation reportedly reduces postoperative pulmonary complications related to general anesthesia[5-7] and improves clinical outcomes of patients without ARDS.[8] Low V_T ventilation is increasingly preferred in mechanically ventilated patients in the ICU, although its efficacy in routine postoperative patients has not been confirmed. Volume controlled ventilation maintains a low V_T; however, interactions with a patient's inspiratory effort can cause ventilator asynchrony, leading to lung injury.[9,10] Patient triggered, pressure-regulated ventilation modes, such as pressure controlled ventilation and pressure support ventilation, are alternatives that can resolve ventilator asynchrony[11]; however, maintaining a low V_T can be difficult in pressure targeted ventilation in subjects with inspiratory effort.

While several studies reported factors associated with low V_T ventilation,[12,13] there is limited information on attainment of low V_T with assisted pressure-regulated ventilation modes in subjects with an inspiratory effort. Low V_T ventilation can be achieved with appropriate sedation,

Drs Koide, Uchiyama, Yamashita, Yoshida, and Fujino are affiliated with the Department of Anesthesiology and Intensive Care Medicine, Osaka University Graduate School of Medicine, Suita, Japan.

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Correspondence: Akinori Uchiyama MD PhD, Department of Anesthesiology and Intensive Care Medicine, Osaka University Graduate School of Medicine, Yamadaoka 2-15, Suita, Osaka Prefecture, 565-0871, Japan. E-mail: auchiyama@hp-icu.med.osaka-u.ac.jp.

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ventilator settings, and the maintenance of arterial blood gases. However, the efficacy of these approaches has not been confirmed in subjects maintaining an inspiratory effort. Due to the depressive effects of sedatives on respiration, sedation is expected to reduce V_T by attenuating respiratory drive. Chen et al[12] reported that adherence to a low-V_T strategy was associated with the depth of sedation. Even in deep sedation, some subjects exhibited a high V_T due to a persistent strong inspiratory effort. Patients often exhibit a strong inspiratory effort because of hypercapnia and abnormal lung mechanics. In addition, other factors such as metabolic acidosis, pain, discomfort, anxiety, and excitation can stimulate the respiratory center. Deep sedation is sometimes necessary to improve the circulatory and respiratory status of patients in the ICU, and it is occasionally needed after cardiac surgery.[14] This study aimed to determine factors associated with low V_T ventilation in deeply sedated subjects on patient triggered pressure-regulated ventilation.

The acid/base balance in blood is one of the vital factors that affect respiratory center function. Umoh et al[15] reported that a low serum HCO^{3-} ($<$ 22 mEq/L) was negatively correlated with a low V_T. However, serum HCO^{3-} is also affected by ventilation and P_{aCO_2}, which hinders the precise elucidation of metabolic and respiratory factors that affect serum acid/base status. The Stewart model considers the following 3 factors as independent variables to determine the acid/base status[16-19]: P_{aCO_2}; strong ion difference (SID), which is the difference between the sums of all strong cations and all strong anions; and total nonvolatile weak anions (A_{TOT}). Accordingly, pH and HCO^{3-} are dependent variables and are altered when one or more of the independent variables change. Thus, the Stewart model facilitates the elucidation of metabolic and respiratory factors separately. Although some studies have utilized the Stewart model to investigate the acid/base status in critically ill subjects,[20-24] the correlation between the characteristics of mechanical ventilation and the acid/base status according to the Stewart model has not been examined extensively. In this retrospective study, we examined ventilatory characteristics, including V_T, using the Stewart model in a consecutive series of ICU subjects.

QUICK LOOK

Current knowledge

Low tidal volume ventilation has become the preferred approach in patients in the ICU. Sedation reduces tidal volume by attenuating respiratory drive. Even in deep sedation, some patients exhibit high tidal volume. Methods of maintaining a low tidal volume in assisted pressure-regulated ventilation remain unclear in deeply sedated patients with a significant inspiratory effort.

What this paper contributes to our knowledge

Management of the buffering function using the Stewart model is a feasible strategy to achieve a low tidal volume.

Methods

Study Population

The medical records of 630 consecutive patients admitted to the medical and surgical ICU of the Osaka University Hospital from January 1, 2014, to December 31, 2014, were reviewed retrospectively. 59.2% of the patients were admitted to the ICU for care after cardiac surgery. Data on arterial blood gases and ventilator and sedation status during the first 14 d after ICU admission were collected from subjects' records. This study was approved by the Institutional Review Board of Osaka University Hospital (No. 15239).

