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End-tidal carbon dioxide measurement in preterm infants with low birth weight

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Abstract

Objective

There are conflicting data regarding the use of end-tidal carbon dioxide ($PetCO_2$) measurement in preterm infants. The aim of this study was to evaluate the effects of different dead space to tidal volume ratios (V_D/V_T) on the correlation between $PetCO_2$ and arterial carbon dioxide pressure ($PaCO_2$) in ventilated preterm infants with respiratory distress syndrome (RDS).

Methods

We enrolled ventilated preterm infants (with assist control mode or synchronous intermittent mandatory mode) with RDS who were treated with surfactant in this prospective study. Simultaneous $PetCO_2$ and $PaCO_2$ data pairs were obtained from ventilated neonates monitored using mainstream capnography. Data obtained before and after surfactant treatment were also analyzed.

Results

One-hundred and one $PetCO_2$ and $PaCO_2$ pairs from 34 neonates were analyzed. There was a moderate correlation between $PetCO_2$ and $PaCO_2$ values ($r = 0.603$, $P < 0.01$). The correlation was higher in the post-surfactant treatment group ($r = 0.786$, $P < 0.01$) than the pre-surfactant treatment group ($r = 0.235$). The values of $PaCO_2$ and $PetCO_2$ obtained based on the treatment stage of surfactant therapy were 42.4 ± 8.6 mmHg and 32.6 ± 7.2 mmHg, respectively, in pre-surfactant treatment group, and 37.8 ± 10.3 mmHg and 33.7 ± 9.3 mmHg, respectively, in the post-surfactant treatment group. Furthermore, we found a significant decrease in V_D/V_T in the post-surfactant treatment group when compared to the pre-surfactant treatment group ($P = 0.003$).

Conclusions

V_D/V_T decreased significantly after surfactant therapy and the correlation between $PetCO_2$ and $PaCO_2$ was higher after surfactant therapy in preterm infants with RDS.

Introduction

Preterm neonates are vulnerable to lung injuries, especially when they are affected by respiratory distress syndrome (RDS) and mechanically ventilated. Because of rapid changes in lung mechanics after surfactant therapy [1], lung injury and abnormal or fluctuating carbon dioxide levels may occur if the ventilator setting is not adjusted immediately [2]. Thus, continuous monitoring of the adequacy of breathing and oxygenation is necessary. Although pulse oximetry is widely used as a noninvasive method for continuous monitoring [3], oxygen saturation may be normal even if there is inadequate ventilation [4]. Previous studies have indicated that both low and high partial pressures of arterial carbon dioxide ($PaCO_2$) are associated with long-term morbidity in preterm and term infants [5]. In addition, fluctuating $PaCO_2$ may lead to lung and brain damage [6, 7], and is associated with retinopathy of prematurity [8].

Mainstream measurement of the partial pressure of end-tidal carbon dioxide ($PetCO_2$) is a continuous and noninvasive method to measure blood carbon dioxide tension using with real-time CO_2 waveforms and numerical values immediately displayed on a monitor [9]. $PetCO_2$ has several advantages, such as reduced arterial blood sampling frequency. It also provides a means for the continuous assessment of ventilation without accompanying iatrogenic anemia and is cost-effective [10]. There is a gradient between $PetCO_2$ and $PaCO_2$ ($P(a\text{-}et)CO_2$), which can be determined based on the relationship between ventilation (V), which is airflow to the alveoli, and perfusion (Q_A), which is blood flow to the pulmonary capillaries [11]. On average, the typical V/Q_A is 0.8 and $PetCO_2$ is normally 2–5 mmHg lower than $PaCO_2$, as the mixing volume is diluted in the conducting airways and ends at the alveolar compartment dioxide from the anatomical dead space [12]. V/Q_A mismatch occurs due to heterogeneity in the ratio of ventilation to blood flow in different lung units. Areas of the lung that are perfused but not ventilated are said to possess a shunt. Any physiological perturbation that leads to low blood flow levels relative to ventilation in the alveoli increases physiologic dead space and leads to increased $P(a\text{-}et)CO_2$ [13]. $P(a\text{-}et)CO_2$ may be caused by shallow breathing, over-inflation of the lung and other cardiac or respiratory pathologies [14]. However, earlier studies examining the effects of changes in dead space to tidal volume ratios (V_D/V_T) on $PetCO_2$ and $PaCO_2$ in newborn infant are scant. The purpose of this study was to evaluate the effects of different V_D/V_T on the correlation between $PetCO_2$ and $PaCO_2$ in ventilated preterm infants with RDS before and after surfactant therapy. We hypothesized that the difference between $PetCO_2$ and $PaCO_2$ in ventilated preterm infants with RDS after surfactant therapy will decrease due to the decrease in V_D/V_T.

