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Respiratory Function in Ventilated Newborn Infants Nursed Prone and Supine

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ABSTRACT

Objectives: Prone positioning has been associated with improved oxygenation in ventilated newborn infants but the physiological basis of this improvement has not been previously studied. We aimed to test the hypothesis that respiratory function measured by composite physiological indices would be improved in the prone compared to the supine position.

Study Design: Prospective observational study of ventilated newborns in a tertiary neonatal unit studied prone and supine at random order.

Methodology: The ventilation to perfusion ratio (V_A/Q) and right to left shunt were non-invasively calculated using the oxyhemoglobin dissociation curve method. The gradient of the arterial to end tidal carbon dioxide ($PaCO_2$ – $EtCO_2$ gradient) was calculated to describe changes in the alveolar dead space.

Results: Forty-six (26 male) infants with a median (IQR) gestational age of 34.8 (33.1–36.3) weeks and birth weight of 2.34 (1.77–2.87) kg were studied after 5 (2–10) hours of invasive ventilation. The V_A/Q was significantly higher in the prone position [0.57 (0.52–0.63)] compared to supine [0.53 (0.46–0.62), $p = 0.001$]. Right to left shunt was significantly lower in prone [7 (0–12) %] compared to supine [9 (1–16) %, $p = 0.003$]. The $PaCO_2$ – $EtCO_2$ gradient was significantly lower in prone [6.3 (3.8–8.4) mmHg] compared to supine [12.1 (7.1–16.0) mmHg].

Conclusions: The prone position in ventilated neonates was associated with improved ventilation to perfusion matching and lower intrapulmonary shunting and alveolar dead space compared to supine.

1 | Introduction

Newborn infants commonly suffer from respiratory disease which might be associated with long term pulmonary morbidity [1]. Optimization of respiratory care in ventilated newborns includes avoidance of invasive ventilation, gentler ventilation strategies such as volume targeted ventilation [2] and high frequency oscillation [3] and pharmacological adjuncts such as systemic corticosteroids [4].

Prone positioning is an alternative intervention to improve respiratory function and has seen wide application in the management of patients with COVID-19 pneumonia [5]. We have previously described that prone positioning was associated with reduced work of breathing in convalescent preterm infants [6]. Although prone positioning is occasionally practiced in neonatal intensive care with a goal to improve oxygenation and ventilation, the quantified effect of this intervention on physiological indices of respiratory function has not been previously reported. Improved ventilation to perfusion matching has been reported in the prone position in a small cohort of preterm infants with evolving bronchopulmonary dysplasia, but this was an observation in a sample of infants who were nursed either

prone or supine at the time of study, rather than a finding of a study where prone positioning was a planned intended intervention [7]. We have also previously used novel, low dead space capnography to measure the alveolar dead space [8] and a noninvasive method to calculate the ventilation to perfusion ratio and the right-to-left shunt in ventilated infants [7].

Our hypotheses were that the alveolar dead space and the right to left shunt would be lower and the ventilation to perfusion ratio would be higher in the prone position compared to supine. Our aims were to test these hypotheses.

2 | Methods

2.1 | Study Design and Subjects

A prospective observational cohort study was conducted in the Tertiary Neonatal Intensive Care Unit of the University Hospital of Patras, Greece from November 1, 2023 to October 31, 2024. The respiratory function parameters were assessed in the prone and supine positions in admitted ventilated infants in the first 72 h of life. The infants were studied after a period of 15 min being stable in each position and the measurements were performed at the end of this period. As the methodology required an alteration of the provided fraction of inspired oxygen (F_IO_2), only infants with an F_IO_2 requirement above 0.21 were included in the study. As per unit practice, ventilated infants were usually nursed supine, and most were thus studied supine first. Since the act of changing position per se might improve respiratory function by mobilizing atelectacic areas irrespective of starting position, a subgroup of infants (one-third of the total cohort) were studied prone first, by studying one infant prone first after every two other consecutive infants studied supine first. The study was approved by the Research Ethics Committee of the University Hospital of Patras (Ref: 737/2023). Informed written consent was given by the parents/legal guardians of all study participants.