The mechanical ventilation strategy in the ICU was as follows. The attending ICU physicians determined the ventilator mode and setting adjustments according to the status of each subject. Generally, target V_T was in the range of 6–8 mL per kg predicted body weight (PBW). However, individual target V_T values were determined by the attending physician according to the status of each subject. The default mechanical ventilation settings were volume controlled synchronized intermittent mandatory ventilation (SIMV) with pressure support ventilation. However, pressure controlled ventilation was used in subjects requiring mechanical ventilation for $>$ 12 h. Pressure targeted ventilation was chosen to maintain better synchrony between the subject's inspiratory effort and the ventilator. Arterial blood gases, which were evaluated regularly every 6 h by the attending nurse or physician, were assessed more frequently if needed. The mechanical ventilation settings at the time of arterial blood gas measurements were recorded on the subjects' charts.

The following sedation strategy was utilized in the ICU. Richmond Agitation Sedation Scale (RASS) scores were evaluated and recorded hourly during sedation by the attending nurse. The primary goal of sedation in subjects receiving invasive mechanical ventilation is to attain RASS scores of 0 to -2. In subjects who were deemed to need deep sedation by the attending physician, the target RASS score was set to -4 or -5. In this study, the primary goal with deep sedation was the stabilization of circulatory status because approximately half of the subjects were in the ICU for care after cardiac surgery. The first-line and second-line sedatives were propofol and dexmedetomidine, respectively, and midazolam was added if these 2 drugs were inadequate. For subjects with significantly unstable

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circulatory status, midazolam was preferred over propofol. If needed, fentanyl or morphine by continuous infusion was used as an analgesic, per the attending physician's evaluation. Bolus opioids were approved and delivered by the attending nurses according to the pain score, which was evaluated every hour based on the critical care pain observation tool.[25] The target level of pain relief was defined as < 2. Because most of the subjects in the current study were in postoperative care, the main reason for the narcotics was pain relief of surgical sites.

The strategy for fluid therapy in the ICU was as follows. The basic infusion rate of maintenance fluids was 24 mL/kg body weight daily. The attending ICU physician determined the detailed composition and actual infusion rate of the maintenance solutions, according to the subject's status. Balanced acetate Ringer's solution was used as the regular resuscitation fluid. If needed, 5% human albumin in saline was administered. The regular threshold of blood transfusion was 8 g/dL hemoglobin, and the decision to start a blood transfusion was made by the attending ICU physician.

Data Collection

Data on body weight, height, age, sex, and reason for the ICU admission were collected from the subjects' medical records. Data on pH, P_{aCO_2}, P_{aO_2}, HCO^{3-}, lactate, Na^+, K^+, and Ca^{2+} were derived from the arterial blood gas measurements using an ABL800 Flex blood gas analyzer (Radiometer, Copenhagen, Denmark). Serum albumin, Cl^-, and inorganic phosphate (P) were measured more than once a day at the laboratory of the study hospital; thus, albumin, Cl^-, and *P* values at times that were closest to the times of arterial blood gas measurements were used. The anion gap was calculated according to the following equation[16]: anion gap $= Na^+ - Cl^- - HCO^{3-}$.

Data sets including mechanical ventilation mode, ventilator setting, ventilator status, blood biochemistry, use of opioids, and body temperature at the time of arterial blood gas measurements were reviewed, and data sets that fulfilled the following inclusion criteria were included in the analyses: $P_{aO_2}/F_{IO_2} < 300$ mm Hg with PEEP ≥ 5 cm H_2O; ventilation modes of continuous mandatory ventilation, SIMV, or CPAP with patient triggered pressure-regulated ventilation modes, including pressure controlled ventilation and pressure support ventilation; the presence of spontaneous inspiratory effort confirmed by the difference between the mandatory ventilator rate setting and the actual breathing frequency (if the difference was ≥ 2, subjects were considered to have a maintained inspiratory effort); and a RASS score ≤ -4. The exclusion criteria were as follows: presence of a neurological complication affecting respiratory center function; absence of an arterial cannula for continuous pressure monitoring and blood sampling; no usage of invasive mechanical ventilation; age < 18 y; support provided by a membrane oxygenation device; and cyanosis due to right–left cardiac shunting. One data set per day was included for each subject; however, if more than one data set fulfilled the study criteria, the data set recorded closest to 12 pm was included in the analyses. Mean V_T was calculated by dividing minute volume by breathing frequency. Pressure target was based on the pressure support ventilation and pressure controlled ventilation settings. In subjects receiving SIMV, mean pressure target was calculated from the ratio of mandatory ventilation rate and the breathing frequency.

