ORIGINAL ARTICLE

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 $V_{d,phys}/V_T$ = 0.46 (IQR, 0.37–0.58)], with no difference in V_T. 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_ECO_2	Expiratory CO_2
$V_{T,E}$	Expired tidal volume
$V_{d,Fowler}$	Fowler dead space

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FiO$_2$	Fraction of inspired oxygen
MAP	Mean airway pressure
MAS	Meconium aspiration syndrome
V_A	Minute alveolar ventilation
V_E	Minute ventilation
PaCO$_2$	Partial pressure of carbon dioxide
PPHN	Persistent pulmonary hypertension of the newborns
$V_{d,phys}$	Physiological dead space
PEEP	Positive end-expiratory pressure
PIP	Positive inspiratory pressure
RR	Respiratory rate
V_T	Tidal volume
RDS	Respiratory distress syndrome
V_{cap}	Volumetric capnography

Introduction

An optimal arterial carbon dioxide concentration, measured by the partial pressure of carbon dioxide (PaCO$_2$), is critical during mechanical ventilation. Both hypercapnia and hypocapnia can contribute to brain damage in immature infants. Tighter control of PaCO$_2$ may be achieved in mechanically ventilated infants by setting appropriate minute ventilation (V_E), defined by tidal volume (V_T) and the respiratory rate (RR) [1]. However, even when V_T or V_E are maintained, hypercapnia can occur. V_T comprises Fowler dead space (($V_{d,Fowler}$) volume of air in instruments and airways), alveolar dead space (($V_{d,alv}$) volume of ventilated alveoli that do not receive blood flow and thus no gas exchange), and alveolar ventilation ((V_A) volume of alveoli with gas exchange). Therefore, minute alveolar ventilation (V_A), which is calculated as $V_A \times$ RR, is the key contributor in maintaining appropriate PaCO$_2$ [2, 3].

The physiological dead space ($V_{d,phys}$), which is the sum of $V_{d,Fowler}$ and $V_{d,alv}$, is commonly calculated in ventilated patients using volumetric capnography (V_{cap}). This method employs a plot of expiratory CO$_2$ (P$_E$CO$_2$) versus expired tidal volume ($V_{T,E}$), and specialised equipment with effective apparatus dead space for newborns with low V_T [4]. We have previously reported the analysis of V_{cap} using ventilator graphics and capnograms with low dead-space cap-ONE (Nihon Kohden, Tokyo, Japan) mainstream capnometers [5].

We hypothesised decreased V_A was caused by increased $V_{d,phys}$ in well-ventilated infants with hypercapnia. The objective of this current study was to clarify the relationship between dead space and PaCO$_2$, and to assess V_A in intubated well-ventilated neonates with hypercapnia, using V_{cap} based on ventilator graphics and capnograms. We present evidence here that hypercapnia is attributed to decreased V_A due to increased $V_{d,phys}$.

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 V_T of approximately 5 mL/kg. We performed volumetric capnography when infants were well-ventilated (200 ml/kg/minute $\leq V_E$, and 3.5 ml/kg $\leq V_T$).

Medical records were reviewed for information regarding the patients' characteristics, and clinical, prenatal, and perinatal data. The diagnosis of respiratory distress syndrome (RDS)
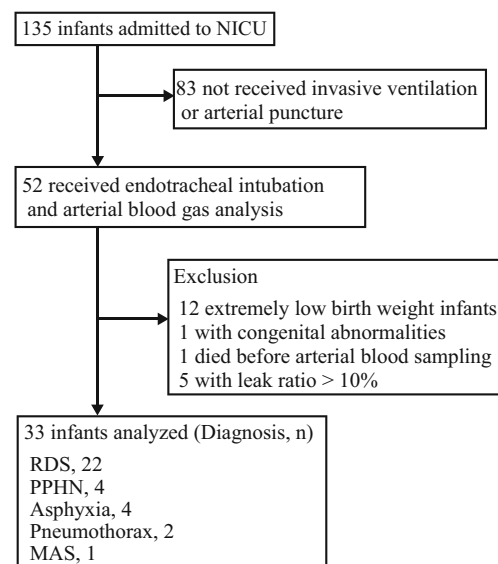

