Volume-targeted versus pressure-limited ventilation for preterm infants

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Abstract

Background: To compare the effects of volume-targeted ventilation (VTV) with pressure-limited ventilation (PLV) in preterm infants.

Methods: A total of 100 preterm infants who required mechanical ventilation during the two study periods were investigated. PLV was used for 50 preterm infants during period 1 and VTV was used for 50 preterm infants during period 2. Clinical outcomes including mortality rate, duration of mechanical ventilation, air leak syndrome, hypocarbia, hypercarbia, hypoxemia, combined outcome of death or bronchopulmonary dysplasia (BPD), intraventricular hemorrhage, and retinopathy of prematurity were evaluated.

Results: There was no significant difference ($p > 0.05$) in the duration of mechanical ventilation, air leak syndrome, hypocarbia, hypoxemia, or BPD between the two study groups. The mortality rate, hypercarbia, and combined outcome of death or BPD were significantly lower ($p < 0.05$) in the VTV group compared with the PLV group.

Conclusion: Preterm infants using VTV had a lower mortality rate, less hypercarbia, and a significant decrease in the combined outcome of death or BPD.

Keywords: Bronchopulmonary dysplasia; Hypercarbia; Hypocarbia; Pressure-limited ventilation; Volume-targeted ventilation

1. INTRODUCTION

Time-cycled pressure-limited ventilation (PLV) has been traditionally used for newborn infants. This form of ventilation uses a designated volume of gas with a preset peak inspiratory pressure (PIP), over a defined time cycle. Both overexpansion (volutrauma) and under expansion/collapse (atelectrauma) have been previously reported during the use of PLV.[1–3] It has also been reported that tidal volume (V_T), rather than inflation pressure, is the main determinant of ventilator-induced lung injury (VILI).[4]

Volume-targeted ventilation (VTV) can regulate and maintain an appropriate V_T. When V_T is the primary control variable, inflation pressure will fall as lung compliance and patient inspiratory effort improve, resulting in real-time weaning of pressure. Real-time lowering of pressure can avoid excessive V_T and achieve a shorter duration of mechanical ventilation. Many previous studies have documented numerous advantages of VTV compared with PLV, including a decrease in the combined outcome of death or bronchopulmonary dysplasia (BPD), a lower rate of pneumothorax, less hypocarbia, a decreased rate of severe intraventricular hemorrhage (IVH)/periventricular leukomalacia (PVL), and a shorter duration of mechanical ventilation.[5–10]

The aim of the current study was to compare the effects and safety of VTV with PLV in preterm infants.

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2. METHODS

2.1. Study design

A retrospective analysis was performed of data from intubated preterm infants (<37 weeks gestational age [GA]), who required mechanical ventilation therapy at the Level III neonatal intensive care unit (NICU) at Chung Shan Medical University Hospital. PLV mode (Servo Ventilator 300, Siemens-Elema, Solna, Sweden) was used for all preterm infants ventilated during period 1 (October 1st 2014 to February 28th 2016). VTV mode (Babylog VN 500, Dräger, Lübeck, Germany) was used for all preterm infants ventilated during period 2 (March 1st 2016 to August 1st 2017).

2.2. Study population

A total of 100 preterm infants who required mechanical ventilation were enrolled in the current study. Term infants or infants with congenital malformations were excluded. PLV was used for 50 preterm infants during period 1; their mean birth weight (BW) was 1.51 ± 0.56 kg (range 0.40 to 2.31 kg) and their mean GA was 30.14 ± 3.15 weeks (range 23 weeks, 1 day to 34 weeks, 6 days). VTV was used for 50 preterm infants during period 2; their mean BW was 1.61 ± 0.50 kg (range 0.45 to 2.30 kg) and their mean GA was 30.78 ± 2.52 weeks (range 23 weeks, 5 days to 34 weeks, 5 days). Heart rate, respiratory rate, blood pressure, and oxygen saturation (SpO_2) were monitored (Nihon Kohden, Nihon Kohden Corporation, Tokyo, Japan) for every patient in the NICU. The characteristics of the patients in the PLV and VTV groups are summarized in Table 1. The underlying diseases in the PLV group were respiratory distress syndrome (RDS) (34 patients), neonatal pneumonia (10 patients), hypoxic-ischemic encephalopathy (HIE) (four patients), and meconium aspiration syndrome (MAS) (two patients). The underlying diseases in the VTV group were RDS (33 patients), neonatal pneumonia (11 patients), HIE (three patients) and MAS (three patients).