The Stewart Model

According to the Stewart model, independent variables to determine the acid/base status are P_{aCO_2}, SID, and A_{TOT}. In our study, the following formulae were used to determine the acid/base status[26]:

- SID $= Na^+ + K^+ + Ca^{2+} + Mg^{2+} - Cl^- -$ lactate$^-$
- $A_{TOT} =$ albumin (g/L) $\times$ (0.123 $\times$ pH $-$ 0.631) + P (mmol/L) $\times$ (0.309 $\times$ pH $-$ 0.469)
- strong ion gap $=$ SID $- A_{TOT} - HCO^{3-}$

Although Mg^{2+} measurements were not included in the routine chemistry profile at the study institution, changes in Mg^{2+} are typically very small and can be neglected, so a constant Mg^{2+} value can be assumed in these formulas. In this study, a constant Mg^{2+} value of 1.7 mEq/L was used, as described previously.[20]

All data sets were described based on the V_T/PBW ratio into low V_T ($<$ 8 mL/kg) and high V_T ($\geq$ 8 mL/kg) groups to determine factors associated with low V_T/PBW. In addition, all collected data were categorized by 2 independent variables, SID and A_{TOT}, according to the Stewart model to evaluate non-respiratory (metabolic) acid/base status. Of note, lower SID and higher A_{TOT} levels are causative factors of metabolic acidosis. Accordingly, the data sets were further divided into 4 groups to examine the achievement of a low V_T/PBW under the Stewart model: high SID with low A_{TOT}, high SID with high A_{TOT}, low SID with low A_{TOT}, and low SID with high A_{TOT}. Median SID and A_{TOT} values were used as cutoff values to categorize the high and low groups for both parameters.

Statistical Analysis

Continuous variables were compared using the Mann-Whitney *U* test or the Kruskal-Wallis test. Categorical variables were expressed as numbers with percentages, and values were compared using the chi-square test. In addition, post hoc analysis was performed as needed per the Steel-Dwass method. Univariate analyses of data set

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characteristics were conducted to determine factors associated with the risk of not adhering to the low V_T ventilation policy. Predictive factors with a $P < .2$ in univariate analyses were included in a multivariate logistic regression model. In addition, linear regression analysis was performed to elucidate the correlation of SID, A_{TOT}, and V_T/PBW with the low V_T ventilation policy. For all analyses, $P < .05$ was considered as statistically significant. All data were analyzed with the JMP statistical software version 12.2 (SAS Institute, Cary, North Carolina).

Results

During the study period, 630 patients were admitted to the ICU; of these, 100 subjects who fulfilled the inclusion criteria provided 235 individual data sets of clinical and ventilator parameters (Fig. 1). Table 1 summarizes the characteristics of the matched data sets included in this study. Of these 235 V_T/PBW data sets, 101 and 134 data sets were in the low and high V_T groups, respectively. In addition, the V_T/actual body weight and PEEP values were lower in the low V_T group than in the high V_T group. Furthermore, the breathing frequency, P_{aCO_2}, HCO^{3-}, and SID were higher in the low V_T group than in the high V_T group, whereas, opioids were used more frequently in the high V_T group than in the low V_T group.

The subjects providing these 235 data sets included 34 subjects in the low V_T group, 49 subjects in the high V_T group, and 17 subjects who overlapped both the low and high V_T groups. The actual body weights of subjects in the high V_T group were higher than those of subjects in the low V_T group; however, the differences in other characteristics among the 3 groups were not significant (Table 2).

Table 3 shows the results of the univariate logistic analysis. PEEP, SID, and absence of opioid administration were associated with the attainment of a low V_T. The multivariate logistic analysis included 7 parameters based on the results of the univariate logistic analysis. The number of mechanical ventilation days represented the disease stage, SOFA score represented the severity of the clinical condition, PEEP represented the mechanical ventilation settings, P_{aO_2}/F_{IO_2} indicated lung function, SID represented the acid/base balance of a strong ion, A_{TOT} represented the acid/base balance of a weak ion, and the use of opioids represented the drug treatment. Table 4 shows the results of the multivariate logistic analysis. SID, A_{TOT}, and the use of opioids were associated with V_T/PBW. The median (interquartile range) V_T/PBW in subjects who were administered intravenous opioids was significantly higher than the median V_T/PBW in subjects who did not receive intravenous opioids (8.36 [7.41–9.50] vs 7.67 [6.57–9.13] mL/kg PBW, $P = .01$). Regression analysis revealed that V_T/PBW and SID exhibited a weak inverse correlation and that V_T/PBW and A_{TOT} had a weak correlation (Fig. 2).