2.2 | Ventilation Practice

The infants were ventilated on volume-targeted or pressure-controlled time-cycled ventilation with the Draeger Babylog VN600 neonatal ventilator (Draeger, Lubeck, Germany) or the SLE5000 (SLE, Croydon, United Kingdom). Intubation and mechanical ventilation was considered, according to unit policy, when the F_IO_2 was > 0.4, the infant had a pH of < 7.25, $PaCO_2$ of > 65 mmHg, or the infant had significant apnea or work of breathing on noninvasive respiratory support. Infants were ventilated with a backup rate of 40–50 inflations/min, positive end-expiratory pressure of 4–5 cm H_2O and inflation time of 0.35–0.40 s. Antenatal corticosteroids were offered to infants below 35 completed weeks of gestation [9]. All intubated preterms and term infants with $F_IO_2 > 0.30$ and evidence of parenchymal lung disease on chest radiography received endotracheal surfactant [9]. Caffeine was started within the first 6 h of life in infants born before 35 completed weeks of gestation [9].

2.3 | Information From the Medical Notes

Baseline demographic data were collected from the medical notes including a full course of antenatal steroids (yes/no) [10], gestational age (weeks), birth weight (kg), sex, mode of delivery (vaginal delivery or cesarean section), administration of surfactant (yes/no), duration of mechanical ventilation at study and during stay (hours), administration of caffeine (yes/no), echocardiographically confirmed haemodynamically significant patent ductus arteriosus (PDA) (yes/no) [11], intraventricular hemorrhage (IVH) grade 3 or 4 or periventricular leucomalacia (PVL) (yes/no) [12], survival to discharge from neonatal care (yes/no), diagnosis of bronchopulmonary dysplasia at 36 weeks (yes/no) [13]. Data on peak inflation pressure (cmH_2O), mean airway pressure (cmH_2O), tidal volume (ml), backup ventilatory rate and F_IO_2 immediately before study were also collected.

2.4 | Ventilation to Perfusion Ratio

We have previously described a noninvasive method to assess ventilation to perfusion relationships (V_A/Q) and right-to-left shunting using the oxyhemoglobin dissociation curve and reported results in extremely preterm infants with bronchopulmonary dysplasia [7], pulmonary interstitial emphysema [14] and healthy term infants [15, 16]. Three to five pairs of preductal transcutaneous oxygen saturation (SpO_2) and F_IO_2 in each of the prone and supine positions were recorded. Broadly, the F_IO_2 was altered sequentially to achieve stable SpO_2 values in the area of 85%, 88%, 92%, 96%, and 100%. Using the paired values of SpO_2 and F_IO_2, two oxyhaemoglobin dissociation curves were constructed for each infant (before and after the intervention), and were compared with an ideal reference neonatal oxyhaemoglobin dissociation curve [17]. Using the paired values of SpO_2 and F_IO_2, the V_A/Q and the percentage of right-to-left shunt were calculated. V_A/Q and right-to-left shunting were derived using software based on the Lockwood algorithm, which derives V_A/Q and shunt results for each data set from a two-compartment model for a single homogeneous ventilated compartment [18]. The hemoglobin level at the time of assessment was used in the calculations.

2.5 | Carbon Dioxide Measurement

An NM3 respiratory profile monitor (Philips Respironics, CT) connected to a mainstream capnograph (Capnostat-5) was used. The expired CO_2 was measured using infrared absorption spectroscopy and the capnography was connected between the ventilator circuit and the endotracheal tube (Figure 1). The respiratory monitor automatically calibrated for CO_2 according to the factory-stored calibrations within the monitor. The partial arterial or capillary pressure of carbon dioxide ($PaCO_2$) was documented from the latest blood gas analysis which was routinely performed by the clinical team within 60 min from the research recordings. Capillary blood gases have been shown to accurately reflect the arterial partial pressure of CO_2 in neonates [19]. The alveolar dead space can be calculated with a methodology which involves the offline construction and analysis of volumetric capnograms [8]. While these calculations can be methodologically challenging, the magnitude of the

