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ORIGINAL ARTICLE

Prediction of prolonged ventilator dependence in preterm infants

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Abstract

Volutrauma is an important factor in the pathogenesis of bronchopulmonary dysplasia (BPD). Our aims were to identify risk factors in the first 24 h for prolonged ventilator dependence and assess volume delivery and carbon dioxide levels in infants with evolving BPD. A retrospective study was undertaken of 41 infants born at less than 32 weeks of gestational age (GA). A higher tidal volume, minute volume and resistance and a lower GA, birth weight and compliance were associated with a significantly higher risk of ventilator dependence at 28 days. The strongest relationships were with birth weight (area under the receiver operating characteristic curve, AUROC = 0.771) and GA (AUROC = 0.813). Tidal volume remained significantly higher after adjusting for GA in those who remained ventilator dependent at 28 days. The 18 who remained ventilator dependent at 28 days had increased mean carbon dioxide (PCO_2) levels with increasing age from a mean of 41 mmHg in the first 24 h to 65 mmHg at 28 days PMA ($p < 0.001$). The increase in PCO_2 occurred despite increases in peak inflation pressures ($p < 0.001$), tidal volumes ($p = 0.002$) and minute volumes ($p < 0.001$).

Conclusion: These results suggest that initial volutrauma may contribute to the development of chronic ventilator dependence.

What is Known:
- *In prematurely born infants, excessive tidal volumes are important in the pathogenesis of bronchopulmonary dysplasia (BPD), but a tidal volume that is too low will increase the risk of atelectasis, work of breathing and energy expenditure.*

What is New:
- *A high tidal volume in the first 24 h was associated with an increased risk of ventilator dependence at 28 days, which remained significant after adjusting for gestational age. Carbon dioxide levels significantly increased over the first month despite increased pressures and volumes in those who remained ventilator dependent.*

Keywords Tidal volume · Compliance · Resistance · Ventilator dependence · Carbon dioxide levels · Gestational age

Abbreviations

ACV	assist control ventilation
BPD	bronchopulmonary dysplasia
CRS	compliance of the respiratory system
GA	gestational age
MV	minute volume
PIP	peak inflation pressure
PLV	pressure limited ventilation
SIMV	synchronised intermittent mandatory ventilation
VEGF	vascular endothelial growth factor
VT	tidal volume

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Introduction

In prematurely born infants, excessive tidal volumes (volutrauma) are an important factor in the pathogenesis of bronchopulmonary dysplasia (BPD) [1]. On the other hand, a tidal volume that is too low will increase the risk of atelectasis, work of breathing, energy expenditure and oxygen consumption [17]. Volutrauma, atelectasis and oxygen toxicity are the main factors contributing to ventilator-induced lung injury [1]. Prolonged ventilation and high levels of oxygen particularly trigger the inflammatory cascade which leads to the development of BPD [7]. The objective of this study was to identify risk factors in the first 24 h for ventilator dependence at 28 days and in particular if the delivered volume in the first 24 h was higher in those who remained ventilator dependent at 28 days. Prediction of prolonged ventilator dependence is important, but previous studies have focused on supplementary oxygen dependence [16]. Ventilator dependence throughout the first 28 days has resource implications, but importantly is likely to lead to more severe BPD with long-term consequence for the infant and family [8]. Airway dilation and dead space to tidal volume ratio have been suggested to increase with chronic mechanical ventilation in prematurely born infants [12], and thus, preterm infants with evolving BPD may require higher tidal volumes with increasing age to maintain effective ventilation. A further aim was to establish the evolution over the neonatal period of carbon dioxide levels and delivered pressures and volumes in prematurely born ventilated infants with evolving BPD.

Materials and methods

Patients

All infants born at less than 32 weeks of gestational age admitted to King's College Hospital NHS Foundation Trust between September 2015 and June 2016 were eligible for this study if they were ventilated on pressure-limited ventilation (PLV) during the first 28 days and had volume monitoring. The patient's medical records were retrieved and basic demographic data extracted. Infants with chromosomal anomalies, pulmonary hypoplasia, or other anomalies of the lungs or upper airway were excluded from the analysis.