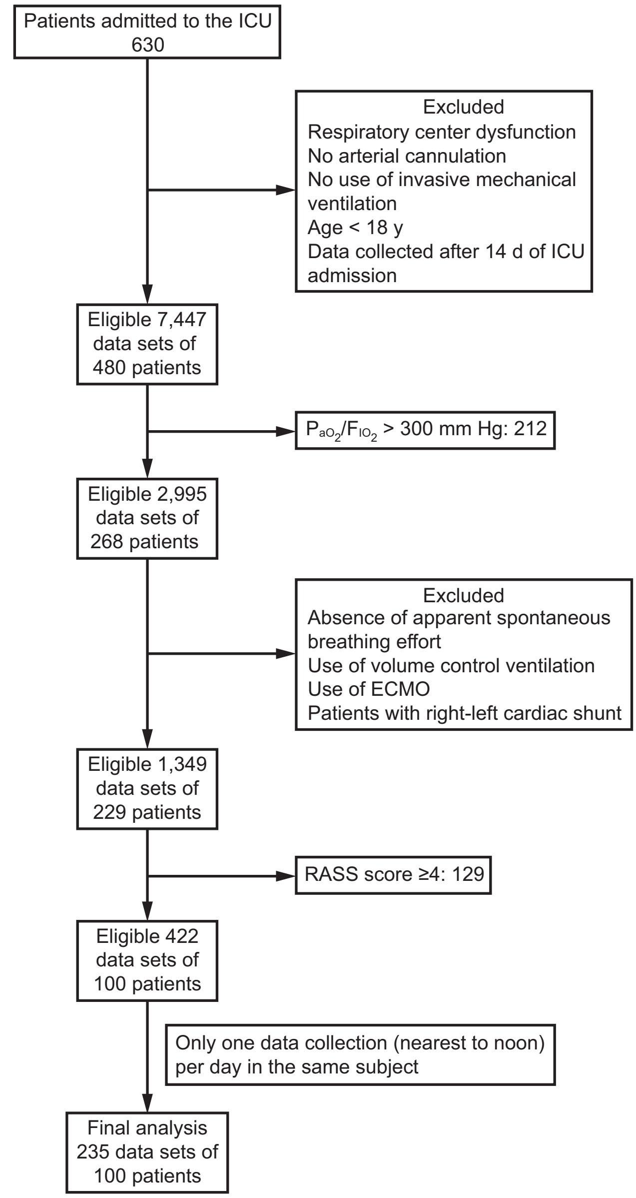

Fig. 1. Flow chart. ECMO = extracorporeal membrane oxygenation.

Figure 3 shows the distribution of all collected data on the A_{TOT}-SID plane. In this study, the distribution of the data sets was as follows: high SID with low A_{TOT} (no. = 46), high SID with high A_{TOT} (no. = 71), low SID with low A_{TOT} (no. = 72), and low SID with high A_{TOT} (no. = 46). The cutoff values for SID and A_{TOT} were median values derived from the data sets of the entire study (41.8 mEq/L for SID and 10.4 mEq/L for A_{TOT}). Importantly, the V_T/PBW in the group with high SID and low A_{TOT} was significantly lower than those in the other 3 groups (Fig. 4).

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Table 1. Characteristics of Data Sets

	All Points (no. = 235)	Low V_T Group (no. = 101)	High V_T Group (no. = 134)	*P*
Subjects, *n*	100	51	66	
V_T/predicted body weight, mL/kg	8.28 (7.24–9.46)	6.94 (6.35–7.55)	9.14 (8.58–10.17)	
V_T/actual body weight, mL/kg	7.61 (6.80–8.70)	7.04 (6.16–7.73)	8.08 (7.45–9.72)	< .001
Duration of mechanical ventilation, d	4 (2–7)	5 (3–8)	4 (2–7)	.066
SOFA score	8 (6–10)	8 (6–10)	8 (6–11)	.34
Body temperature, °C	37.6 (37.1–38.1)	37.5 (37.2–38.1)	37.6 (37.1–38.0)	.97
Mechanical ventilation mode, no.				.89
Assist control	120	50	70	
SIMV	73	33	40	
CPAP	42	18	24	
PEEP, cm H_2O	7 (5–8)	5 (5–8)	7 (5–9)	.004
Pressure target, cm H_2O	14 (10–15)	14 (10–15)	13 (9.75–15)	.42
Mean airway pressure, cm H_2O	10.0 (8.3–13.0)	10.0 (8.3–12.0)	10.0 (8.2–13.0)	.56
Breathing frequency, breaths/min	17 (14–20)	19 (17–25)	16 (14–18)	< .001
Minute volume, L/min	8.0 (6.9–9.5)	8.2 (6.6–9.5)	8.0 (6.9–9.7)	.57
pH	7.429 (7.395–7.459)	7.427 (7.394–7.458)	7.431 (7.400–7.459)	.83
P_{aCO_2}, mm Hg	39.2 (35.7–43.0)	41.4 (38.1–45.1)	37.6 (34.7–41.0)	< .001
P_{aO_2}, mm Hg	109.0 (95.7–119.0)	106.0 (96.8–117.0)	110.0 (95.3–120.0)	.35
HCO^{3-}, mEq/L	25.7 (22.9–27.9)	27.2 (24.7–29.2)	24.9 (22.1–26.8)	< .001
P_{aO_2}/F_{IO_2}, mm Hg	242.3 (208.0–275)	248.8 (224.0–278.5)	236.5 (197.9–267.5)	.052
Lactate, mg/dL	10 (8–14)	10 (8–15)	11 (8–14)	.41
Anion gap, mEq/L	9.8 (8.5–11.7)	10.0 (8.5–11.5)	9.5 (8.4–11.9)	.65
SID, mEq/L	41.8 (38.7–43.9)	43.0 (41.4–44.8)	40.2 (37.9–43.0)	< .001
A_{TOT}, mEq/L	10.4 (9.2–11.5)	10.1 (9.0–11.1)	10.4 (9.4–11.8)	.07
SIG, mEq/L	5.3 (3.7–6.8)	5.5 (3.9–7.0)	5.1 (3.6–6.7)	.30
Use of opioids, *n*	178	67	111	.004