Fig. 1 Flow diagram showing the number of included neonates with diagnosis. RDS, respiratory distress syndrome; PPHN, persistent pulmonary hypertension of the newborns; MAS, meconium aspiration syndrome

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_{cap} based on waveforms

$P_E CO_2$ 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 $P_E CO_2$ and $V_{T,E}$ 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, $P_E CO_2$ was plotted against $V_{T,E}$ for a single breath. $V_{d,Fowler}$, $V_{d,alv}$, and V_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. $V_{d,phys}$ was calculated as $V_{d,Fowler} + V_{d,alv}$. V_E and V_A were calculated as follows: $V_E = V_T \times RR$, and $V_A = V_A \times RR$, respectively.

We performed regression analysis to evaluate the correlation between $PaCO_2$ and V_T/kg or dead space from the obtained samples. Next, hypocapnia measurements ($PaCO_2 < 35$ mmHg) were excluded due to the small sample number and the remaining data points were classified as either normocapnia (35 mmHg ≤ $PaCO_2$ < 45 mmHg), or hypercapnia (45 mmHg ≤ $PaCO_2$) 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 $PaCO_2$ 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
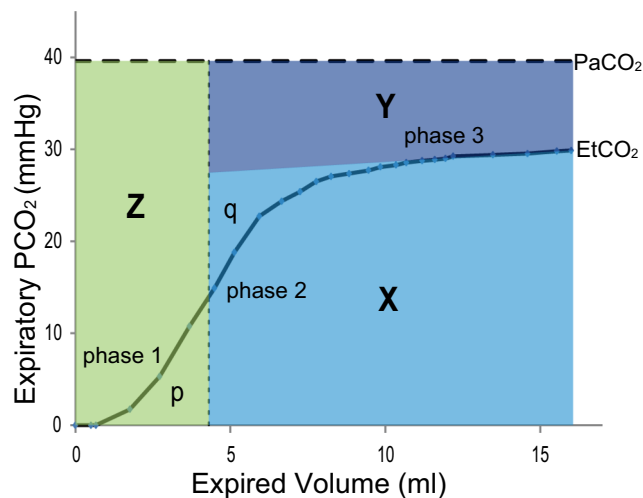

Fig. 2 Volumetric capnography and calculation of the dead space. The resulting curve comprises three phases: phase 1 represents carbon dioxide–free gas from the airways and apparatus dead space, phase 2 represents the volume of transition between the airway and alveolar gas, and phase 3 reflects the pure alveolar gas compartment and volume exhaled from the rest of the alveoli. A tangential line was constructed at the alveolar plateau between 90 and 98% of V_T, and a vertical line was inserted in the middle of phase 2, such that two equal triangles were created. The area below the arterial carbon dioxide line can be divided into three parts: X, which represents V_A; Y, which represents $V_{d,alv}$; and Z, which represents $V_{d,Fowler}$. $V_{d,Fowler}$, $V_{d,alv}$, and V_A were calculated from respective area ratios to V_T.

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 $PaCO_2$ and V_T/kg or each dead space. Figure 3 shows that $PaCO_2$ values were positively correlated with $V_{d,alv}/V_T$ ($r = 0.54$, $p < 0.001$) and $V_{d,phys}/V_T$ ($r = 0.48$, $p < 0.001$), but not with V_T/kg ($r = 0.09$, $p = 0.35$) and $V_{d,Fowler}/V_T$ ($r = 0.14$, $p = 0.12$).