Table 1

Characteristics of the study patients

Characteristics	PLV group; (n = 50)	VTV group; (n = 50)	*p*
Sex (male/female)	26/24	30/20	0.420
Birth weight, kg	1.51 ± 0.56	1.61 ± 0.50	0.400
Gestational age, wk	30.14 ± 3.15	30.78 ± 2.52	0.264
No. of patients receiving iNO therapy, %	5 (10%)	6 (12%)	0.749
Maximal iNO concentration, p.p.m.	14.0 ± 4.18	12.5 ± 6.92	0.682
Duration of iNO therapy, d	5.0 ± 3.6	5.0 ± 1.9	1.0
No. of patients receiving surfactant therapy	23 (46.0%)	21 (42.0%)	0.687
Underlying diseases			
RDS	34 patients	33 patients	0.832
Pneumonia	10 patients	11 patients	0.806
HIE	4 patients	3 patients	0.695
MAS	2 patients	3 patients	0.646

HIE = hypoxic ischemic encephalopathy; iNO = inhaled NO; MAS = meconium aspiration syndrome; No = number; PLV = pressure-limited ventilation; RDS = respiratory distress syndrome; VTV = volume-targeted ventilation.

Inhaled nitric oxide (iNO) therapy was used for five patients in the PLV group and six patients in the VTV group who presented with evidence of pulmonary hypertension. All patients using iNO therapy received an echocardiographic examination and Doppler (Siemens Medical Solution USA, Inc. MountainView, CA, USA) measurements of the tricuspid regurgitation jet, direction of patent ductus arteriosus (PDA) shunt, and direction of atrial shunt were taken. Echocardiographic findings of pulmonary hypertension, including elevated pulmonary artery (PA) pressure, right-to-left or bidirectional PDA, or patent foramen ovale shunting, were found in all patients using iNO therapy.

2.3. Ventilation strategy

During the acute phase of illness, infants in the PLV group were placed in the assist/control (A/C) mode. The initial settings were as follows: rate 30 to 60 breaths per minute (bpm), inspiratory time (i-time) 0.4 seconds, positive end-expiratory pressure (PEEP) 5 to 8 cmH_2O, PIP 12 to 25 cmH_2O adapted to the infant's chest movement and CO_2 elimination. Once the infants were recovering from their acute respiratory illness (PIP < 18 cmH_2O and FiO_2 < 0.3), the ventilatory mode was changed from A/C mode to synchronized intermittent mandatory ventilation mode. The target was to keep arterial blood gases at a pH between 7.25 and 7.45, PaO_2 between 50 and 70 mmHg, $PaCO_2$ between 35 and 55 mmHg, and SpO_2 at 90% to 95%. If the following ventilatory settings were achieved, PIP < 16 cmH_2O, PEEP < 5 cmH_2O, rate ≤ 20 bpm, and FiO_2 ≤ 0.3 extubation were considered. After extubation, the infants were placed on nasal bubble CPAP, using 5 to 6 cmH_2O delivered through short binasal prongs.

Ventilatory settings were selected according to the practical guide for neonatal VTV as described by Klingenberg et al[11] and Keszler et al.[12] The initial V_T for preterm infants was set at 4.0 to 6.0 mL/kg. No sedation and no muscle relaxants were administered to either group during the study time.