During the study, the SLE 5000 was used to deliver pressure-limited ventilation which consisted of assist control ventilation (ACV), synchronised intermittent mandatory ventilation (SIMV) or intermittent positive pressure ventilation. Shouldered endotracheal tubes were used which have been shown to have minimal or no leak [11]. Routine clinical practice was to start pressure-limited ventilation with adjustments of peak inflation pressure (PIP), rate and inflation time to achieve target blood gases initially of pH 7.35–7.45 and $PaCO_2$ 35–55 mmHg and pulse oxygen saturation values of 92 to 95%. After the first week, $PaCO_2$ levels up to 65 mmHg were tolerated (permissive hypercapnia) providing the pH remained above 7.25. Infants were extubated on to continuous positive airway pressure or heated humidified high flow nasal cannula oxygen therapy. Bronchopulmonary dysplasia (BPD) was diagnosed in infants who were dependent on supplementary oxygen at 28 days. BPD was classified as mild, moderate or severe at 36 weeks postmenstrual age (PMA) according to standard criteria [13]. All infants less than 34 weeks of PMA received caffeine at a maintenance dose of 5 mg/kg/day.

Infants had serial cranial ultrasounds which were recorded as normal if there was no intraventricular haemorrhage or intracranial pathology. We also collected data on administration of antenatal steroids, treatment for patent ductus arteriosus (medical or surgical), echocardiographic evidence of pulmonary hypertension, use of inotropes and administration of postnatal corticosteroids for the prevention/treatment of BPD [6].

To assess expired tidal volume, the SLE 5000 flow sensor, a dual hot-wire anemometer, was used. According to the manufacturer's information, the flow sensor has a dead space less than 1 ml and an accuracy of ± 8% (SLE Limited, South Croydon, Surrey, UK). The flow sensor was placed between the endotracheal tube and ventilator circuit. Tidal volume (V_T) was derived by digital integration of the flow signal. Birth weight was used to calculate V_T/kg on days 2 and 2 and actual weight was used for days 7, 14 and 28. Compliance of the respiratory system (CRS) was calculated by dividing the expiratory volume by the peak pressure minus the PEEP of the previous inflation. Resistance of the respiratory system (RRS) was calculated from the applied pressure divided by the peak expiratory flow. Minute ventilation was calculated by multiplying the recorded tidal volume and the set ventilator rate. At the time of each blood gas measurement, the ventilator rate, fraction of inspired oxygen, the measured V_T, ventilator settings, arterial or capillary pH and pCO_2 were documented. Recordings were averaged for the first 24 h and also on each of days 2, 7, 14 and 28.

Statistical analysis

Data were tested for normality using Kolmogorov-Smirnov test and found to be normally distributed. Differences in the results between infants who remained ventilator dependent at 28 days and those who were extubated before 28 days were assessed for statistical significance using the Students' *t* test for continuous variables and Chi-squared test for categorical variables. The differences in Vt, CO_2, PIP, MV, RRS and CRS on days 1, 2, 7, 14 and 28 were evaluated by one-way analysis of variance for repeated measurements. The number of paired V_T and blood gas observations for individual patients varied; hence, the mean V_T/kg and pCO_2 for each infant for each of

the study days was calculated and these mean values were then used in the analysis of variance. Analysis of outcomes was conducted unadjusted and after adjustment for gestational age using logistic and linear regression analysis. The ability of variables to predict ventilator dependency at 28 days PMA was assessed by calculating the area under receiver operating characteristic curves (AUROC). The analysis was performed using SPSS version 22.0 (SPSS, Inc. Chicago, IL).

Results

Forty-one infants were admitted to the neonatal unit during the study period and had volume monitoring. Their mean (SD) gestational age was 26.8 (± 2.3) (range 23.4–31.7) weeks and their birth weight was 840 (± 256) (range 530–1690) grams. Ninety-five percent of the mothers received antenatal steroids prior to delivery and all infants had received at least one dose of surfactant. Eighteen infants (11 males, 7 females) remained ventilator dependent at 28 days; their mean (SD) GA was 25.6 (± 1.8) weeks and birth weight was 715 (± 125) grams. The other infants were intubated at birth but were extubated before 28 days. All infants that were extubated before 28 days and 17 of the 18 infants that were remained ventilated at 28 days had received antenatal corticosteroids.