Materials and methods

Patient population

This single-center, prospective, non-randomized, consecutive enrollment study was approved by the Institutional Review Board of Chang Gung Memorial Hospital in Taoyuan, Taiwan. Preterm infants with RDS who were admitted to the neonatal intensive care unit (NICU) at Chang Gung Memorial Hospital and treated with survanta (berectant, bovine-derived natural

surfactant, AbbVie) between May 2013 and December 2014 were enrolled. Informed consent was obtained from the parents or legal guardians of the patients. Patients with structural cardiopulmonary malformation, those undergoing high-frequency ventilation, and those requiring extracorporeal membrane oxygenation were excluded from the study. The diagnosis of RDS was made based on the classical radiographic appearance, clinical evidence of respiratory distress, laboratory abnormalities due to impaired gas exchange, and the requirement of respiratory support [15]. Surfactant was administered at a dosage of 100 mg/kg, and was divided into 4 quarters following the manufacturer's recommendation when patients failed to maintain saturations in the normal range when FiO_2 was >0.4. A second dose of surfactant may be administered if required at least 6 hours after the preceding dose [16]. The patients were ventilated using pressure-limited, time-cycled ventilators in either assist control mode or synchronous intermittent mandatory ventilation mode. The mechanical ventilators (Babylog 8000 Plus, Dräger Medical) were equipped with basic airway graphic monitors and were calibrated following the manufacturer's recommendations. The initial settings of the ventilator, which were determined using a standard NICU protocol, included a starting respiratory rate of 20 to 40 breaths per minute (bpm) used to maintain a pH of 7.22 to 7.35 and a $PaCO_2$ of 40 to 60 mmHg, a peak inspiratory pressure (PIP) of 15 to 25 cmH_2O, a tidal volume of 4 to 6 ml/kg to produce adequate chest-wall movement, a positive end expiratory pressure (PEEP) of 4 to 6 cmH_2O to maintain adequate lung expansion, and FiO_2 adjusted to maintain arterial partial pressure of oxygen (PaO_2) of 60 to 80mmHg. Infants with very low birth weight (VLBW) whose birth weights were less than 1,500 g were intubated with size 2.5 mm or 3.0 mm endotracheal tubes without cuffs. Non-VLBW (NVLBW) infants whose birth weights were between 1,500 and 2,499 g were intubated using size 3.0 mm or 3.5 mm endotracheal tubes without cuffs.

Blood sampling

The sampling of arterial blood gas (ABG) was carried out before and 1 hour after surfactant administration, and at 24 hours of age during routine medical care. ABG was measured mainly at the umbilicus arterial catheter, although it was measured at peripheral arteries if the umbilicus arterial catheter was not available. Blood gas determination was performed using a blood gas analyzer (Siemens Rapidlab 248 Blood Gas Analyzer).

