Reduction in minute alveolar ventilation causes hypercapnia in ventilated neonates with respiratory distress

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Abstract

Hypercapnia occurs in ventilated infants even if tidal volume ($V_T$) and minute ventilation ($V_E$) are maintained. We hypothesised that increased physiological dead space ($V_{d,phys}$) caused decreased minute alveolar ventilation ($V_A$; alveolar ventilation ($V_A$) × respiratory rate) in well-ventilated infants with hypercapnia. We investigated the relationship between dead space and partial pressure of carbon dioxide ($PaCO_2$) and assessed $V_A$. Intubated infants ($n$ = 33; mean birth weight, 2257 ± 641 g; mean gestational age, 35.0 ± 3.3 weeks) were enrolled. We performed volumetric capnography ($V_{cap}$), and calculated $V_{d,phys}$ and $V_A$ when arterial blood sampling was necessary. $PaCO_2$ was positively correlated with alveolar dead space ($V_{d,alv}$) ($r$ = 0.54, $p$ < 0.001) and $V_{d,phys}$ ($r$ = 0.48, $p$ < 0.001), but not Fowler dead space ($r$ = 0.14, $p$ = 0.12). Normocapnia (82 measurements; 35 mmHg ≤ $PaCO_2$ < 45 mmHg) and hypercapnia groups (57 measurements; 45 mmHg ≤ $PaCO_2$) were classified. The hypercapnia group had higher $V_{d,phys}$ (median 0.57 (IQR, 0.44 – 0.67)) than the normocapnia group (median $V_{d,phys}$/VT = 0.46 (IQR, 0.37–0.58)), with no difference in VT. The hypercapnia group had lower $V_A$ (123 (IQR, 87–166) ml/kg/min) than the normocapnia group (151 (IQR, 115–180) ml/kg/min), with no difference in $V_E$.

Conclusion: Reduction of $V_A$ in well-ventilated neonates induces hypercapnia, caused by an increase in $V_{d,phys}$.

What is Known:
• Volumetric capnography based on ventilator graphics and capnograms is a useful tool in determining physiological dead space of ventilated infants and investigating the cause of hypercapnia.

What is New:
• This study adds evidence that reduction in minute alveolar ventilation causes hypercapnia in ventilated neonates.

Keywords Alveolar dead space • Alveolar ventilation • Hypercapnia • Neonatal intensive care unit • Physiological dead space • Volumetric capnography

Abbreviations

$V_{d,alv}$ Alveolar dead space
$V_A$ Alveolar ventilation
$P_{E,CO_2}$ Expiratory CO$_2$
$V_{T,E}$ Expired tidal volume
$V_{d,Fowler}$ Fowler dead space

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Introduction

An optimal arterial carbon dioxide concentration, measured by the partial pressure of carbon dioxide (PaCO₂), is critical during mechanical ventilation. Both hypercapnia and hypocapnia can contribute to brain damage in immature infants. Tighter control of PaCO₂ may be achieved in mechanically ventilated infants by setting appropriate minute ventilation (Vₑ), defined by tidal volume (Vₜ) and the respiratory rate (RR) [1]. However, even when Vₜ or Vₑ are maintained, hypercapnia can occur. Vₜ comprises Fowler dead space (Vₜ,Fowler) volume of air in instruments and airways), alveolar dead space (Vₜ,alv volume of ventilated alveoli that do not receive blood flow and thus no gas exchange), and alveolar ventilation (Vₜ,alv volume of alveoli with gas exchange). Therefore, minute alveolar ventilation (Vₑ), which is calculated as Vₑ × RR, is the key contributor in maintaining appropriate PaCO₂ [2, 3].

The physiological dead space (Vₑ,phys), which is the sum of Vₑ,Fowler and Vₑ,alv, is commonly calculated in ventilated patients using volumetric capnography (Vₜ,cap). This method employs a plot of expiratory CO₂ (Pₜ,CO₂) versus expired tidal volume (Vₑ), and specialised equipment with effective apparatus dead space for newborns with low Vₑ [4]. We have previously reported the analysis of Vₜ,cap using ventilator graphics and capnograms with low dead-space cap-OONE (Nihon Kohden, Tokyo, Japan) mainstream capnometers [5].