Data sets were stratified based on V_T with threshold < 8 mL/kg predicted body weight. Data are shown as medians (interquartile ranges).
V_T = tidal volume
SOFA = Sequential Organ Failure Assessment
SIMV = synchronized intermittent mandatory ventilation
Anion gap = Na − Cl − HCO^{3-}
SID = strong ion difference ($Na^+ + K^+ + Ca^{2+} + Mg^{2+} - Cl^- -$ lactate$^-$)
A_{TOT} = total nonvolatile weak anions (albumin × [0.123 × pH − 0.631] + *P* × [0.309 × pH − 0.469])
SIG = strong ion gap (SID − A_{TOT} − HCO^{3-})

Table 2. Characteristics of Subjects Whose Data Sets Were Classified as High V_T, Low V_T, and Overlapping V_T Groups

	Low V_T	High V_T	Overlapping V_T	*P*
Subjects, *n*	34	49	17	
Age, y	62 (48–74)	66 (60–75)	66 (60–71)	.27
Male, *n*	26	36	12	.90
Body weight, kg	56.3 (49.3–64.0)	62.3 (57.3–72.0)*	61.0 (53.6–69.5)	.034
Body length, cm	166.5 (154.4–170.6)	161.5 (156.1–165.2)	162.5 (153.7–169.9)	.36
Reason for admission to ICU, *n*				.45
Post-cardiac surgery	24	42	14	
Post-thoracic surgery	1	2	1	
Post-transplantation	3	3	0	
Cardiac failure	0	1	1	
Renal failure	2	0	0	
Respiratory failure	3	1	1	
Sepsis	1	0	0	

The threshold was V_T < 8 mL/kg predicted body weight. Data are shown as medians (interquartile ranges).
* $P < .05$ compared to the low V_T with post-hoc Steel-Dwass test.
V_T = tidal volume

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Table 3. Univariate Analysis of Variables Associated With Attainment of Low V_T Ventilation

Exposures	Odds Ratio (95% CI)	*P*
Duration of mechanical ventilation, d	1.06 (0.98–1.13)	.15
SOFA score	0.93 (0.84–1.02)	.10
Body temperature, °C	1.03 (0.73–1.45)	.88
Mechanical ventilation mode		.89
CPAP/assist control	0.95 (0.47–1.96)	.89
SIMV/assist control	0.87 (0.48–1.56)	.63
CPAP/SIMV	1.10 (0.51–2.38)	.81
PEEP*, cm H_2O	0.87 (0.76–0.97)	.01
Pressure target, cm H_2O	1.02 (0.96–1.10)	.48
pH, $\times 10^{-2}$	0.99 (0.94–1.04)	.69
P_{aO_2}, mm Hg	1.00 (0.98–1.01)	.37
P_{aO_2}/F_{IO_2}, mm Hg	1.00 (1.00–1.01)	.10
Lactate, mg/dL	0.99 (0.94–1.03)	.55
Anion gap, mEq/L	1.00 (0.91–1.11)	.94
SID*, mEq/L	1.19 (1.10–1.29)	< .001
A_{TOT}, mEq/L	0.89 (0.75–1.04)	.15
SIG, mEq/L	1.06 (0.95–1.18)	.28
RASS score, −5/−4	0.93 (0.46–1.93)	.85
Use of continuous intravenous drugs		
Propofol	1.35 (0.73–2.52)	.34
Midazolam	1.13 (0.63–2.02)	.69
Dexmedetomidine	0.98 (0.58–1.65)	.94
Opioid*	0.41 (0.22–0.75)	.004

Odds ratios (95% CIs) are represented with a comparison of the values in the low V_T group against those in the high V_T group. The odds ratio indicates a 1-unit increase in odds for each continuous or binary exposure variable.
* $P < .05$ significant in univariate analysis.
V_T = tidal volume
SOFA = Sequential Organ Failure Assessment
SIMV = synchronized intermittent mandatory ventilation
SID = strong ion difference ($Na^+ + K^+ + Ca^{2+} + Mg^{2+} - Cl^- -$ lactate$^-$)
A_{TOT} = total nonvolatile weak anions (albumin × [0.123 × pH − 0.631] + *P* × [0.309 × pH − 0.469])
SIG = strong ion gap (SID − A_{TOT} − HCO^{3-})
RASS = Richmond Agitation Sedation Scale
Anion gap = Na − Cl − HCO^{3-}
PEEP = positive end expiratory airway pressure
Opioids = intravenous administration of morphine and/or fentanyl

Table 4. Multivariate Analysis of Variables Associated With the Attainment of Low V_T Ventilation

