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

Hsin-Ju Lin¹,², Ching-Tzu Huang¹,²,³, Hsiu-Feng Hsiao¹,³, Ming-Chou Chiang¹,³,⁴‡, Mei-Jy Jeng²,⁵‡ *

¹ Department of Respiratory Therapy, Chang Gung Memorial Hospital, Taoyuan, Taiwan, ² Institute of Emergency and Critical Care Medicine, National Yang-Ming University, Taipei, Taiwan, ³ Chang Gung University College of Medicine, Taoyuan, Taiwan, ⁴ Division of Neonatology, Department of Pediatrics, Chang Gung Memorial Hospital, Taoyuan, Taiwan, ⁵ Department of Pediatrics, Children’s Medical Center, Taipei Veterans General Hospital, Taipei, Taiwan

☯ These authors contributed equally to this work.
‡ These authors also contributed equally to this work.
* newborntw@gmail.com (MCC); mjeng@vghtpe.gov.tw (MJJ)

Abstract

Objective
There are conflicting data regarding the use of end-tidal carbon dioxide (PetCO₂) 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 PetCO₂ and arterial carbon dioxide pressure (PaCO₂) 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 PetCO₂ and PaCO₂ 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 PetCO₂ and PaCO₂ pairs from 34 neonates were analyzed. There was a moderate correlation between PetCO₂ and PaCO₂ 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 PaCO₂ and PetCO₂ 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

\(\frac{V_D}{V_T}\) 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 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\(_2\) (\(P(a-et)CO_2\)), 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 \(P(a-et)CO_2\) [13]. \(P(a-et)CO_2\) 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 surfactant (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 FiO2 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 PaCO2 of 40 to 60 mmHg, a peak inspiratory pressure (PIP) of 15 to 25 cmH2O, 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 cmH2O to maintain adequate lung expansion, and FiO2 adjusted to maintain arterial partial pressure of oxygen (PaO2) of 60 to 80 mmHg. 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**

PetCO2 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 PetCO2 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 PetCO2 was placed prior to blood sampling at each time point. We ensured that the waveform of PetCO2 was continuous and steady by measuring expired CO2 throughout the ventilator cycle. This allowed us to obtain simultaneous PetCO2 and PaCO2 measurements. P(a-et)CO2 was recorded along with additional data including the mode of ventilation, tidal volumes, PIP, PEEP, total respiratory rate, mean airway pressure (MAP), oxygenation index (FiO2 x MAP/PaO2), PaO2/FiO2 ratio, oxygen saturation, blood pressure, and demographic details.

**Dead space to tidal volume ratio (Vd/VT)**

Vd/VT was calculated using the Enghoff modification of the Bohr equation [18]: Vd/VT = (PaCO2 – PetCO2) / PaCO2.
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$_2$O), mean MAP ($9.3 ± 1.2$ cmH$_2$O), mean PEEP ($5.1 ± 0.4$ cmH$_2$O), 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)          |         |
| 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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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.

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

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Table 2. Comparison of parameters according to the treatment 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   |
| PaO₂/FiO₂ ratio, M ± SD  | 190.3±97.4     | 223.6±84.5      | 0.066   |
| PaCO₂, M ± SD, mm Hg     | 42.4±8.6       | 37.8±10.3       | 0.018   |
| PetCO₂, M ± SD, mm Hg    | 32.6±7.2       | 33.7±9.3        | 0.439   |
| P(a-et)CO₂, M ± SD, mm Hg| 9.8±9.9        | 4.1±6.5         | 0.004   |

P(a-et)CO₂ = The gradient between PetCO₂ and PaCO₂

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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 PetCO₂ and PaCO₂. Some researchers argue that PetCO₂ may not accurately predict PaCO₂.
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.
Data curation: Hsiu-Feng Hsiao.
Resources: Ming-Chou Chiang.
Supervision: Mei-Jy Jeng.

Validation: Hsiu-Feng Hsiao.