We hypothesised decreased Vₑ was caused by increased Vₑ,phys in well-ventilated infants with hypercapnia. The objective of this current study was to clarify the relationship between dead space and PaCO₂, and to assess Vₑ in intubated well-ventilated neonates with hypercapnia, using Vₜ,cap based on ventilator graphics and capnograms. We present evidence here that hypercapnia is attributed to decreased Vₑ due to increased Vₑ,phys.

Materials and methods

Patient population

This was a single-centre, prospective, non-randomised study with consecutive patient enrolment, approved by the clinical ethics committee of the National Hospital Organization Maizuru Medical Center in Kyoto, Japan. Informed consent was obtained from all parents. Ventilated infants with arterial lines admitted to the NICU between December 2017 and December 2019 were enrolled. Infants with a greater than 10% air leak, or with extremely low birth weights, were excluded (Fig. 1). Infants received either volume-targeted or pressure-controlled time-cycled ventilation at the discretion of each neonatologist via a VN500 (Dräger Medical, Lübeck, Germany) in synchronous intermittent mandatory ventilation mode. Infants who weighed < 2500 g were intubated using either 2.5-mm or 3.0-mm endotracheal tubes without cuffs (Portex: Smiths Medical Japan, Tokyo, Japan). Infants weighing 2500 g or more were ventilated with 3.0-mm endotracheal tubes with cuffs (MicrocuffPET: Halyard, GA, USA) to reduce air leakage. We adjusted the positive end-expiratory pressure (PEEP) and fraction of inspired oxygen to maintain the saturation of percutaneous oxygen between 90 and 98%; we set the peak inspiratory pressure (PIP) to achieve a Vₑ of approximately 5 mL/kg. We performed volumetric capnography when infants were well-ventilated (200 ml/kg/minute ≤ Vₑ, and 3.5 ml/kg ≤ Vₑ).

Medical records were reviewed for information regarding the patients’ characteristics, and clinical, prenatal, and perinatal data. The diagnosis of respiratory distress syndrome (RDS)
was defined as infants who had clinical manifestations (tachypnoea, nasal flaring, and or grunting), and radiologic signs such as air bronchogram or widespread granular opacities. We administered surfactant to infants diagnosed with RDS who had severe clinical symptoms. The diagnosis of persistent pulmonary hypertension of the newborns (PPHN) was confirmed by echocardiography with evidence of increased pulmonary pressure with demonstrable right-to-left shunts across the ductus arteriosus or foramen ovale. Pneumothorax and meconium aspiration syndrome (MAS) were diagnosed according to medical history, clinical manifestations, and chest X-ray.

**Waveform sampling and \( V_{\text{cap}} \) based on waveforms**

\( P_{\text{ET}} \text{CO}_2 \) was continuously monitored using cap-ONE (sampling frequency, 40 Hz; dead space, 0.5 mL) placed between the endotracheal tube and flow sensor of the ventilator circuit. While ventilated neonates received arterial blood sampling necessary for treatment, we simultaneously obtained the capnogram waveforms of cap-ONE and volume waveforms of the ventilator in the supine position, using a screen capture programme, with ventilator parameters. Our method of analysis has previously been described [5]. Briefly, we manually superimposed the capnogram waveforms and volume waveforms at the beginning of inspiration, and measured the \( P_{\text{ET}} \text{CO}_2 \) and \( V_{\text{T,E}} \) values at the same time at 30–50 points from the start to the end of expiration using ImageJ software (http://rsb.info.nih.gov/ij/). Subsequently, \( P_{\text{ET}} \text{CO}_2 \) was plotted against \( V_{\text{T,E}} \) for a single breath. \( V_{\text{d,Fowler}} \), \( V_{\text{d,alv}} \), and \( V_{\text{A}} \) were calculated from the resulting curve, as described by Fletcher [6] (Fig. 2). The mean of at least three consecutive breaths was normalised to body weight at measurement. \( V_{\text{d,phys}} \) was calculated as \( V_{\text{d,Fowler}} + V_{\text{d,alv}} \). \( V_{\text{E}} \) and \( V_{\text{A}} \) were calculated as follows: \( V_{\text{E}} = V_{\text{T}} \times RR \), and \( V_{\text{A}} = V_{\text{A}} \times RR \), respectively.

We performed regression analysis to evaluate the correlation between \( \text{PaCO}_2 \) and \( V_{\text{T/kg}} \) or dead space from the obtained samples. Next, hypocapnia measurements (\( \text{PaCO}_2 < 35 \text{ mmHg} \)) were excluded due to the small sample number and the remaining data points were classified as either normocapnia (\( 35 \text{ mmHg} \leq \text{PaCO}_2 < 45 \text{ mmHg} \)), or hypercapnia (\( 45 \text{ mmHg} \leq \text{PaCO}_2 \)) to clarify the normative reference data.