Exposures	Odds Ratio (95% CI)	*P*
Duration of mechanical ventilation, d	1.00 (0.92–1.10)	.94
SOFA score	1.01 (0.89–1.14)	.88
PEEP, cm H_2O	0.87 (0.74–1.01)	.066
P_{aO_2}/F_{IO_2}, mm Hg	1.00 (0.99–1.01)	.79
SID, mEq/L*	1.22 (1.12–1.33)	< .001
A_{TOT}, mEq/L*	0.79 (0.65–0.96)	.02
Use of continuous intravenous opioids*	0.39 (0.19–0.78)	.008

Odds ratio (95% CIs) are represented with a comparison of the values in the low V_T group against those in the high V_T group. The odds ratio indicates a 1-unit increase in odds for each continuous or binary exposure variable.
* $P < .05$ significant in multivariate analysis.
V_T = tidal volume
SOFA = Sequential Organ Failure Assessment
SID = strong ion difference ($Na^+ + K^+ + Ca^{2+} + Mg^{2+} - Cl^- -$ lactate$^-$)
A_{TOT} = total nonvolatile weak anions (albumin × [0.123 × pH − 0.631] + *P* × [0.309 × pH − 0.469])

Discussion

In this retrospective study, SID, A_{TOT}, and the use of opioids were associated with the attainment of low V_T in deeply sedated subjects with preserved inspiratory effort. V_T/PBW was significantly lower in in the presence of high SID with low A_{TOT}, indicating a tendency of metabolic alkalosis.

The inspiratory drive of the respiratory center is affected by the pH of the cerebrospinal fluid in the medulla as well as the serum pH level detected by the peripheral chemoreceptor.[27] The inspiratory drive can be controlled by the management of the buffering function of the serum. Our multivariate logistic analysis suggested that SID and A_{TOT} were associated with adherence to low V_T ventilation. In the context of the acid/base balance, higher SID and lower A_{TOT} might reduce V_T/PBW in deeply sedated patients with persistent inspiratory effort. The current findings suggested that V_T/PBW correlated with SID and A_{TOT}. Despite the weak effects of a higher SID and a lower A_{TOT}, efficient management of the buffering function of the serum might be a feasible strategy to achieve low V_T ventilation. For example, SID can be increased by the administration of sodium bicarbonate, whereas a low serum albumin level can attain a low A_{TOT}.

It is difficult to determine the normal ranges of SID and A_{TOT} because their definitions differ among studies. In our study, the cutoff values of SID and A_{TOT} were 41.8 and 10.4 mEq/L, respectively. In a study by Dubin et al,[21] the mean SID and A_{TOT} of normal volunteers were 40.8 and 15.0 mEq/L, respectively, whereas those of the ICU subjects (n = 935) were 39.7 and 11.0 mEq/L, respectively. In addition, Boniatti et al[22] reported that the mean SID and A_{TOT} of survivors were 35.5 and 10.5 mEq/L, respectively, and those of non-survivors were 32.9 and 8.6 mEq/L, respectively, among a cohort of 175 ICU subjects; they also defined the normal ranges of SID as 40–44 mEq/L. Kaplan and Kellum[23] demonstrated that the mean SID of survivors and non-survivors were 37.5 and 31.4 mEq/L, respectively, among a cohort of trauma subjects requiring vascular repair. The cutoff values in our study, therefore, were within previously reported normal ranges for ICU patients. In addition, SID demonstrated a weak positive correlation with A_{TOT}, which was described previously.[24] Metabolic alkalosis due to a low A_{TOT}, such as that induced by hypoalbuminemia, might have been compensated by a decrease in SID.

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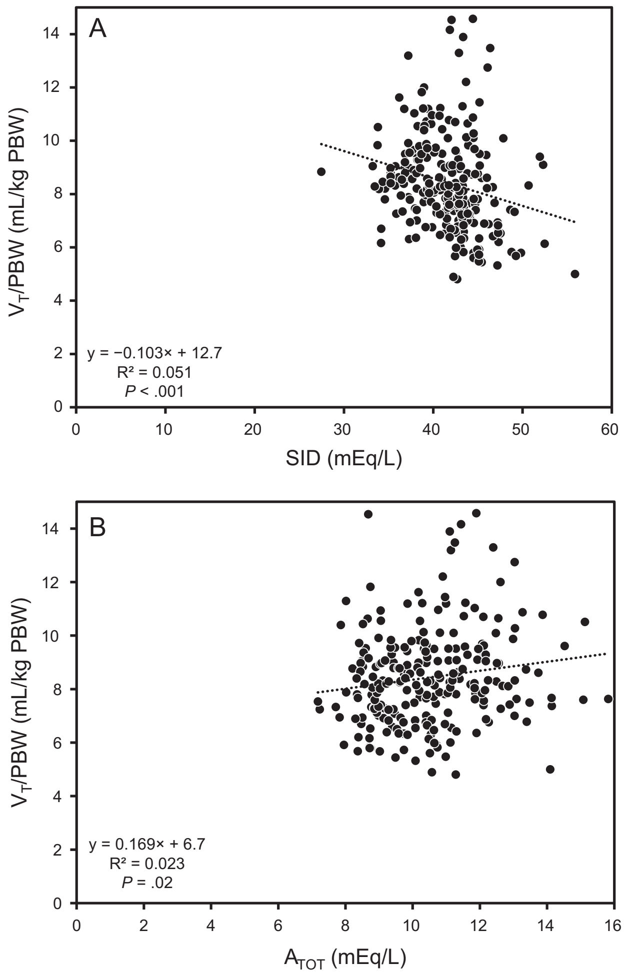