Writing – original draft: Hsin-Ju Lin.

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

References

1. Baraldi E, Pettenazzo A, Filippone M, Magagnin GP, Saia OS, Zacchello F. Rapid improvement of static compliance after surfactant treatment in preterm infants with respiratory distress syndrome. Pediatr Pulmonol. 1993; 15: 157–162. PMID: 8327278

2. Attar MA, Donn SM. Mechanisms of ventilator-induced lung injury in premature infants. Seminars in Neonatology 2002; 7: 353–360. PMID: 12464497

3. Niknafs P, Norouzi E, Bahman Bijari B, Baneshi MR. Can we Replace Arterial Blood Gas Analysis by Pulse Oximetry in Neonates with Respiratory Distress Syndrome, who are Treated According to INSURE Protocol? Iran J Med Sci. 2015; 40:264–267. PMID: 25999627

4. Ortega R, Connor C, Kim S, Djang R, Patel K. Monitoring ventilation with capnography. N Engl J Med. 2012; 367: e27. https://doi.org/10.1056/NEJMvcm1105237 PMID: 23134404

5. Bruschetti M, Romsik O, Zappettini S, Ramenghi LA, Calevo MG. Transcutaneous carbon dioxide monitoring for the prevention of neonatal morbidity and mortality. Cochrane Database Syst Rev. 2016; 2: CD011494. https://doi.org/10.1002/14651858.CD011494.pub2 PMID: 26874180

6. Lim WH, Lien R, Chiang MC, Fu RH, Lin JJ, Chu SM, et al. Hypernatremia and grade III/IV intraventricular hemorrhage among extremely low birth weight infants. J Perinatol. 2011; 31: 193–198. https://doi.org/10.1038/jp.2010.86 PMID: 20671713

7. Fabres J, Carlo WA, Phillips V, Howard G, Ambalavanan N. Both extremes of arterial carbon dioxide pressure and the magnitude of fluctuations in arterial carbon dioxide pressure are associated with severe intraventricular hemorrhage in preterm infants. Pediatrics. 2007; 119(2):299–305. https://doi.org/10.1542/peds.2006-2434 PMID: 17272619

8. Hauspurg AK, Allred EN, Vanderveen DK, Chen M, Bednarek FJ, Cole C, et al. Blood gases and retinopathy of prematurity: the ELGAN Study. Neonatology. 2011; 99(2):104–11. https://doi.org/10.1159/000308454 PMID: 20689332

9. Thompson JE, Jaffe MB. Capnographic waveforms in the mechanically ventilated patient. Respir Care. 2005; 50(1):100–8; discussion 8–9. PMID: 15636648

10. Trevisanuto D, Giuliotto S, Cavallin F, Doglioni N, Toniazzo S, Zanardo V. End-tidal carbon dioxide monitoring in very low birth weight infants: correlation and agreement with arterial carbon dioxide. Pediatr Pulmonol. 2012; 47: 367–372. https://doi.org/10.1002/ppul.21558 PMID: 22102598

11. Cheifetz IM, Myers TR. Respiratory therapies in the critical care setting. Should every mechanically ventilated patient be monitored with capnography from intubation to extubation? Respir Care. 2007; 52: 423–438, discussion 38–42. PMID: 17417977

12. Sullivan KJ, Kissoon N, Goodwin SR. End-tidal carbon dioxide monitoring in pediatric emergencies. Pediatric Emergency Care. 2005; 21: 327–332, quiz 33–35. PMID: 15874818

13. Siobal MS. Monitoring Exhaled Carbon Dioxide. Respir Care. 2016; 61: 1397–1416. https://doi.org/10.4187/respcare.04919 PMID: 27601718

14. Walsh BK, Crotwell DN, Restrepo RD. Capnography/Capnometry during mechanical ventilation: 2011. Respir Care. 2011; 56: 503–509. https://doi.org/10.4187/respcare.01175 PMID: 21255512