End-tidal carbon dioxide monitoring

$PetCO_2$ was continuously monitored using mainstream capnography (Philips M2501A Mainstream Capnography). Since the dead space of the sensors and response times may result in false interpretations of $PetCO_2$ readings [17], the sensor was designed for infants with <1 ml of dead space and rise times <60 ms. The infant-type airway adaptor was placed between the endotracheal tube and the Y connection of the ventilator circuit. The capnography device was calibrated according to the manufacturer's instructions. The sensor for $PetCO_2$ was placed prior to blood sampling at each time point. We ensured that the waveform of $PetCO_2$ was continuous and steady by measuring expired CO_2 throughout the ventilator cycle. This allowed us to obtain simultaneous $PetCO_2$ and $PaCO_2$ measurements. $P(a\text{-}et)CO_2$ was recorded along with additional data including the mode of ventilation, tidal volumes, PIP, PEEP, total respiratory rate, mean airway pressure (MAP), oxygenation index (FiO_2 x MAP/PaO_2), PaO_2/FiO_2 ratio, oxygen saturation, blood pressure, and demographic details.

Dead space to tidal volume ratio (V_D/V_T)

V_D/V_T was calculated using the Enghoff modification of the Bohr equation [18]: $V_D/V_T = (PaCO2 - PetCO_2) / PaCO_2$.

Statistical analysis

Continuous data are expressed as mean ± standard deviation. Statistically significant differences were defined using $P < 0.05$. P(a-et)CO_2 was assessed using the Bland-Altman technique. The precision of $PetCO_2$ and the relationship between $PetCO_2$ and $PaCO_2$ in various clinical situations was evaluated using Pearson's correlation coefficients and analyzed using the Statistical Package for the Social Sciences (version 19.0 software). Categorical variables were assessed using chi-square tests. Analyses of variables were performed using independent t tests, while comparisons between the pre-surfactant treatment and post-surfactant treatment groups were carried out using paired t tests. When we compared the parameters according to the treatment stage of surfactant therapy, only the first dose of surfactant was considered.

Results

One-hundred and one $PetCO_2$ and $PaCO_2$ pairs were analyzed from 34 neonates who required ventilation due to RDS and were treated with surfactant. The ventilator parameters were calculated according to the first admission sample and were as follows: mean total respiratory rate (53.8 ± 10.5 bpm), mean tidal volume (5.9 ± 0.2 ml), mean ventilation volume per minute (0.4 ± 0.2 L/min.), mean PIP (16.8 ± 2.5 cmH_2O), mean MAP (9.3 ± 1.2 cmH_2O), mean PEEP (5.1 ± 0.4 cmH_2O), and mean FiO_2 (40.1 ± 10.5%). Sixteen of the infants were NVLBW (mean gestational age 32.3 ± 1.9 weeks and birth weight 1,967 ± 316.5 g). Eighteen infants were VLBW infants (mean gestational age 28.3 ± 1.8 weeks and birth weight 1,084.6 ± 242.6 g). One- hundred and one paired samples (53 from VLBW infants and 48 from NVLBW infants) were used for analysis. The descriptive characteristics of the enrolled patients are depicted in Table 1. There was a significant difference in antenatal corticosteroid use (72.2% vs. 25%,

Table 1. Descriptive characteristics of the enrolled subjects.

Measure	ALL(N = 34)	VLBW(N = 18)	NVLBW(N = 16)	*p*-value
Male/female, *N*	19/15	6/12	13/3	0.005
Birth weight, *M* ± *SD*, *grams*	1499.9 ± 525.2	1084.6 ± 242.6	1967.2 ± 316.5	<0.001
Gestational age, *M* ± *SD*, *weeks*	30.2 ± 2.7	28.3 ± 1.8	32.3 ± 1.9	<0.001
Antenatal corticosteroid use, *n (%)*	17(50.0)	13(72.2)	4(25.0)	0.010
One dose, *n (%)*	6(17.6)	5(27.8)	0(0)	
Second dose, *n (%)*	10(29.4)	8(44.4)	4(25.0)	
Surfactant dose, *n (%)*	34(100)	18(100)	16(100)	0.021
One dose, *n (%)*	27(79.4)	17(94.4)	10(62.5)	
Second dose, *n (%)*	7(20.6)	1(5.6)	6(37.5)	
Diagnosis				
BPD, *n (%)*	12(35.3)	8(44.4)	4(25)	0.253
Mild, *n (%)*	4(11.8)	2(11.1)	2(12.5)	
Moderate, *n (%)*	4(11.8)	2(11.1)	2(12.5)	
Severe, *n (%)*	4(11.8)	4(22.2)	0(0.0)	
PDA, *n (%)*	13(38.2)	9(50.0)	4(25.0)	0.134
Post ligation, *n (%)*	7(20.6)	5(27.8)	2(12.5)	
Ibuprofen treated, *n (%)*	6(17.6)	4(22.2)	2(12.5)	

