Early volume targeted ventilation in preterm infants born at 22-25 weeks of gestational age

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Author contributions: LW conceived the study, participated in its design, was responsible for the collection, statistical analysis and interpretation of clinical data, and the preparing the first draught of the manuscript**.** AS participated in the design of the study, collection and interpretation of data, and preparation of the manuscript**.** RS took part in conceiving the study, participated in its design, participated in the interpretation of data and the preparation/revision of the manuscript

ABSTRACT

Background: Early hypocapnia in preterm infants is associated with intraventricular haemorrhage (IVH) and bronchopulmonary dysplasia (BPD)**.** Volume targeted ventilation (VTV) has been shown to reduce hypocapnia in moderately preterm infants. Less is known of VTV in infants born at <26 weeks gestational age (wGA).

Objectives: Our aim was to investigate the short- and long-term benefits of early VTV as compared to assist-control ventilation (ACV) in extremely preterm infants on incidence of hypocapnia, days on ventilatory support, IVH and BPD.

Study Design: A retrospective observational study of 104 infants born at 22-25 wGA ($24^{+0}\pm1^{+1}$wGA; birth weight 619±146g), ventilated with either VTV (n=44) or ACV (n=60) on their first day of life. Ventilatory data and blood gases were collected at admission and every fourth hour during the first day of life, together with perinatal characteristics and outcomes.

Results: Positive inspiratory pressure (PIP) was lower in the VTV-group than in the ACV-group during the first 20 hours of life ($p<0.05$), without any difference in end-expiratory pressure, respiratory rate or FiO_2. Incidence of hypocapnia ($PaCO_2$<4.5kPa) was lower with VTV than ACV during the first day of life (32% vs 62%; $p<0.01$). Infants in the VTV-group were more frequently extubated at 24 hours (30% vs 13%; $p<0.05$). IVH grade ≥3, BPD and time on mechanical ventilation did not differ between the groups.

Conclusions: VTV is safe to apply in infants born at <26 wGA and was observed to have lower incidence of hypocapnia compared to infants ventilated by ACV, without any differences in outcomes.

INTRODUCTION

During the last twenty years the survival of the most premature infants have increased due to medical treatments such as surfactant, antenatal steroids, and centralisation of the medical care [1-4]. Also, the comprehensive approach of taking care of infants at the edge of viability has improved survival without necessarily increasing the morbidity. Still, there is an association between morbidity and low gestational age (GA), and the incidence of bronchopulmonary dysplasia (BPD) has not decreased despite an increase in survival [1,5,7-8]. BPD is associated with prolonged hospital stay and poor long-term outcomes, as neurodevelopmental impairment and reduced lung function [9-10].

Invasive ventilation increases the risk of lung injury as assisted ventilation might induce volutrauma in underdeveloped and immature lung [11-13]. Despite an established preference to apply non-invasive ventilatory support, many of the extremely premature newborn infants are still in need of invasive ventilation during their stay in the Neonatal Intensive Care Unit (NICU). The EXPRESS study in Sweden showed that 85 % of infants born below 27 gestational weeks received invasive ventilation, and the Neonatal Research Network in the US reported that 83-90% of infants born ≤28 gestational weeks required periods of mechanical ventilation [1,14].

During volume targeted ventilation (VTV) the tidal volume (V_T) is set and positive inspiratory pressure (PIP) fluctuates according to changes in compliance and/or breathing efforts. Usually a PIP limit is set to avoid excessive tidal volumes. The ventilator measures V_T during inspiration (V_{Ti}) and/or expiration (V_{Te}) to regulate V_T delivery by adjusting PIP and flow, and within a set or adjusted inflation time [15]. Thus the ventilator is able to compensate for variations in lung compliance and to some extent resistance. In a Cochrane meta-analysis from 2017, including 20 randomised trials, the authors compared

volume targeted (VTV) and pressure limited (PLV) ventilation modes in neonates, and they concluded that VTV was associated with a reduced rate of death and/or BPD at 36 weeks postmenstrual age (PMA), days of mechanical ventilation, hypocapnia and severe intraventricular haemorrhage [16]. VTV has also been associated with a lower PIP and mean airway pressure (MAP) in studies of newborn infants, but also in reducing excessively large tidal volumes compared with PLV [15,17]. However, there is a limited amount of studies on the application of VTV in infants born specifically before 26 weeks GA, a group which is usually only presented as a subgroup in the studied populations [18-19].