Thirteen of the 18 infants (72%) who remained ventilator dependent at 28 days and 19 of 23 infants (83%) that were extubated before 28 days had an intraventricular haemorrhage ($p = 0.425$). Twelve of the 18 infants (67%) who remained ventilator dependent at 28 days and 12 of 23 infants (52%) that were extubated before 28 days were treated with inotropes for hypotension ($p = 0.350$). Fifteen of the 18 infants (83%) who remained ventilator dependent at 28 days and four of 23 infants (17%) that were extubated before 28 days were treated for a patent ductus arteriosus ($p < 0.001$). Two of the 18 infants (11%) who remained ventilator dependent at 28 days and three of 23 infants (13%) that were extubated before 28 days had echocardiographic evidence of pulmonary hypertension ($p = 0.851$). Ten of the 18 infants (56%) who remained ventilator dependent at 28 days and five of 23 infants (22%) that were extubated before 28 days were eventually diagnosed with severe BPD at 36 weeks postmenstrual age ($p = 0.025$). Three of the 18 infants (56%) who remained ventilator dependent at 28 days and five of 23 infants (22%) that were extubated before 28 days received postnatal corticosteroids for prevention and treatment of BPD.

Infants who remained ventilator dependent at 28 days had significantly lower gestational ages, birth weights and CRS levels and had significantly higher tidal volumes, minute volumes and RRS levels in the first 24 h (Table 1). Only the difference in tidal volumes, however, remained statistically significant after adjusting for gestation age (Table 1). The strongest relationships with ventilator dependency at 28 days PMA were with birthweight (AUROC = 0.771) and gestational age (AUROC = 0.813).

In infants who remained ventilator dependent at 28 days, carbon dioxide levels increased significantly with increasing age (Fig. 1) despite increases in peak inflation pressures ($p < 0.001$), tidal volumes ($p = 0.002$) and minute volumes ($p < 0.001$) (Table 2). RRS also increased with increasing postnatal age ($p < 0.001$) (Table 2).

Discussion

We have demonstrated that in infants born at less than 32 weeks of gestational age that expiratory tidal volumes in the first 24 h were significantly higher in those who remained ventilator dependent at 28 days. Furthermore, despite the difference in the mean tidal volumes in the first 24 h being relatively small, the range of tidal volumes in those who remained chronically ventilator dependent was shifted to higher tidal volumes. In addition, the higher tidal volumes predicted chronic ventilator dependence. Gestational age and birth weight, however, were the strongest predictors of ventilator dependence at 28 days. Nevertheless, our results suggest that volutrauma in the first 24 h may contribute to the development of BPD. Even in the delivery suite, high delivered volumes in animal models have been shown to impair lung function [3, 21]. We have demonstrated that high-frequency oscillation compared to conventional mechanical ventilation initiated in the first hours after birth in very prematurely born infants is associated with superior lung function at 11 to 14 years of age [23]. Those results are biologically plausible as the more alveolar cells are stretched the more interleukin (IL8] is produced [19, 20] and in a alveolar analogue model conventional mechanical stretch compared to HFO resulted in higher IL6 and IL8 levels [9]. The elevation of such inflammatory cytokine results in disrupted vascular endothelial growth factor (VEGF) signalling and decreased angiogenesis and altered vascular structure as well as reduced alveolarization [18]. Indeed, in in vitro models, in the model mimicking high-frequency oscillation compared to the model mimicking conventional ventilation, there was a lower inflammatory response [10]. Similarly, volume targeted ventilation [15] may reduce BPD by limiting the stretch of alveolar cells compared to pressure limited ventilation. Unfortunately, in this study, we did not assess inflammation and so cannot comment whether it was higher in the infants who had prolonged ventilator dependence.