Abbreviations: VLBW, very low birth weight, birth weight < 1500gm; NVLBW, non-VLBW, birth weight≧1500gm; BPD, Bronchopulmonary dysplasia; PDA, Patent ductus arteriosus; P(a-et)CO_2, The gradient between $PetCO_2$ and $PaCO_2$;V_D/V_T = Dead space to tidal volume ratio

M ± *SD* = mean ± SD

Analysis of *P* value between VLBW and NVLBW

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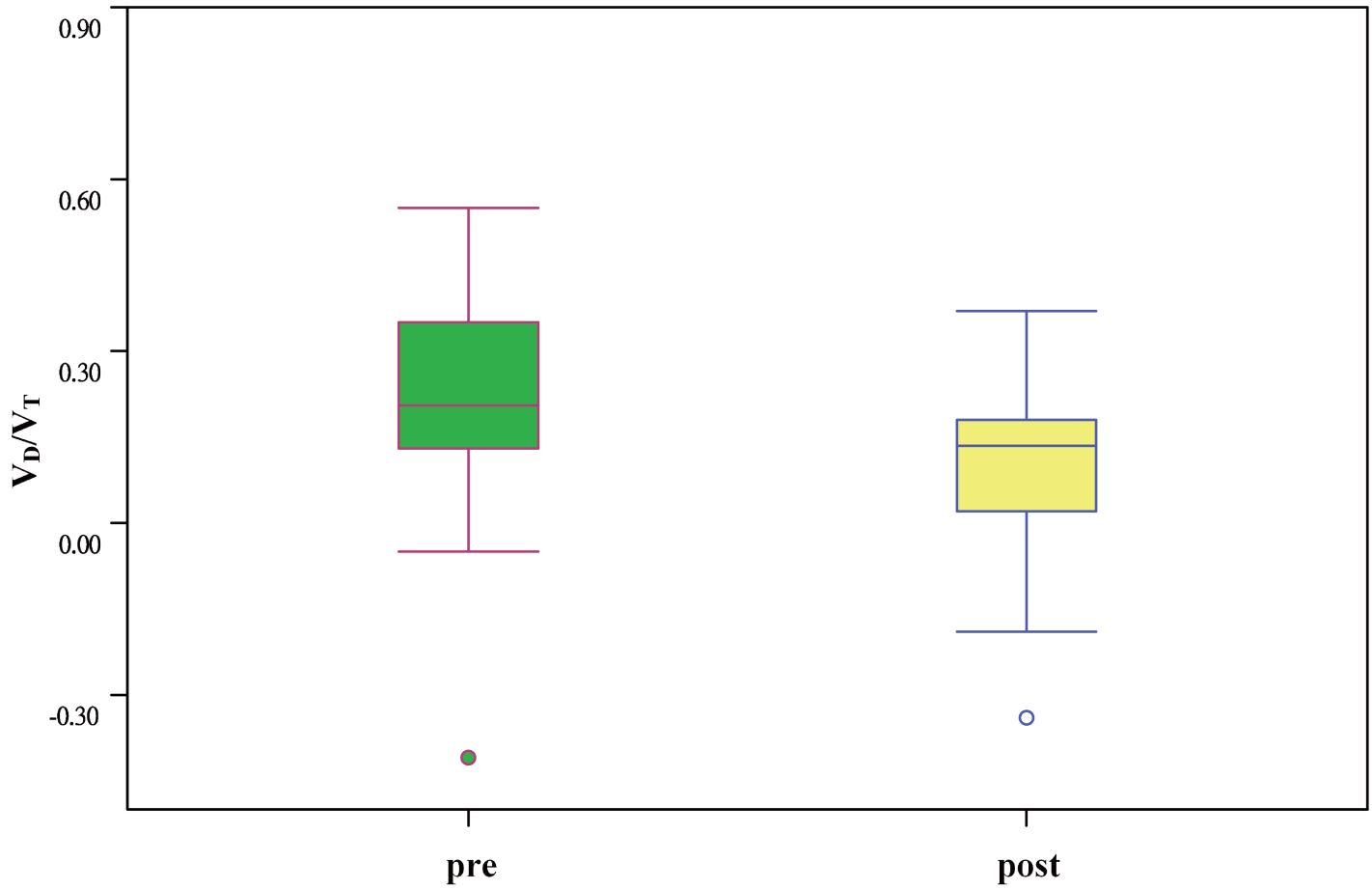