One of the technical challenges in VTV is that the tidal volumes in infants below 26 weeks GA are small (2-4 ml) and the ventilator needs to be able to recognise small changes in flow, and preferable V_{Te} is measured close to the airway opening [18,20]. Keszler et al studied tidal volumes during VTV mode in infants weighing below 800g (24-29 weeks GA) and found that the optimal tidal volume to accomplish normocapnia defined as 35-50 mm Hg (4.7-6.7 kPa)) was 5 ml/kg during the first days and increased over the first three weeks of life [21]. There seems to be some caution using VTV mode in the most preterm infants according to published data, but theoretically this population should benefit the most from using limited tidal volumes as they are more prone to be in need of longer periods with mechanical ventilation and at higher risk of developing short and long term lung diseases, and co-morbidities related to BPD [22].

Excessive tidal volumes are related to low arterial pCO_2 ($PaCO_2$), causing hypocapnia and a reduction in cerebral blood flow, as carbon dioxide is a regulator of vascular tension [23]. Hence, a close association between hypocapnia and periventricular leukomalacia has been defined in several studies, and episodes of hypocapnia has been reduced when ventilating newborn and premature infants with VTV compared to PLV [18, 24-28].

The aim of this study was to investigate if an early application of VTV in infants born at 22-26 gestational weeks is associated with improved ventilatory parameters, blood gases and outcomes when compared to assist control ventilation (ACV).

MATERIALS AND METHODS

This was a retrospective observational study comparing the ventilatory modes VTV and ACV, during two epochs (2017-2018 and 2014-2015 respectively), in extremely preterm born infants requiring invasive ventilation after initial stabilization in a tertiary NICU (Uppsala University Children's Hospital, Uppsala, Sweden). The study was approved by the Uppsala Ethical Board (Dnr 2019-01069).

Patients

Infants born at 22-26 weeks of gestational age and in need of mechanical ventilation during the first day of life were considered eligible for inclusion. Exclusion criteria were infants born in other hospitals, death during the first 24 hours, congenital anomalies, extubation within 4 hours, and ventilatory modes other than VTV or ACV during the defined time periods. The criteria for intubation and surfactant administration were similar for both periods, and mechanical ventilation was initiated in the delivery room in infants with apnea or significant respiratory distress. Study objects received uncuffed endotracheal tube (ETT) (2.0-2.5 mm) at intubation and were ventilated using the Stephanie or Sophie Ventilator (Fritz Stephan GmbH, Germany). In both modes, the ventilator rate was initially set to 60 breaths per minute, inspiratory time was set at 0.33 seconds and inspiratory-to-expiratory ratio of 1:2. In infants ventilated by VTV the standard initial set tidal volume was 5.0 ml/kg. Target $PaCO_2$ during the first days of life on invasive ventilation was 4.5-6.0 kPa (34-45 mmHg) during both studied epochs. VTV was maintained as a primary invasive mode during the first week of life until extubation, unless excessive leakage of more than 50% was detected or the clinical situation necessitated a change of mode as assessed by the attending physician.