We have demonstrated that prematurely born infants who remain ventilator dependent at 28 days with evolving BPD had increasing CO_2 levels despite increased pressure and volume delivery throughout the neonatal period. This may be explained by, in infants who remained ventilator dependent at 28 days, the RRS progressively increased over the first

Table 1 Comparison of day 1 respiratory outcomes between those who remained ventilator dependent at 28 days or were extubated before 28 days. Data are presented as median (SD)

	Ventilated at 28 days	Extubated before 28 days	*P* value unadjusted	*P* value (adjusted)	AUROC
N	18	23			
Gestational age (weeks)	25.6(1.8)	27.9(2.2)	0.001		0.813
Birth weight (grams)	715(125)	940(350)	0.006		0.771
Peak inflation pressure cmH_2O	18.2 (2.0)	16.8 (3.0)	0.133	0.204	0.633
Mean airway pressure cmH_2O	8.5(1.5)	8.0(1.0)	0.432	0.254	0.551
Tidal volume ml/kg	5.2(0.4) Range 4.7–7.1	4.8(0.5) Range 3.9–6.0	0.013	0.047	0.723
Minute volume ml/kg/min	270(48)	237(36)	0.020	0.124	0.714
CO_2 (mmHg)	41(7)	40(7)	0.661	0.834	0.534
CRS (ml/cm/H_2O/kg)	0.4(0.1)	0.6(0.2)	0.010	0.121	0.705
RRS (cm/H_2O/l/s)	357(108)	277(88)	0.015	0.210	0.706

month after birth and the compliance remained low. In addition, infants with evolving BPD have an increasing physiological dead space, which is the fraction of the tidal volume that does not participate in gas exchange [22]. Physiological dead space in ventilated new born infants has been shown to be significantly related to gestational age, days of ventilation and expiratory airway function and was higher in prematurely born infants who developed BPD compared to those who did not develop BPD [4]. Furthermore, the process of mechanical ventilation per se might partially explain the increasing volume and peak inflation pressure requirements over time in infants with evolving BPD, as we have recently demonstrated that alveolar dead space which likely reflects an iatrogenic lung injury secondary to mechanical ventilation, also increases with increasing duration of invasive ventilation [5]. The anatomical dead space may also increase due to the progressive dilation of the immature trachea and bronchi resulting from cyclic stretch [2]. A further explanation is that chronic respiratory support may result in thickening of the blood gas barrier, poorer perfusion and evolving structural lung disease.

Our results have implications for clinical practice as they would suggest that, in infants with evolving BPD, higher volume targeted levels should be used with increasing postnatal age. Indeed, it has been shown [14] that using volume targeted ventilation and permissive hypercapnia amongst 26 extremely low birth weight (ELBW) infants, the mean exhaled V_T increased over the first 21 days. Furthermore, we have recently demonstrated that in such infants that only a V_T of 7 ml/kg