Fig 1. Distribution of V_D/V_T ratio values according to the treatment stage of surfactant therapy (n = 34).

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$P < 0.001$) between the VLBW and NVLBW groups. The incidence of bronchopulmonary dysplasia (44.4% vs.25%, $P = 0.253$) and that of patent ductus arteriosus (50% vs.25%, $P = 0.134$) were not different between VLBW and NVLBW groups, as shown in Table 1.

We analyzed difference between patients receiving surfactant before vs. after therapy according to the first dose of surfactant. There was a significant change in V_D/V_T, in the post-surfactant treatment group when compared to the pre-surfactant treatment group ($P = 0.003$) (Fig 1). The correlation was higher in the post-surfactant treatment group (r = 0.786, $P < 0.01$) than in the pre-surfactant treatment group (r = 0.235). A significant change in $PaCO_2$ (42.4 ± 8.6 mmHg vs. 37.8 ± 10.3 mmHg, $P = 0.018$) and P(a-et)CO_2 (9.8 ± 9.9 mmHg vs. 4.1 ± 6.5 mmHg, $P = 0.004$) was noted between pre-surfactant and post-surfactant treatment (Table 2). When considering the overall sample data, we found a moderate correlation (r = 0.603, $P < 0.01$) between $PetCO_2$ and $PaCO_2$. The mean P(a-et)CO_2 was 5.9 ± 7.6 mmHg. Bland- Altman plots of the comparison of the mean versus the difference in values between $PaCO_2$ and $PetCO_2$ are shown in Fig 2. A scattergram plot of the $PetCO_2$-$PaCO_2$ relationship is shown in Fig 3.

Table 2. Comparison of parameters accoding to the treatement stage of surfactant therapy.

Measure	pre-surfactant	post-surfactant	p-value
Oxygen index, *M* ± *SD*	6.9±5.2	5.0±3.5	0.055
PaO_2/FiO_2 ratio, *M* ± *SD*	190.3±97.4	223.6± 84.5	0.066
$PaCO_2$, *M* ± *SD*, *mm Hg*	42.4±8.6	37.8±10.3	0.018
$PetCO_2$, *M* ± *SD*, *mm Hg*	32.6±7.2	33.7±9.3	0.439
$P(a\text{-}et)CO_2$, *M* ± *SD*, *mm Hg*	9.8±9.9	4.1±6.5	0.004

$P(a\text{-}et)CO_2$ = The gradient between $PetCO_2$ and $PaCO_2$

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Discussion

In this study, we performed mainstream capnography in infants with RDS who were treated with surfactant. We found that there was moderate correlation, but poor agreement, between $PetCO_2$ and $PaCO_2$. Some researchers argue that $PetCO_2$ may not accurately predict $PaCO_2$.