2.4. Definitions

$PaCO_2$ and PaO_2 were measured by arterial blood gas analysis. Arterial blood gas was measured every 12 hours for all study infants <72 hours old, and thereafter every 24 hours until extubation. Hypocarbia was defined as $PaCO_2$ <35 mmHg, and hypercarbia was defined as $PaCO_2$ > 60 mmHg. Episodes of hypocarbia and hypercarbia were determined according to the arterial blood gas analysis data. Hypoxemia was defined as SpO_2 < 80% lasting for >20 seconds or PaO_2 < 50 mmHg as determined by the arterial blood gas analysis data. RDS was diagnosed on the basis of radiological and clinical findings. BPD was defined as treatment with FiO_2 > 0.21 for at least 28 days plus failure of the room air challenge test with or without respiratory support at 36 weeks postmenstrual age. Sepsis was defined as a positive blood culture, which was treated with antibiotics for at least 7 days. IVH was defined as either IVH with or without ventricular dilatation or intracerebral (parenchymal) hemorrhage on a cranial ultrasound.[13] Pulmonary hemorrhage was defined as detection of blood in the endotracheal tube and a positive chest radiography finding for focal or diffuse ground-glass opacities. Retinopathy of prematurity (ROP) stage was defined according to the international classification for ROP. ROP stages 3 to 5 were defined as severe ROP. Stage 3 ROP had a ridge with fibrovascular extension into the vitreous, stage 4 ROP had partial retinal detachment, and stage 5 ROP had total retinal detachment. The present study was approved by the Ethical Committee at Chung Shan Medical University Hospital.

2.5. Statistical analysis

Data were analyzed using IBM SPSS, version 22 for Windows software package (IBM SPSS Inc., Chicago, IL, USA). Means were compared using the Student's *t*-test. χ^2 test or Fisher's exact test for categorical data were used as appropriate. A two sided $p < 0.05$ was considered to indicate a statistically significant difference.

3. RESULTS

Table 1 summarizes the characteristics of the infants included in the present study. There were no significant differences ($p > 0.05$) in BW, GA, gender, the number of patients receiving surfactant therapy, the number of patients receiving iNO therapy, the maximal iNO concentration, and the duration of iNO therapy between the PLV and VTV groups.

Table 2 summarizes the outcomes of the study infants. There were no significant differences ($p > 0.05$) in the duration of ventilation, air leak syndrome, the number of patients with hypoxemia, BPD, and the total number of episodes of hypocarbia between the PLV and VTV groups. The mortality rate was significantly lower ($p = 0.031$) in the VTV group (one patient) compared with the PLV group (eight patients). The total number of episodes of hypercarbia was significantly lower ($p = 0.036$) in the VTV group compared with the PLV group. The combined outcome of death or BPD was also significantly lower ($p = 0.008$) in the VTV group compared with the PLV group. There were no significant differences ($p > 0.05$) in pulmonary hemorrhage, severe ROP, patients receiving laser photocoagulation therapy, sepsis, IVH grade 1 to 2, IVH grade 3 to 4 and PVL between the PLV and VTV groups.

4. DISCUSSION

Time-cycled, PLV has been the standard of care for neonatal ventilation for over 30 years. Traditional PLV mode uses a fixed peak inflating pressure, whereas V_T delivery varies from inflation to inflation as the baby breathes and the compliance and resistance changes. This may lead to overexpansion (volutrauma) or a low V_T, which makes breathing harder and can lead to acidosis.[14] It has been previously reported that V_T, rather than inflation pressure, was the critical determinant of VILI.[4] Dreyfuss et al demonstrated that severe acute lung injury occurred in