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 $V_{d,alv}$, $V_{d,phys}$, and V_A was statistically significant between the normocapnia and hypercapnia groups, while V_T and $V_{d,Fowler}$ showed no difference. $V_{d,alv}$ and $V_{d,phys}$ were higher

Table 1 Descriptive characteristics of the enrolled patients

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

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 $PaCO_2$ 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.
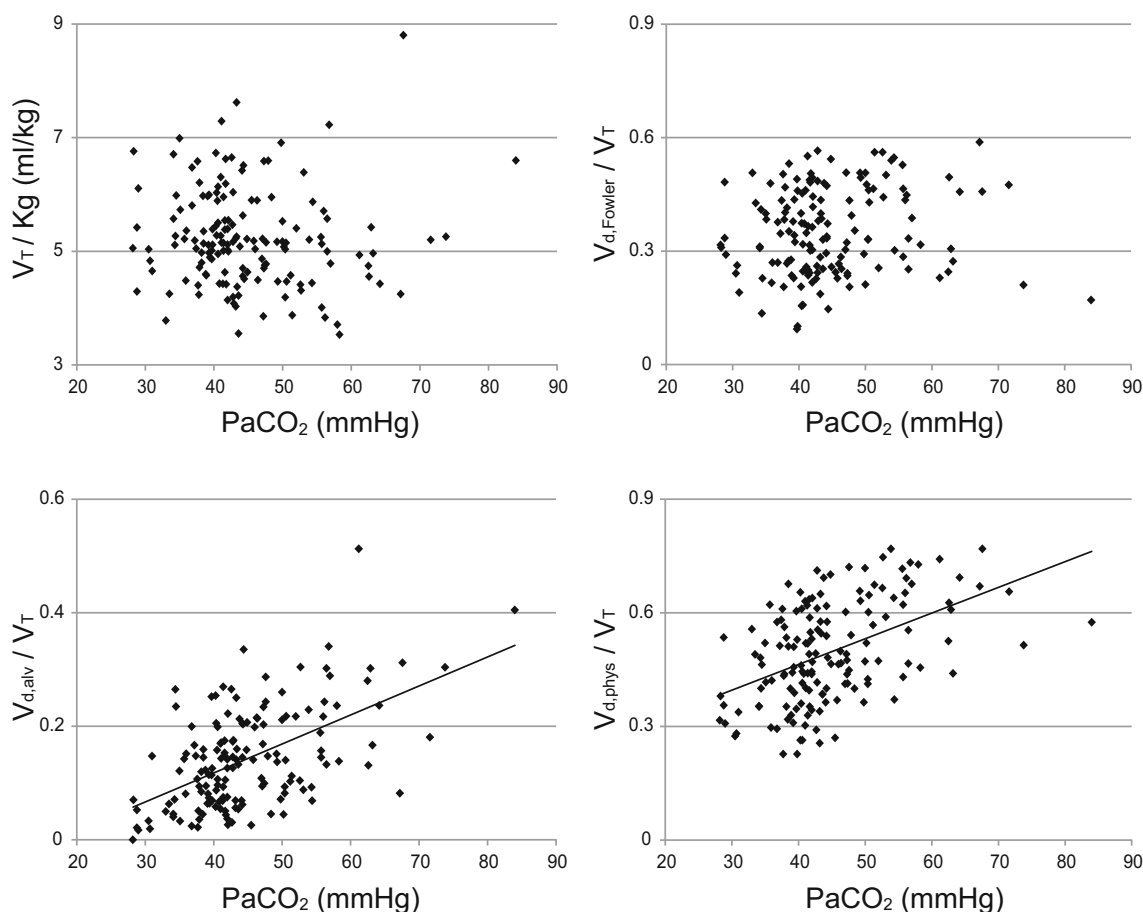

Fig. 3 Correlation analysis between $PaCO_2$ and dead space. $PaCO_2$ values were positively correlated with $V_{d,alv}$ ($r = 0.54$, $p < 0.001$) and $V_{d,phys}$ ($r = 0.48$, $p < 0.001$), but not V_T/kg ($r = 0.09$, $p = 0.35$) and $V_{d,Fowler}$ ($r = 0.14$, $p = 0.12$). $PaCO_2$, pressure of carbon oxide; $V_{d,Fowler}$, Fowler dead space; $V_{d,alv}$, alveolar dead space; V_T, tidal volume; $V_{d,phys}$, physiological dead space