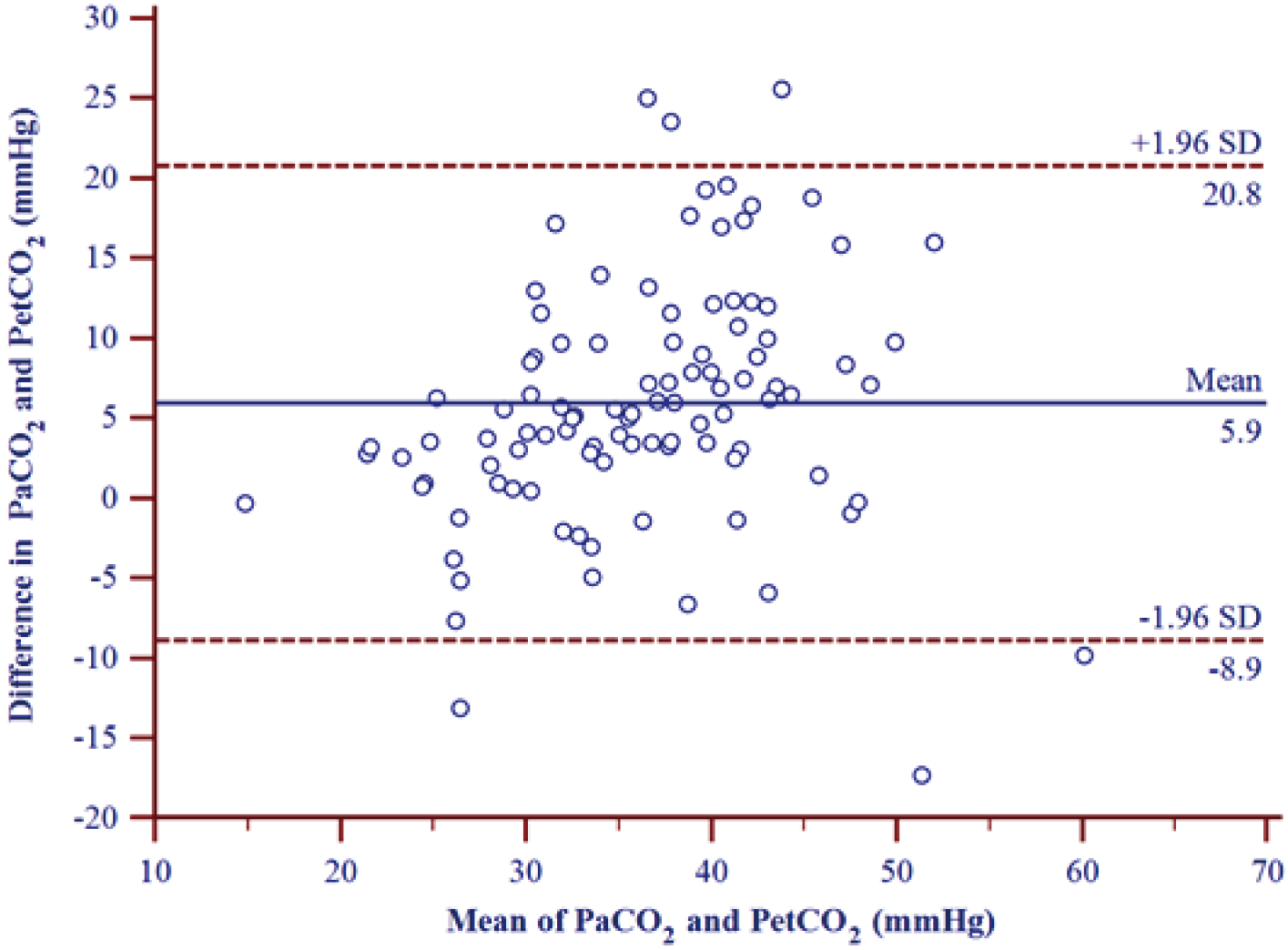

Fig 2. Bland-Altman plot of the difference between the end tidal and arterial CO_2 levels versus the average of the two simultaneous measurements.