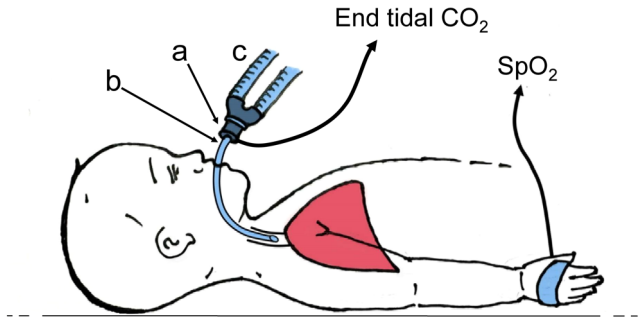

FIGURE 1 | Position of the capnograph (a) between the endotracheal tube (b) and the ventilator circuit (c) to measure end tidal carbon dioxide. Pre-ductal transcutaneous oxygen saturation (SpO_2) was measured from the right hand. [Color figure can be viewed at wileyonlinelibrary.com]

alveolar dead space can be clinically estimated by the difference of the arterial to the end-tidal carbon dioxide pressures ($PaCO_2$–$EtCO_2$ gradient) [20]. This gradient incorporates information not only on the alveolar dead space, but also on the anatomical and apparatus dead space [21], these latter compartments however, will remain relatively constant for each individual infant during the measurements. Thus, we used the $PaCO_2$–$EtCO_2$ gradient as a surrogate index for the change in the alveolar dead space in the studied positions [22].

2.5.1 | Sample Size

As the effect of prone positioning on the V_A/Q and right-to-left shunt have not been previously described, we based our calculations on the largest published study reporting values of V_A/Q in 219 preterm infants [23]. In that study, the mean V_A/Q in infants requiring home oxygen was 0.38 versus 0.59 in the ones who did not, therefore, the clinically significant difference of V_A/Q was 0.21. We have previously reported that the standard deviation of V_A/Q in a population of 145 term infants without respiratory pathology was 0.21 [15]. To detect the above clinically significant difference with 95% power at the 1% level of significance, a population of 36 infants would be required. Allowing for patient drop out and data quality control, we aimed to recruit a sample of 45 ventilated infants.

2.5.2 | Statistical Analysis

Continuous data were tested for normality with the Kolmogorov-Smirnov test and found to be non-normally distributed and were therefore presented as median and interquartile range (IQR). The primary analysis aimed to compare the V_A/Q, right to left shunt and the $PaCO_2$–$EtCO_2$ gradient in the prone and supine positions. Comparison was performed using the Wilcoxon rank sum non-parametric test for related samples. The difference in the V_A/Q between supine and prone (delta V_A/Q) was calculated as the difference in the V_A/Q in prone minus the V_A/Q in the supine position. The delta V_A/Q was compared in infants studied supine first versus infants studied prone first, to examine whether the order of testing affected the results. The relationship of the delta V_A/Q with the gestational age, birth weight, F_IO_2 at study and hours of ventilation at study was examined with Spearman's rho correlation analysis to explore if the change in V_A/Q was influenced by these parameters. The delta V_A/Q was also compared in binary conditions such as administration of antenatal corticosteroids, male sex, cesarean section and caffeine at study using the Mann Whitney U non parametric test for non-related samples. Statistical analysis was performed using SPSS software, version 27.0 (SPSS Inc., Chicago, Illinois, USA).

3 | Results

In the study period a total of 64 infants were invasively ventilated in the Neonatal Unit. Eighteen infants were not recruited due to lack of consent, unavailability of the research team or not requiring supplemental oxygen. Forty-six infants with a median (IQR) gestational age of 34.8 (33.1–36.3) weeks and birth weight of 2.34 (1.77–2.87) kg were included in the study. The included infants were ventilated for a total duration of 22 (12–72) hours. The demographic parameters and clinical outcomes are presented in Table 1. The infants were studied at a median (IQR) duration of ventilation of 5 (2–10) hours, requiring a F_IO_2 of 0.31 (0.26–0.41) and a mean airway pressure of 8.1 (7.0–9.5) cm H_2O. The mechanical ventilation parameters are presented in Table 2.