Fig. 2. Regression analysis between strong ion difference (SID) (A), and total nonvolatile weak anion (A_{TOT}) (B) and ratio of tidal volume (V_T) to predicted body weight (V_T/PBW). V_T/PBW exhibits a weak inverse correlation with SID. V_T/PBW and A_{TOT} exhibit a weak correlation.

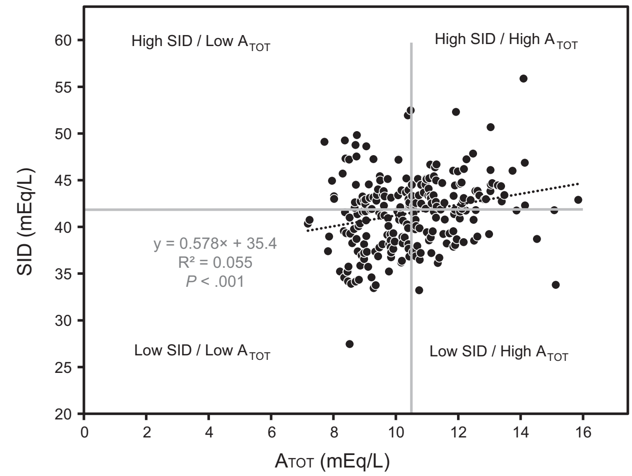

Fig. 3. Distribution of all collected data on the total nonvolatile weak anion (A_{TOT}) and strong ion difference (SID) plane. SID and A_{TOT} exhibit a weak correlation. The data are divided into 4 groups: high SID with low A_{TOT}, high SID with high A_{TOT}, low SID with low A_{TOT}, and low SID with high A_{TOT}. The high and low cutoff values for SID and A_{TOT} are based on median values (41.8 mEq/L SID; 10.4 mEq/L A_{TOT}).

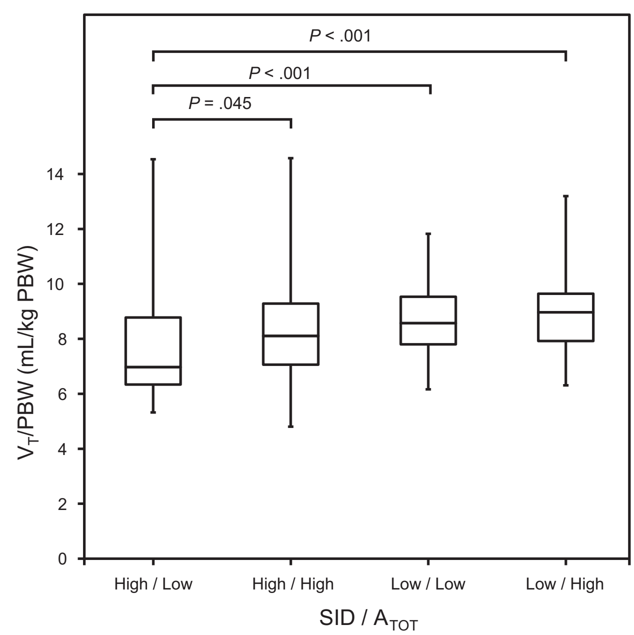

Fig. 4. Tidal volume (V_T)/predicted body weight (V_T/PBW) in the 4 groups divided according to strong ion difference (SID) and total nonvolatile weak anion (A_{TOT}) values. The data are expressed as a medians with interquartile ranges. V_T/PBW in the group with high SID and low A_{TOT} is significantly lower than those in the other 3 groups.