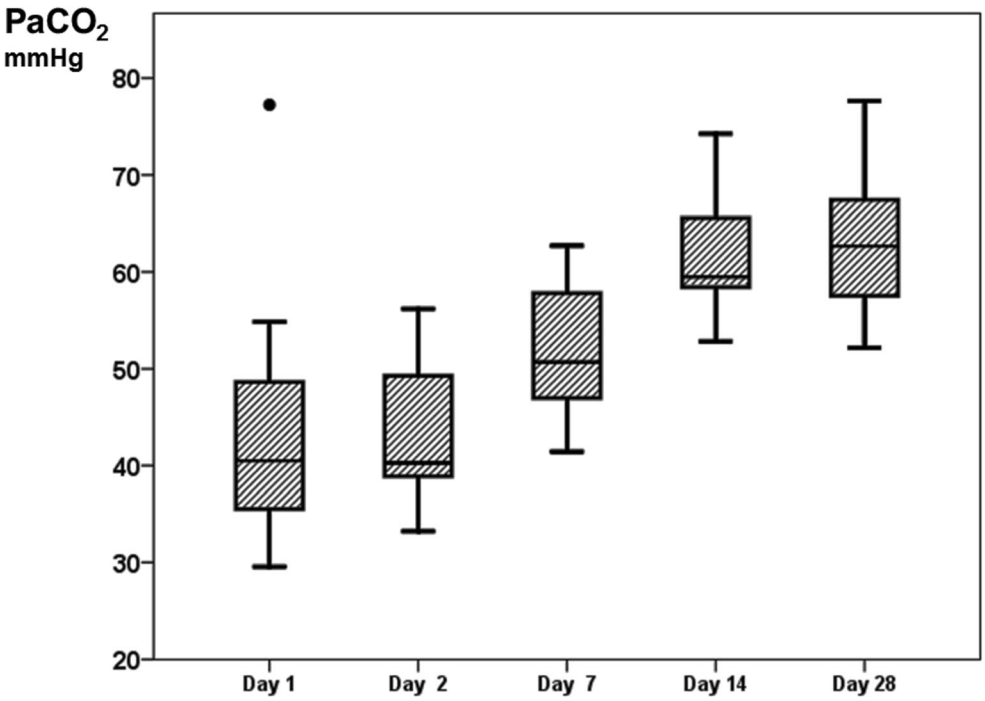

Fig. 1 Box and whisker plot of $PaCO_2$ levels in the first month after birth

Table 2 Volumes, CO_2 levels and respiratory function over the first month in infants who remained ventilator dependent at 28 days. Data presented as mean (SD)

	First measurement	Day 1	Day 2	Day 7	Day 14	Day 28	*P* value
V_T (ml/kg)	5.5 (1.4)	5.2 (0.4)	5.2 (0.6)	5.8 (1.0)	5.8 (0.7)	6.4 (1.1)	0.002
CO_2 (mmHg)	39 (7)	41 (7)	44 (7)	52 (7)	60 (4)	65 (6)	< 0.001
PIP (cmH_2O)	19 (3)	18 (2)	18 (3)	19 (2)	22 (3.5)	23 (3.6)	< 0.001
MV (ml/kg/min)	286 (96)	270(48)	248(42)	293(70)	317(73)	368(97)	< 0.001
RRS ($cm/H_2O/l/s$)	475 (145)	357(108)	338(102)	390(61)	410(85)	481(107)	0.001
CRS ($ml/cm/H_2O/kg$)	0.25 (0.09)	0.36(0.14)	0.40(0.26)	0.33(0.12)	0.24(0.07)	0.42(0.22)	0.066

compared to lower levels (4–6 ml/kg) was associated with a lower work of breathing than at baseline (i.e., without volume targeting) [12].

Our study has strengths and some limitations. We report the results of consecutive preterm infants who had volume measurements during pressure limited ventilation. The ventilator recorded the expiratory rather than the inspiratory volume to minimise errors due to leak. In addition, our routine practice was to use shouldered endotracheal tubes which have been shown to have minimal or no leak around them [11]. It was not possible, however, to determine how much the infants contributed to the minute volume. Nevertheless, as the peak inspiratory pressure progressively increased over the first 28 days, it seems probable that the increase in tidal volume reflected an increased delivered volume by the ventilator. Initial comparison corrected for body weight showed significant differences in CRS and RRS. We additionally corrected for gestational age as infants may be IUGR or large for gestational age. Importantly, this analysis demonstrated that there were no significant differences in lung function, as reflected by the CRS and RRS results between the two groups. We did not document the tidal volume of spontaneous breathing, but did record the expired tidal volume related to mechanical inflations ± spontaneous breathing which would likely be larger than spontaneous breaths alone. As a consequence, if volutrauma is to be avoided in ventilated infants, our results emphasise that the ventilator delivered tidal volumes may need to be reduced. We describe a convenience sample, but they were studies within a defined time period and we demonstrate significant results.

In conclusion, higher tidal volumes in the first 24 h after birth were associated with ventilator dependence at 28 days. After adjusting for gestational age, this did not reflect initial worse lung function as reflected by a significantly lower compliance or higher resistance. Our results, therefore, highlight the importance of ensuring that the minimal optimal volume is delivered in the first 24 h.

Authors' contributions KA and AG designed the study. KA, SK and IC collected the data. KA, TD and AG analysed the data. All authors were involved in the preparation of the manuscript, critically reviewed the manuscript and approved the final manuscript as submitted.

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Compliance and ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Routinely collected data were analysed, hence informed consent was not required.

Conflict of interest AG has held grants from various manufacturers (Abbot Laboratories, MedImmune) and ventilator manufacturers (SLE). Professor Greenough has received honoraria for giving lectures and advising various manufacturers (Abbot Laboratories, MedImmune) and ventilator manufacturers (SLE). Professor Greenough is currently receiving a non conditional educational grant from SLE.

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