The V_A/Q was significantly higher in the prone position [0.57 (0.52–0.63)] compared to supine [0.53 (0.46–0.62), $p = 0.001$] and the shunt was significantly lower in prone [7 (0–12) %] compared to supine [9 (1–16) %, $p = 0.003$, Table 3, Figure 2]. The $PaCO_2$–$EtCO_2$ gradient was significantly lower in the prone [6.3 (3.8–8.4) mmHg] compared to the supine position [12.1 (7.1–16.0) mmHg] signifying a lower alveolar dead space in prone compared to supine (Table 3, Figure 2).

TABLE 1 | Characteristics and major outcomes of the study population.

Antenatal steroids	30 (65)
Gestational age (weeks)	34.8 (33.1–36.3)
	Range: 24.6–40.2
Preterm (< 37 weeks)	36 (78)
Birth weight (kg)	2.34 (1.77–2.87)
	Range: 0.75–3.82
Male sex	26 (57)
Cesarean Section	41 (89)
Surfactant	35 (76)
Total duration of ventilation (hours)	22 (12–72)
	Range: 2–696
Caffeine at study	37 (80)
Patent Ductus arteriosus	1 (2)
Intraventricular Hemorrhage	2 (4)
Retinopathy of Prematurity	3 (7)
Bronchopulmonary dysplasia	5 (11)
Survival to discharge	45 (98)

Note: Data presented as median (interquartile range) or N (%).

TABLE 2 | Ventilation parameters at study.

	Median (IQR)	Range
Duration of ventilation at study (hrs)	5 (2–10)	0.5–96
Age at study (days)	2 (1–3)	1–3
Fraction of inspired oxygen	0.31 (0.26–0.41)	0.23–0.70
Hemoglobin (g/dL)	16.1 (15.0–17.5)	12.7–20.5
Peak inflation pressure (cmH_2O)	16 (13–18)	11–19
Mean airway pressure (cmH_2O)	8.1 (7.0–9.5)	5.1–11.0
Tidal volume (ml)	11.5 (10.0–14.3)	3.5–20.0
Tidal volume (ml/kg)	5.1 (4.4–5.8)	3.4–7.4
Backup ventilatory rate (inflations/minute)	45 (40–50)	30–50
$PaCO_2$ (mmHg)	37.7 (35.7–40.1)	23.2–64.0

TABLE 3 | Respiratory function parameters in prone and supine positions.

	Supine	Prone	*p* value
V_A/Q	0.53 (0.46–0.62)	0.57 (0.52–0.63)	0.001
	Range: 0.26–0.84	Range 0.36–1.08	
Right to left Shunt (%)	9 (1–16)	7 (0–12)	0.003
	Range: 0–24	Range: 0–20	
$EtCO_2$ (mmHg)	27. 1 (24.1–31.4)	31.6 (28.9–36.1)	< 0.001
	Range: 16.9–44.5	Range: 20.3–44.2	
$PaCO_2$-$EtCO_2$ gradient (mmHg)	12.1 (7.1–16.0)	6.3 (3.8–8.4)	< 0.001
	Range: 2.3–27.4	Range: 0.6–23.7	

Note: Data presented as median (interquartile range).
Abbreviations: $EtCO_2$, end tidal carbon dioxide; $PaCO_2$, partial arterial pressure of carbon dioxide; V_A/Q, ventilation to perfusion ratio.

The median (IQR) delta V_A/Q in the whole cohort was 0.04 (0.00–0.11). The delta V_A/Q was not significantly different in the infants studied prone first ($N = 16$) compared to the infants studied supine first ($N = 30$, $p = 0.367$). The delta V_A/Q was not significantly related to the gestational age ($p = 0.249$, rho = 0.174), birth weight ($p = 0.270$, rho = 0.166), hours of ventilation at study ($p = 0.778$, rho = -0.043) and F_IO_2 at study ($p = 0.320$, rho = -0.150). The delta V_A/Q was not significantly different in infants who received antenatal corticosteroids versus the ones who did not ($p = 0.234$), male versus female infants ($p = 0.190$), infants born via cesarean section versus infants born vaginally ($p = 0.658$) or in infants treated with caffeine versus not ($p = 0.255$).

4 | Discussion

We have demonstrated that ventilated newborn infants nursed in the prone position exhibited significantly improved ventilation to perfusion matching, lower intrapulmonary shunting and a lower alveolar dead space compared to supine.