Data collection

Perinatal data and outcome parameters were collected from the electronic health record system Cosmic® (Cambio Healthcare Systems, Stockholm, Sweden). Detailed information regarding ventilatory and vital parameters were collected from admission and every fourth hour for 24 hours from the patient data monitoring systems ICCA® (IntelliSpace Critical Care and Anesthesia, Philips Healthcare, Eindhoven, Netherlands) and Metavision® (iMDsoft, Needham, MA, USA). Measured PIP and positive end-expiratory pressure (PEEP) were collected for both study groups. PIP during VTV was collected and calculated as a mean of 10 registered PIPs per breath at the specified time intervals. There was a change of data monitoring systems between the studied periods; both systems record parameters in real time, but tidal volumes were not registered in ICCA®, and are thus not available for analysis in the ACV population. Infants on continuous positive airway pressure (CPAP) or high frequency oscillation ventilation (HFOV) were excluded from the analysis of ventilatory parameters, thereby changing the number of presented infants in both groups over time (Table 2). Blood gases during the first day of life were collected from both the monitoring systems and the journals. The first blood gas was collected at the time of umbilical arterial catheter placement after the initial stabilisation in the delivery ward, and thus reflects the effect of the initial resuscitation (Table 3).

The Swedish National Quality Register (SNQ) was used to collect data regarding outcome parameters such as days of mechanical ventilation, supplementary oxygen and BPD, but these data were also collected in a manually day-by-day analysis from the data monitoring systems. Moderate BPD was defined as the need of <30% supplemental oxygen at 36 weeks post-menstrual age (PMA), and severe BPD was defined as the need of ≥30 % oxygen or positive pressure respiratory support at the same time point [29-31].

Statistical analysis

ANOVA together with two-tailed Student's t-test was performed to assess significant differences between the groups. X^2 test or Fisher's exact test were applied for categorical variables. A $p<0.05$ was considered as a significant difference.

RESULTS

167 infants born between 22 and 26 gestational weeks were admitted to the NICU during the study period. 63 infants were excluded from the study, with referral infants born accidently in other hospitals being the most common reason for exclusion (57%; Figure 1). Of the 104 infants included in the study, 44 received VTV and 60 received ACV during the first day of life (Figure 1). Patient characteristics such as gestational age gender, birth weight, antenatal steroids and Apgar score at 5 and 10 minutes did not differ between the groups (Table 1). All infants received surfactant during the first half hour of life. (Table 1). No infants received sedatives or analgesia during mechanical ventilation after intubation during the first 24 hours of life. In the entire population included in this study the survival rate was 72%, with 68% survival in subjects born at 22^{+0}-23^{+6} weeks GA (36/53) and 76 % (39/51) in subjects born at 24^{+0}-25^{+6} weeks GA. The overall survival rate of the 167 infants born during the study period was 70% (117/167).

At 4, 8, 12, 16 and 20 hours of age, PIP and MAP were lower in the VTV-group than in the ACV-group, but there were no differences at 24 hrs of age (Table 2). There were no differences in PEEP, respiratory rate (RR) or supplementary oxygen between the groups during the first day of life (Table 2). Tidal volume per kg during VTV did not differ between the studied time points (mean 4.8±1.4 ml/kg).

Hypocapnic episodes defined as $PaCO_2$ <4.5 kPa, was detected in 32% (14/44) of the infants in the VTV-group and in 64% (37/58) of the infants in the ACV-group ($p<0.01$; Table 4). Arterial blood gases were not available in 2 infants in the ACV-group. Hypocapnia was present in 13% (29/225) of collected blood gases in the VTV-group and 20% (64/324) in the ACV-group during the first day of life ($p=0.03$). The number of collected blood gases per infant did not differ between the groups (5 ±1 in VTV-group and 6±1 in ACV- group; $p=0.12$.) Arterial pH was lower and $PaCO_2$ higher at 4 hrs and 24 hrs in the VTV-group

(Table 3). The lowest detected $PaCO_2$ in each infant was also higher in the VTV-group compared to the ACV-group ($p<0.01$; Table 4).

Infants ventilated by VTV mode were more frequently extubated at 24 hours of age compared with the ACV-group (30% [13/44)] vs 13% [8/63]; p=0.03), and the median age at first extubation was 2 (IQR 1-6) and 5 (IQR 1-25) days respectively (p=0.08).