**Statistical analyses**

The data were tested for normality with the Kolmogorov–Smirnov test; data were non-normally distributed. We analysed the correlation between \( \text{PaCO}_2 \) and each dead space using Spearman’s correlation coefficients, and compared normocapnia and hypercapnia using the Mann–Whitney \( U \) test with Excel Tokei 2019 (Social Survey Research Information, Tokyo, Japan). Statistical significance was set at \( p < 0.05 \).

**Results**

The study population consisted of 33 ventilated infants with a mean gestational age of 35.0 ± 3.3 weeks and a mean birth weight of 2257 ± 641 g (Table 1). The predominant reasons for mechanical ventilation were as follows: RDS (66%), PPHN (12%), asphyxia (12%), pneumothorax (6%), and MAS (3%).

One hundred fifty-four measurements obtained from 33 ventilated infants were used for the regression analysis of the relationship between \( \text{PaCO}_2 \) and \( V_{\text{T/kg}} \) or each dead space. Figure 3 shows that \( \text{PaCO}_2 \) values were positively correlated with \( V_{\text{d,alv}}/V_{\text{T}} (r = 0.54, p < 0.001) \) and \( V_{\text{d,phys}}/V_{\text{T}} (r = 0.48, p < 0.001) \), but not with \( V_{\text{T/kg}} (r = 0.09, p = 0.35) \) and \( V_{\text{d,Fowler}}/V_{\text{T}} (r = 0.14, p = 0.12) \).

There were 82 normocapnia and 57 hypercapnia measurements. Table 2 presents the ventilator parameters and measurement values for each group. Higher respiratory settings such as PIP and MAP, but not PEEP, were needed in the hypercapnia group than in the normocapnia group. The difference in \( V_{\text{d,alv}} \) and \( V_{\text{d,phys}} \) between the normocapnia and hypercapnia groups, while \( V_{\text{T}} \) and \( V_{\text{d,Fowler}} \) showed no difference. \( V_{\text{d,alv}} \) and \( V_{\text{d,phys}} \) were higher...
in the hypercapnia group (median $V_{d,alv}/V_T = 0.17$ (IQR, 0.11–0.24); median $V_{d,phys}/V_T = 0.57$ (IQR, 0.44–0.67)), compared with the normocapnia group (median $V_{d,alv}/V_T = 0.12$ (IQR, 0.07–0.16); median $V_{d,phys}/V_T = 0.46$ (IQR, 0.37–0.58)). $V_A$ was lower in the hypercapnia group (median $V_A/V_T = 0.43$ (IQR, 0.33 to 0.54)) compared with the normocapnia group (median $V_A/V_T = 0.54$ (IQR, 0.42–0.62)).

Moreover, the hypercapnia group had a lower median $V_A$ (123 (IQR, 87–166) ml/kg/min) relative to the normocapnia group (151 (IQR, 115–180) ml/kg/min), even though there was no difference in $V_E$.

**Discussion**

The present study demonstrated that $\text{PaCO}_2$ values and dead-space ratios were correlated, and that ventilated infants with hypercapnia had a higher $V_{d,phys}$, which resulted in a decrease of $V_A$ in the absence of a difference in either $V_T$ or $V_E$.

| Parameter                      | Clinical data of the study population ($n = 33$) |
|--------------------------------|-----------------------------------------------|
| Gestational age, weeks         | 35.0 ± 3.3                                    |
| 32–36 weeks, $n$ (%)           | 14 (42)                                       |
| <32 weeks, $n$ (%)             | 7 (21)                                        |
| Birth weight, g                | 2257 ± 641                                    |
| 1500–2500 g, $n$ (%)           | 13 (39)                                       |
| 1000–1500 g, $n$ (%)           | 5 (15)                                        |
| Male/female, $n$               | 20/13                                         |
| Cesarean section, $n$ (%)      | 22 (66)                                       |
| Twin birth, $n$ (%)            | 7 (21)                                        |
| Apgar score at 1 min           | 5.8 ± 3.0                                     |
| Apgar score at 5 min           | 7.1 ± 2.6                                     |
| Surfactant treatment $n$ (%)   | 15 (45)                                       |
| Antenatal corticosteroids $n$ (%) | 12 (33)                                   |
| Endotracheal tubes             |                                               |
| 3.0 mm with cuff $n$ (%)       | 13 (39)                                       |
| 3.0 mm without cuff $n$ (%)    | 15 (45)                                       |
| 2.5 mm without cuff $n$ (%)    | 5 (15)                                        |

Values are represented as means (± standard deviations) or medians (interquartile ranges), unless specified otherwise.