Although the quantified effect of proning on composite respiratory function parameters has not been previously reported in the neonatal population, our results are in agreement with previous studies that have reported *enhanced oxygenation* in the prone compared to the supine position. In a smaller study of a similar population of ventilated infants with gestational ages ranging from 25 to 36 weeks and studied within 7 days from birth, the authors reported that the prone position was associated with a higher SpO_2 and fewer episodes of oxygen desaturation [24]. The latest Cochrane analysis on infant position of ventilated neonates reported that the prone position was associated with an increase in arterial oxygen tension (PaO_2) and SpO_2 improvement compared to supine [25]. Similarly, enhanced oxygenation has been reported in premature infants receiving continuous positive airway pressure with higher SpO_2 and improved thoraco-abdominal synchrony measured by respiratory inductive plethysmography in the prone compared to the supine position [26]. We have also previously reported a lower work of breathing measured by the diaphragmatic pressure time product in convalescent preterm infants when measured prone compared to supine [6]. Our results from this current study agree with the aforementioned studies and complement the literature by quantifying the positive effect of prone positioning by using composite indices of respiratory function.

Although quantifying respiratory function improvement in the prone position by indices of oxygenation alone (such as the PaO_2 and the SpO_2) is clinically useful, this approach does not answer the pathophysiological question of *how* this improvement is achieved. In our study we reported an increase in V_A/Q and a decrease in intrapulmonary shunt in prone compared to supine as well as a decrease of the $PaCO_2$-$EtCO_2$ gradient (used as a proxy index for the

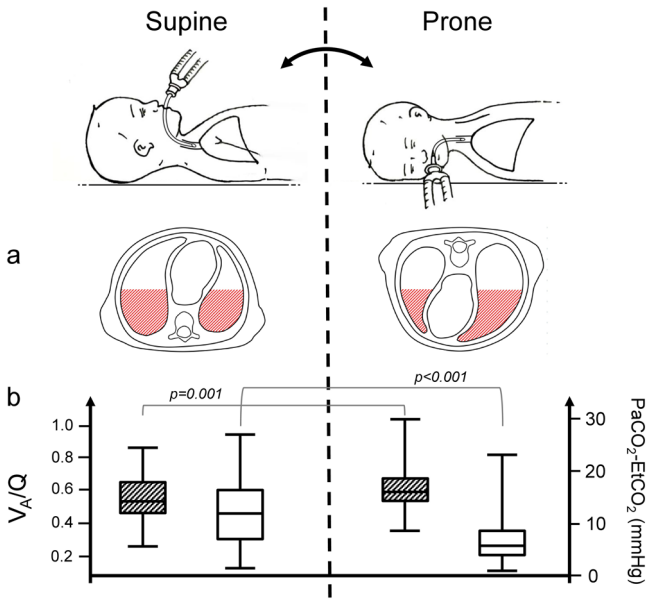

FIGURE 2 | Respiratory function differences in the prone and supine positions. (a): Schematic presentation of the larger non-dependent areas (dependent areas marked with diagonal lines) in prone compared to supine position. (b): The ventilation to perfusion ratio (V_A/Q) is presented in boxes with diagonal lines, and the $PaCO_2$-$EtCO_2$ gradient in plain white boxes. In each data bar the horizontal line represents the median, the bottom and top of the bars the 25th and 75th percentiles, and the whisker bars the range. [Color figure can be viewed at wileyonlinelibrary.com]

alveolar dead space). It is possible that ventilation to perfusion matching is improved in the prone position because of an improvement in pulmonary perfusion. This can possibly be explained by a higher vascular conductance in the dorsal lung regions compared to the ventral ones, due to the effect of gravity [27]. The ensuing increase in pulmonary perfusion would translate to a decrease in alveolar dead space as more ventilated areas would be sufficiently perfused. Similarly, ventilation might be higher in the dorsal compared to the ventral parts of the lungs in the prone position by recruitment of the previously atelectatic larger dorsal lung areas for ventilation, while the smaller ventral lung areas become less ventilated (Figure 2) [28]. Although this theory is predominantly based on adult data, comparative studies of regional ventilation distribution by electrical impedance tomography in healthy infants and adults have demonstrated that the distribution of ventilation was geometrically similar in infants and adults [29].