15. Donn SM, Sinha SK. Manual of Neonatal Respiratory Care. Springer International Publishing; 2017.

16. Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Plavka R, et al. European Consensus Guidelines on the Management of Respiratory Distress Syndrome—2016 Update. Neonatology. 2016; 111: 107–125. https://doi.org/10.1159/000448985 PMID: 27649091

17. Schmalisch G. Current methodological and technical limitations of time and volumetric capnography in newborns. Biomedical engineering online. 2016; 15:104. https://doi.org/10.1186/s12938-016-0228-4 PMID: 27676441

18. Verschueren S, Massion PB, Verschuren F, Damas P, Magder S. Volumetric capnography: lessons from the past and current clinical applications. Crit Care. 2016; 20: 184. https://doi.org/10.1186/s13054-016-1377-3 PMID: 27334879

19. Watkins AM, Weindling AM. Monitoring of end tidal CO2 in neonatal intensive care. Arch Dis Child. 1987; 62: 837–839. PMID: 3116949
20. Garcia Canto E, Gutierrez Laso A, Izquierdo Macian I, Alberola Perez A, Morcillo Sopena F. [The value of capnography and exhaled CO2 in neonatal intensive care units]. An Esp Pediatr. 1997; 47: 177–180. PMID: 9382351

21. Urbano J, Cruzado V, Lopez-Herce J, del Castillo J, Bellon JM, Carrillo A. Accuracy of three transcutaneous carbon dioxide monitors in critically ill children. Pediatr Pulmonol. 2010; 45: 481–486. https://doi.org/10.1002/ppul.21203 PMID: 20425856

22. Wu CH, Chou HC, Hsieh WS, Chen WK, Huang PY, Tsao PN. Good estimation of arterial carbon dioxide by end-tidal carbon dioxide monitoring in the neonatal intensive care unit. Pediatr Pulmonol. 2003; 35: 292–295. https://doi.org/10.1002/ppul.10260 PMID: 12629627

23. Bhat YR, Abhishek N. Mainstream end-tidal carbon dioxide monitoring in ventilated neonates. Singapore Med J. 2008; 49: 199–203. PMID: 18363000

24. Billman D, Nicks J, Schumacher R. Exosurf rescue surfactant improves high ventilation-perfusion mismatch in respiratory distress syndrome. Pediatr Pulmonol. 1994; 18: 279–283. PMID: 7898965

25. Hand IL, Shepard EK, Krauss AN, Auld PA. Ventilation-perfusion abnormalities in the preterm infant with hyaline membrane disease: a two-compartment model of the neonatal lung. Pediatr Pulmonol. 1990; 9: 206–213. PMID: 2124345

26. Chung EH, Ko SY, Kim IY, Chang YS, Park WS. Changes in dead space/tidal volume ratio and pulmonary mechanics after surfactant replacement therapy in respiratory distress syndrome of the newborn infants. Journal of Korean medical science. 2001; 16: 51–56. https://doi.org/10.3346/jkms.2001.16.1.51 PMID: 11289401

27. McSwain SD, Hamel DS, Smith PB, Gentile MA, Srinivasan S, Meliones JN, et al. End-tidal and arterial carbon dioxide measurements correlate across all levels of physiologic dead space. Respir Care. 2010; 55: 288–293. PMID: 20196877

28. Singh BS, Gilbert U, Singh S, Govindaswami B. Sidestream microstream end tidal carbon dioxide measurements and blood gas correlations in neonatal intensive care unit. Pediatr Pulmonol. 2013; 48: 250–256. https://doi.org/10.1002/ppul.22593 PMID: 22589000

29. Balogh AL, Petak F, Fodor GH, Tolnai J, Csorba Z, Babik B. Capnogram slope and ventilation dead space parameters: comparison of mainstream and sidestream techniques. British Journal of Anaesthesia. 2016; 117: 109–117. https://doi.org/10.1093/bja/aew127 PMID: 27317710