**Fig. 3** Correlation analysis between $\text{PaCO}_2$ and dead space. $\text{PaCO}_2$ values were positively correlated with $V_{d,alv}$ ($r = 0.54$, $p < 0.001$) and $V_{d,phys}$ ($r = 0.48$, $p < 0.001$), but not $V_T/kg$ ($r = 0.09$, $p = 0.35$) and $V_{d,Fowler}$ ($r = 0.14$, $p = 0.12$). $\text{PaCO}_2$, pressure of carbon oxide; $V_{d,phys}$, physiological dead space; $V_{d,alv}$, alveolar dead space; $V_T$, tidal volume; $V_{d,Fowler}$, Fowler dead space.
A previous study of low-birth-weight infants ventilated for RDS showed that PaCO₂ correlates reasonably well with V̇E, and that setting appropriate V̇E may allow closer targeting of PaCO₂ [1]. However, it is known that the dead-space ratio depends on birth weight or gestational weeks, the volume of devices such as endotracheal tubes, and various respiratory conditions [2, 3, 7–9]. In our study, the regression analysis revealed that PaCO₂ values were positively correlated with V̇d,phys and V̇d,alv, but not V̇d,Fowler. Generally, V̇d,alv increases with high PEEP and lung hypoperfusion [2]. Although PEEP remained unchanged between the two groups in our study, low pulmonary circulation in the hypercapnia group could be responsible for the observed increase in V̇d,alv. The pulmonary transition at birth relies on an immediate drop in pulmonary vascular resistance with a concomitant increase in pulmonary blood flow. The main reasons for ventilator management in the NICU (RDS, MAS, infection, and asphyxia) may increase pulmonary vascular resistance [10]. Even in well-ventilated infants, a reduction in effective ventilation volumes can lead to hypercapnia, due to higher V̇d,phys because of decreased pulmonary blood flow.

Few studies have reported neonate V̇d,alv values [7, 11]. Dassios et al. reported a median V̇d,alv of 0.3 ml/kg in prematurely born infants with a median weight of 1.18 kg, and 0.1 ml/kg for infants with a median weight of 3.3 kg; we report a higher mean V̇d,alv 0.6–1.0 ml/kg [7]. This discrepancy might be explained by the fact that the previous study investigated infants during a clinically stable state when they were ready for extubation, while the present study examined infants during respiratory failure.

Several clinical implications can be derived from our study. Cases with a higher dead space could be detected at bedside to determine suitable ventilator settings, including a moderate level of PEEP and higher respiratory rates to maintain appropriate V̇A. In addition, measurements of V̇d,alv are useful for the diagnosis of PPHN with lung hypoperfusion, as these techniques could estimate the effectiveness of inhaled nitric oxide, which induces pulmonary vasodilation.

The limitations of our study included the absence of an evaluation of pulmonary blood flow and calculations of the physiological dead space using the Enghoff approach, which estimates not only the true dead space but also intrapulmonary right to left shunting and low ventilation–perfusion regions of the lung [12–14]. Enghoff’s V̇d,alv may be overestimated in infants with collapsed alveoli caused by surfactant deficiency. Furthermore, the term and preterm neonates included in this study were intubated for various reasons. In future studies, it will be important to study more homogenised samples to clarify the pathophysiology of the infants’ respiratory diseases.
Conclusion

We discovered that volumetric capnography in ventilated neonates with hypercapnia presents with a reduction of minute alveolar ventilation volume, in the absence of a decrease in minute ventilation volume. We believe that hypercapnia in newborns with otherwise good ventilation is attributable to an increase in physiological dead space.

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Authors’ contributions

MZ designed and performed the experiments, derived the models and analysed the data. YN, KK, ST, UM and TK assisted with data collection. MZ wrote the manuscript in consultation with KH who supervised the project. All authors approved the manuscript to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflict of interest.

Ethics approval

Approval was obtained from the clinical ethics committee of the National Hospital Organization Maizuru Medical Center. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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