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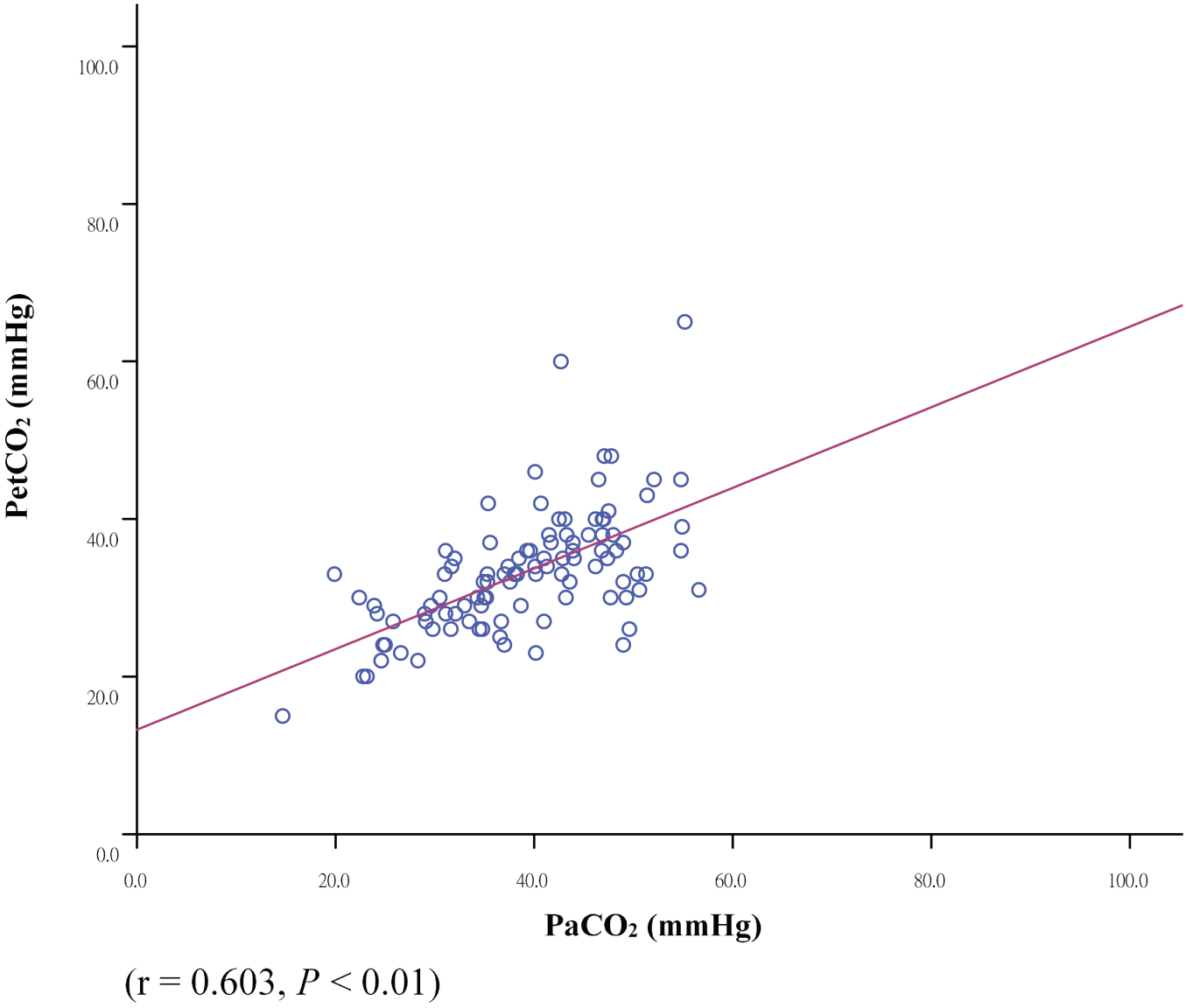

Fig 3. Scattergram plot of the relationship between $PaCO_2$-$PetCO_2$.