Days of invasive ventilation did not differ between the two groups, neither did days on nasal CPAP or total days with supplementary oxygen until discharge from the ward (Table 5). Median length of first stay at the level III NICU was 48 days(IQR 20-93) in infants ventilated by VTV and 40 (IQR 18-77) days in the ACV-group (p=0.3; Table 5).

There were no differences between the groups in outcome parameters such as IVH ≥ grade III, operated NEC, ROP≥ stage 3 requiring treatment, BPD, or death (Table 5). PDA-ligation was more frequent in the ACV-group (Table 5).

DISCUSSION

In this cohort of extremely premature infants, born between 22^{+0} and 25^{+6} gestational weeks, we found that early VTV is applied safely and without increases in oxygen demand, episodes of hypocarbia, severe IVH or prolonged time on mechanical ventilation before extubation.

The ability of VTV to reduce unwanted large tidal volumes and thereby minimizing volutrauma, should provide optimal conditions for gentle mechanical ventilation, especially in the most immature infants [15,17,32]. As most infants born <26 weeks GA will develop infant respiratory distress syndrome and will be treated with surfactant during the first day of life, there is need of a ventilation mode that can interact with rapid changes in lung compliance to achieve stable V_T and gas exchange. In studies of extremely premature infants it has been shown that lung mechanics change over time and that increased PEEP and V_T are needed to accomplish optimal ventilation during the first days of life [33,21].

Based on previous studies on extremely premature infants born between 24 to 29 GA weeks, the tidal volume during our study period was set at 5 ml/kg [20-21]. The delivered volumes were close to targeted V_T despite uncuffed ETTs and small tidal volumes (mean V_{Te} 4.8±1.4 ml/kg; mean birth weight 595±119g). Application of VTV is dependent on reliable measurements of tidal volumes which is affected by the leakage of uncuffed ETTs and by the ability of the ventilator to make accurate measurements [34-35]. Eventually the endotracheal leakage increases over time, as the trachea is eventually dilated, which requires frequent evaluations of lung mechanical parameters, as well as information on gas exchange for adjusting target tidal volumes or changing to larger ETTs if continued need of invasive ventilation [21,36]. Also, a V_T set too low will increase the work of breathing, promoting asynchrony with the ventilator and increasing pCO_2 [37].

In view of the very low tidal volumes (mean 2.7±0.9mL) delivered to the infants in our study, the influence of dead space might be a cause of concern. In a study investigating the influence of dead space (3mL/kg) on ventilation in low-weight infants (range 24-29 GA; birth weight 400-790g), the authors concluded that effective alveolar ventilation occurs even when the difference between V_T and dead-space is low [20]. Our infants accomplished normal gas exchange with even smaller tidal volumes, which is concordance with the suggested explanation that high flow rates might overcome the interference of dead space and thereby enable gas exchange at tidal volumes close to dead space volumes [20].

In our study-population PIP and MAP was lower during VTV compared with ACV during the first twenty hours of life with no difference in PEEP between the groups. Tidal volumes during ACV was not possible to collect retrospectively, but one could assume them to be higher than during VTV as PEEP did not differ between the two groups, comparable amounts of surfactant were delivered and more episodes of hypocapnia were detected in the ACV-group. The VTV-group had a higher mean $PaCO_2$ at 4 hours and 24 hours compared to the ACV-group (Table 2), which might indicate that set target tidal volume needs to be increased during the first days of life, as earlier suggested by Keszler et al [21]. Although within an acceptable range, the higher $PaCO_2$ during VTV could have been expected to influence the respiratory rate, which did not differ between the two groups, suggesting that this modest raise in $PaCO_2$ is well tolerated in these infants. Never the less, the observed increase in $PaCO_2$ at the end of the first day, might indicate that set target tidal volumes need to be adjusted earlier in these extremely preterm infants than described previously in studies of more mature infants [21] .