Table 2 Ventilator parameters and measurements by volumetric capnography

Parameter	Normocapnia (82 samples)	Hypercapnia (57 samples)	p
Days of measurement	2 (1–5)	2 (1–4)	$p = 0.30$
$PaCO_2$	41.0 (38.9–42.7)	52.3 (48.2–56.8)	$p < 0.001$
FiO_2	0.30 (0.25–0.4)	0.35 (0.28–0.55)	$p = 0.06$
PIP, cmH_2O	14.1 (12.1–16.1)	17.0 (14.1–18.1)	$p = 0.004$
PEEP, cmH_2O	6.1 (5.1–6.4)	6.1 (5.4–6.6)	$p = 0.30$
RR	59 (46–64)	60 (50–72)	$p = 0.14$
MAP, cmH_2O	8.2 (7.4–9.4)	9.1 (7.8–10.1)	$p = 0.007$
V_T/kg, mL/kg	5.2 (4.7–5.9)	5.1 (4.5–5.5)	$p = 0.13$
$V_{d,Fowler}$/kg, mL/kg	1.8 (1.4–2.4)	1.8 (1.4–2.4)	$p = 0.40$
$V_{d,Fowler}/V_T$	0.35 (0.26–0.44)	0.37 (0.27–0.48)	$p = 0.18$
$V_{d,alv}$/kg, mL/kg	0.6 (0.4–0.8)	0.9 (0.5–1.3)	$p = 0.001$
$V_{d,alv}/V_T$	0.12 (0.07–0.16)	0.17 (0.11–0.24)	$p < 0.001$
$V_{d,phys}$/kg, mL/kg	2.4 (1.9–3.1)	2.8 (2.3–3.3)	$p = 0.01$
$V_{d,phys}/V_T$	0.46 (0.37–0.58)	0.57 (0.44–0.67)	$p < 0.001$
V_A/kg, mL/kg	2.7 (2.2–3.3)	2.1 (1.6–2.8)	$p < 0.001$
V_A/V_T	0.54 (0.42–0.62)	0.43 (0.33–0.54)	$p < 0.001$
V_E/kg, mL/kg/min	295 (235–362)	304 (241–372)	$p = 0.55$
V_A/kg, mL/kg/min	151 (115–180)	123 (87–166)	$p = 0.006$

The following is the list of abbreviations used in the above table along with their full terms: $PaCO_2$, pressure of carbon oxide; FiO_2, fraction of inspired oxygen; PIP, positive inspiratory pressure; $PEEP$, positive end-expiratory pressure; RR, respiratory rates; MAP, mean airway pressure; V_T, tidal volume; $V_{d,Fowler}$, Fowler dead space; $V_{d,alv}$, alveolar dead space; $V_{d,phys}$, physiological dead space; V_A, alveolar ventilation volume; V_E, minute tidal volume; V_A, minute alveolar ventilation volume. Values are represented as medians (interquartile ranges)

A previous study of low-birth-weight infants ventilated for RDS showed that $PaCO_2$ correlates reasonably well with V_E, and that setting appropriate V_E may allow closer targeting of $PaCO_2$ [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 $PaCO_2$ values were positively correlated with $V_{d,phys}$ and $V_{d,alv}$, but not $V_{d,Fowler}$. Generally, $V_{d,alv}$ 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 $V_{d,alv}$. 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 $V_{d,phys}$ because of decreased pulmonary blood flow.

Few studies have reported neonate $V_{d,alv}$ values [7, 11]. Dassios et al. reported a median $V_{d,alv}$ 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 $V_{d,alv}$ 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 V_A. In addition, measurements of $V_{d,alv}$ 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 $V_{d,alv}$ 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.

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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