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Watkins et al. have reported poor correlation between $PetCO_2$ and $PaCO_2$ in 19 infants with pulmonary disease [19]. Garcia Canto et al. also reported that $PetCO_2$ did not have a good correlation with $PaCO_2$ in 9 ventilated newborns with severe lung illnesses [20]. More recently, Javier et al. reported that there was larger bias and higher precision between $PetCO_2$ and $PaCO_2$ than between $PaCO_2$ and transcutaneous CO_2 [21]. This negative result may have been due to the fact that some samples were obtained from babies who were diagnosed with heart failure [21], and that the response time for the $PetCO_2$ reading (<150 ms) [19] was much longer than normal (<60 ms). In contrast, Wu et al. observed a higher correlation (r = 0.818, $P < 0.001$) between $PetCO_2$ and $PaCO_2$ in 61 infants [22]. In 2012, Daniele et al. reported a positive correlation (r = 0.69, $P < 0.0001$) between $PetCO_2$ and $PaCO_2$ in 45 infants with VLBW [10].

Most previous studies of $PetCO_2$ measurements have not considered the severity of lung diseases. Recently, Bhat et al. reported the correlation between $PetCO_2$ and $PaCO_2$ in a post-surfactant replacement therapy group and concluded that it was more accurate than that in a pre-surfactant replacement therapy group [23]. Similarly, we found a higher correlation between $PetCO_2$ and $PaCO_2$ in the post-surfactant replacement therapy group than the pre-surfactant therapy group. Furthermore, our results showed that V_D/V_T was decreased significantly after surfactant therapy and that the correlation between $PetCO_2$ and $PaCO_2$ was higher after surfactant therapy. Based on our finding that the correlation between $PetCO_2$ and $PaCO_2$ was higher after surfactant therapy, we speculated that our observations may be due to the fact that lung regions with both high and low V_A/Q can occur simultaneously in patients with RDS [24, 25], while V_D/V_T decreases and the oxygenation index is improved after surfactant therapy [26].

McSwain et al. reported that the correlation between $PetCO_2$ and $PaCO_2$ improved significantly in patients admitted to the pediatric intensive care unit with lower V_D/V_T (<0.4) [27]. Bindya et al. also reported sidestream $PetCO_2$ monitoring provided a more accurate reflection of the $PaCO_2$ in patients with lower V_D/V_T (<0.3) [28]. Therefore, $PetCO_2$ may be more accurate in post-surfactant treated infants because of the improvement in V_D/V_T. Whether sidestream or mainstream $PetCO_2$ monitoring is more accurate and suitable for neonates is still controversial [17, 29]. Instead of sidestream $PetCO_2$ monitoring, we used mainstream $PetCO_2$ monitoring in this study and made similar observation in infants with significant improvements in the $PetCO_2/PaCO_2$ correlation when V_D/V_T was decreased.

This study had some limitations. First, the rate of exposure to antenatal corticosteroids was low in the current study. Only 50% of the patients had received antenatal corticosteroids. However, 72.2% of infants with VLBW received antenatal corticosteroids. Second, we did not measure pulmonary mechanical parameters, such as respiratory resistance and dynamic compliance. Evaluation of these parameters may have been helpful in understanding how physiological abnormalities affect the correlation between $PaCO_2$ and $PetCO_2$.

Conclusions

This study was the first to explore the effects of different V_D/V_T values on the correlation between $PetCO_2$ and $PaCO_2$ in ventilated preterm infants with RDS before and after surfactant therapy. Since ABG analysis is not suitable for the collection of continuous data and the observance of trends, more long-term follow-up studies are required to validate the usefulness of $PetCO_2$ for monitoring and evaluating the response to respiratory therapies.

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Author Contributions

Conceptualization: Hsin-Ju Lin, Ching-Tzu Huang, Ming-Chou Chiang, Mei-Jy Jeng.

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Validation: Hsiu-Feng Hsiao.

Writing – original draft: Hsin-Ju Lin.

Writing – review & editing: Ching-Tzu Huang, Ming-Chou Chiang, Mei-Jy Jeng.

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