During the first day of life, episodes of hypocapnia defined as PaCO2<4.5 kPa were less frequent in infants ventilated by VTV (64% vs 32%). We also found that the lowest detected $PaCO_2$ per infant was higher in the VTV-group compared with the ACV-group

(4.9±1.1 and 4.3±0.6 kPa, p<0.01; Table 4). The known association between hypocapnia and IVH makes these findings important [38]. The reduction of hypocapnia in our material is also consistent with other studies comparing VTV to PLV which was thus accomplished with V_{Ti} set at 5 ml/kg during the first day of life [18,26-27].

We did not identify any differences in the over-all duration of mechanical ventilation between the groups, which is in accordance with the Cochrane meta-analysis of infants with a birth weight of <1000g, where no statistical difference in duration of mechanical ventilation was identified between VTV and PLV [16]. Our studied population is yet another selection of infants in comparison to previous studies, as 51% (53/104) of the included infants were born at 22 or 23 weeks GA, and thereby comprises a category of infants that should benefit the most from more normocapnic and non-volutraumatic ventilation.

In the VTV-group more infants were extubated at 24 hours of age. The visualization of low PIPs to achieve the targeted V_T during VTV might have encouraged the clinican to consider earlier extubation even in these very preterm infants, where no detrimental effects were detected in comparison to the ACV-group. Infants born before 26 weeks GA have not been studied with respect to VTV and successful extubation, and therefore needs to be evaluated in future randomized controlled studies.

The high incidence of moderate or severe BPD (76%) illustrates that this group of extremely preterm infants are associated with long periods of ventilatory support and supplemental oxygen before discharge. A reduction in incidence of BPD in VTV compared to PLV have been described [39], but this was not confirmed in our material. This might be explained by: a) the time chosen to evaluate VTV in this study was 24 hrs; b) the studied infants are more premature than in most other studies; c) and the chosen definition for BPD

differs between studies. Interestingly the analysis of a subgroup of infants <1000g in the Cochrane review from 2017 showed no difference in incidence of BPD [16]. In our retrospective study the first hour of life was selected as a time-frame for analysing the feasability of early VTV in this population extremely preterm infants with a mean GA of 24 weeks, as an extension of the concept of gentle ventilation during the first Golden Hour [40]. With time, and after extubation, a greater diversity might be seen in the clinical settings concerning ventilation modes, chosen target V_T, PEEP and also a shift in targeted $PaCO_2$ towards permissive hypercapnia. For these reasons we did not include total time of VTV as a parameter, but the total duration of applied VTV needs to be investigated with regard to days on mechanical ventilation and BPD in this population of extremely preterm infants. We also could not identify any differences in mortality between the groups, where the reported mortality of 28% (29/104) includes the first year of life. There were no deaths due to severe BPD beyond 5 months of life in the VTV-group, but there were four deaths in the ACV-group. This population at the limit of viability, has had an increase in survival over the last decades [1,6], and also increases the prevalence of BPD, which stresses the need to thouroughly investigate ventilatory strategies such as VTV.

This study has obvious limitations as it is a retrospective observational analysis comparing two time epochs where changes in care could have differed over time. The collection of ventilatory data does not include tidal volumes during ACV as the PDMS was not compatible for transferral of this data during that epoch. Randomised studies are needed to evaluate if VTV is of benefit in terms of long-term outcomes and to identify standardized optimization of tidal volumes over time in this population of the most extremely premature and vulnerable infants.

Conclusion

Early VTV is safe to apply in infants born below 26 gestational weeks, with observed lower PIP, fewer episodes of hypocapnia compared to infants ventilated by ACV, and without any detrimental effects on long term outcomes such as mortality, IVH, BPD and/or mortality.

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FIGURE LEGENDS

Figure 1. Study population: selection and exclusion.

Table 1. Characteristics of infants in ACV-group and VTV-group

Table 2. Ventilation characteristics in ACV-group and VTV-group at 4, 8, 12, 16, 20 and 24 hours of life.

Table 3. Arterial blood gases at start and at 4 and 24 hours in ACV-group and VTV-group.

Table 4. Incidence and severity of hypocapnia during the first day of life in ACV-group and VTV-group.

Table 5. Neonatal outcomes.