The normal target V_T range is 6–8 mL/kg PBW in the ICU. Targeted V_T for lung protection differs among published studies, with the strictest threshold reported as < 6 mL/kg PBW in subjects with ARDS.[28] Fuiter et al[5] reported that the use of 6–8 mL/kg PBW as target V_T during general anesthesia for major abdominal surgery was associated with improved clinical outcomes and reduced health care utilization. In a meta-analysis, Neto et al[8] reported that a mean V_T of 6.45 mL/kg ideal body weight was associated with improved outcomes in subjects without ARDS. In our study, we selected < 8 mL/kg PBW as the low V_T ventilation threshold, which was similar to that selected by Cooke et al.[29] Although < 8 mL/kg PBW is a lenient definition of low V_T ventilation, it is within the upper 95% CI boundary of the low V_T ventilation arm of the ARDSNet ARMA study.[2]

Reducing V_T in critically ill patients on mechanical ventilation is not easy. Bellani et al[30] reported a V_T of > 8 mL/kg PBW in more than one third of all subjects with ARDS. In a systematic review of 93 studies in subjects with ARDS, conducted after the ARMA study, Jaswal et al[28] concluded that achieving a V_T of ≤ 6 mL/kg PBW might not be easy because the mean V_T was > 6 mL/kg PBW. Neto et al[8]

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reported that low V_T ventilation was achieved in 50.2% of subjects without ARDS in their meta-analysis. In our study, 43.0% of the matched V_T/PBW data sets were classified as low V_T. Despite the lenient low V_T criterion in the current study, the rate of low V_T ventilation attainment was lower than that reported in previous studies.

The most popular approach to attain low V_T ventilation is a reduction in the pressure target. Neto et al[8] reported that the mean pressure target was lower in subjects with low V_T (10.2 cm H_2O) than those with high V_T (17.9 cm H_2O). In our study, the mean pressure target of the low and high V_T groups did not differ and were comparable to that of subjects with low V_T levels in the study by Neto et al.[8] One difference between our study and previous reports is the presence of a spontaneous breathing effort, which was not explicitly reported in a majority of previous studies. In our study, V_T would have decreased if the pressure target had been set lower by the attending physicians. However, an increasing inspiratory drive might preserve V_T. Restricting the pressure target levels might have a limited effect on reducing the V_T in patients with persisting inspiratory efforts. Chen et al[12] reported that the adherence to a low V_T strategy was related to the use of muscle relaxants that suppressed inspiratory muscle activity.

Limitations

The subjects in our study were selected based on the P_{aO_2}/F_{IO_2} ratio according to the Berlin ARDS definition for lung oxygenation. We used the Berlin ARDS definition because subjects with deteriorated lung oxygenation are considered to be affected more by low V_T ventilation. Low V_T ventilation might be associated with improved outcomes in ICU patients receiving ventilatory support for other reasons. Further investigation is thus needed to examine the attainment of low V_T ventilation in subjects without impaired lung oxygenation.

Most of the subjects in our study were admitted to the ICU after cardiac surgery and put under deep sedation for circulatory stabilization. However, the cause could not be determined in all subjects. The study subjects differed from other critically ill populations, especially those intubated for primary respiratory failure. Therefore, it remains unclear whether the results would be different in subjects with respiratory issues as the primary cause of deep sedation.

Our results suggest that the absence of opioid administration was associated with the attainment of low V_T ventilation. This finding does not conflict with known respiratory center depression by opioids, which is mainly evident as a decrease in the breathing frequency. The administration of opioids can also affect the depth of sedation. The nurses in the ICU evaluated the subjects using the RASS scale and pain score every hour, and opioids and sedatives were administered accordingly. To date, no methods can precisely evaluate the depth of sedation and analgesia in ICU patients. In this study, we used RASS scores to evaluate the depth of sedation, which is challenging in patients in the ICU, and the actual depth of sedation might not have been comparable between the groups. It is very difficult to evaluate pain relief in deeply sedated patients, and the difficulty of separating the effects of sedatives from those of opioids is a limitation of this study. Further study is needed to examine the sole effect of opioids on V_T in ICU subjects on mechanical ventilation.

The presence of an inspiratory effort was confirmed by a difference between the total and set breathing frequency and the ventilation frequency settings, as described previously.[29,30] However, it is challenging to assess the level of inspiratory effort precisely. Hence, the presence of an inspiratory effort in entire synchrony with ventilator support remains a possibility. In this study, there is a possibility that not all data sets of the existing inspiratory efforts were collected. Because monitoring esophageal pressure or diaphragmatic electromyography is necessary for precise detection of the inspiratory effort, further studies are warranted to assess the effects of inspiratory effort on low V_T ventilation.

Rapid changes in their status, as well as baseline characteristics of the subjects, affected V_T. Therefore, although subject and ventilation data were collected daily in this study, the volume of data collected differed among the subjects. A previous study demonstrated that adherence to a low V_T strategy was associated with the severity of lung injury,[12] thus the results regarding adherence to low V_T ventilation might have been significantly affected by the subject characteristics in this study. Therefore, due to the inherent limitations of a retrospective single-center study, a prospective study is warranted to investigate the effects of baseline subject characteristics and instantaneous changes in subject status on the attainment of low V_T ventilation in critically ill subjects.

Conclusion

Despite the weak effects of SID and A_{TOT}, efficient management of the buffering function of the serum might be a feasible strategy to achieve low V_T ventilation. Absence of opioid administration was also associated with the attainment of low V_T ventilation in subjects with persisting inspiratory effort.

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