The alveolar dead space can be precisely calculated using offline construction and analysis of volumetric capnograms [30]. As these calculations are methodologically cumbersome and prone to synchronization error, we attempted to clinically evaluate the presence and magnitude of the alveolar dead space by the difference of the $PaCO_2$–$EtCO_2$ gradient, which has been used as a proxy index for the alveolar dead space, even in different subjects where the anatomical dead space might not be constant [20]. Furthermore the $PaCO_2$–$EtCO_2$ gradient, unlike the alveolar dead space, is readily accessible by the clinical team in most neonatal units where tidal capnography is routinely used. Arguably, the $PaCO_2$–$EtCO_2$ gradient incorporates information not only on the alveolar dead space, but also on the anatomical and apparatus dead spaces [21], however these latter compartments would remain relatively constant for each individual infant during the measurements. We should note that although we used the $PaCO_2$-$EtCO_2$ gradient as a proxy for the alveolar dead space, some differences in position might affect the anatomical compartment of the total physiological dead space too. It is possible that prone positioning might lead to less compression of the airways which are mostly dorsally located in the thorax and a corresponding increase of the intrathoracic anatomical dead space. We have, however, previously reported an improvement of similar magnitude in this gradient in ventilated infants with resolving pulmonary hypertension, who were all nursed supine. We reported that the change in the gradient was similar (from 10.7 to 3.3 mmHg) and was predominantly attributable to the resolution of pulmonary hypertension [22].

It was interesting that in our cohort the improvement in the V_A/Q in the prone position was not related to any of the tested demographic or clinical parameters. For example, infants with a higher oxygen requirement (possibly signaling more severe lung disease) did not benefit more by proning as demonstrated by the lack of association of the delta V_A/Q with the F_IO_2, the gestational age or other demographic parameters. This finding implies that a fixed improvement can be incurred by changing to prone which is possibly related to the aforementioned anatomical reasons, irrespective of anthropometric differences or disease severity. This improvement, however, was modest with an increase in the median V_A/Q of only 0.04 and a reduction in the median $EtCO_2$ of 4.5 mmHg. The clinical applicability of our study might, thus, lie in a small fixed improvement in gas exchange, which could be of limited clinical benefit for infants without severe respiratory disease but possibly important in critical cases where achieving adequate oxygenation remains persistently challenging.

Our study has strengths and some limitations. This was the first study to approach the pathophysiological basis of improved gas exchange in ventilated newborn infants nursed prone. We applied a validated methodology and studied an adequate population to report significant improvements in V_A/Q, right to left shunt and the $PaCO_2$-$EtCO_2$ gradient. We should note that our cohort was heterogeneous in gestational age at birth and modest in size, and consisted of relatively mature preterms with a median gestational age of 34 completed weeks. As such, our results might not be generalizable to extremely preterm infants, where position changing might affect cardiorespiratory interactions with unknown consequences. We also included a population with a high percentage of delivery via cesarean section and might thus have not sufficiently elucidated the possible moderating effect of vaginal birth on respiratory disease. Methodologically, the noninvasive oxyhaemoglobin dissociation curve method cannot differentiate the origin of right to left shunt as cardiac or intrapulmonary. Unfortunately we did not have full echocardiographic data on all infants to exclude cardiac right to left shunting. We have, however, previously reported that although a patent ductus arteriosus is common in extreme preterms infants, pure cardiac right-to-left shunt is rare [31].

Future work could focus on replicating our results in independent populations, in more preterm infants and on how different pathophysiological conditions, such as restrictive versus resistive lung disease, may impact the response to changing position.

In conclusion we have demonstrated that prone position was associated with improved respiratory function in ventilated neonates compared to the supine position.

Author Contributions

Konstantina Barka: writing – original draft, writing – review and editing, data curation, Investigation, software, formal analysis. **Eleni Papachatzi:** Investigation, Writing – review and editing, project administration, resources. **Sotirios Fouzas:** supervision, project administration, writing – review and editing. **Gabriel Dimitriou:** supervision, resources, project administration, writing – review and editing, validation. **Theodore Dassios:** conceptualization, methodology, writing – original draft, Writing – review and editing, investigation, supervision, project administration, software, visualization.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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