Table 2

Outcomes of the study infants

Outcomes	PLV group; (n = 50)	VTV group; (n = 50)	*p*
Duration of ventilation, d	11.74 ± 8.80	11.16 ± 7.79	0.728
Air leak syndrome, %*	3 (6.0)	2 (4.0)	1.000
Any episode of hypocarbia	232	198	0.280
Any episode of hypercarbia	97	36	0.036
No. of patients with SpO_2 < 80%	19 (38.0%)	19 (38.0%)	1.000
No. of patients with PaO_2 < 50 mmHg	22 (44.0%)	21 (42.0%)	0.840
Death, %*	8 (16.0%)	1 (2.0%)	0.031
BPD, %	12 (24%)	7 (14%)	0.202
Combined outcome of death or BPD, %	20 (40.0%)	8 (16.0%)	0.008
Pulmonary hemorrhage, %	7 (14%)	4 (8.0%)	0.338
Severe ROP, %*	5 (10.0%)	3 (6.0%)	0.715
No. of patients receiving laser therapy*	2 (4.0%)	1 (2.0%)	1.000
Sepsis, %*	5 (10.0%)	4 (8.0%)	1.000
IVH grade 1–2, %*	2 (4.0%)	2 (4.0%)	1.000
IVH grade 3–4, %*	4 (8.0%)	3 (6.0%)	1.000
PVL, %*	3 (6.0%)	2 (4.0%)	1.000

*Fisher's exact test.

BPD = bronchopulmonary dysplasia; IVH = intraventricular hemorrhage; No = number; PLV = pressure-limited ventilation; PVL = periventricular leukomalacia; ROP = retinopathy of prematurity; SpO_2 = oxygen saturation; VTV = volume-targeted ventilation.

animals ventilated with a large V_T, regardless of whether that volume was generated by a high or low inflation pressure.[4]

In VTV, automatic adjustments are made to the peak positive pressure and the duration of the ventilator cycle to maintain a target V_T. VTV mode has been proposed as a means to reduce VILI caused by ventilation with excessive or insufficient V_T during conventional pressure-controlled ventilation.

A previous systemic review has shown that VTV reduced the duration of ventilation, the combined outcome of death or BPD, pneumothorax, hypocarbia, and PVL/severe IVH, compared with PLV.[5,6]

Lista et al[9] reported that VTV resulted in decreased levels of the inflammatory mediators interleukin-6 (IL)-6 and IL-8 in tracheal aspirate fluid, in preterm infants with RDS. Peng et al[7] reported that preterm infants ventilated using the VTV mode had a reduced duration of mechanical ventilation, incidence of BPD, failure of the primary mode of ventilation, hypocarbia, grade 3/4 IVH, pneumothorax, and PVL.

Volume guarantee (VG) ventilation is one of the most commonly used types of VTV in neonates. In VG ventilation, the peak pressure of each ventilator cycle is adjusted to maintain a target V_T, based on the exhaled V_T measured during previous cycles. VG ventilation was proposed to avoid both extremes of V_T and to achieve a constant reduction in peak pressure. Keszler et al[15] reported that VG ventilation significantly reduced hypocarbia and excessively large V_T. Jain et al[16] reported that the use of VG during routine clinical conditions caused a modest reduction in the duration of hypoxemic episodes (SpO_2 < 85%) compared with pressure control ventilation; however, the use of VG did not reduce the more severe hypoxemia episodes.

The current study revealed that mortality rate, hypercarbia, and the combined outcome of death or BPD were all significantly lower (p < 0.05) in the VTV group compared with the PLV group, which is concurrent with the previous findings.[6] Wheeler et al[6] reported that the use of VTV mode ventilation resulted in a reduction in the combined outcome of death or BPD.

In the present study, five patients in the PLV group and six patients in the VTV group, who had positive echocardiographic findings for pulmonary hypertension, received iNO therapy. A number of previous studies have showed that iNO therapy could improve oxygenation in preterm infants with hypoxic respiratory failure and pulmonary hypertension.[17,18] In the current study, iNO was only used in infants with hypoxemia and echocardiographic findings positive for pulmonary hypertension. Many previous studies have demonstrated that the use of VTV mode led to a reduction in the rate of hypocarbia compared with PLV mode.[5–7] Cheema et al[19] found that VG significantly reduced the incidence of out-of-range $PaCO_2$ and hypocarbia in infants over 25 weeks gestation.

In the present study, VTV notably reduced hypercarbia; however, there was no significant difference (p > 0.05) between the VTV and PLV groups. Hypocarbia and hypercarbia have been found to have a positive association with brain damage in preterm infants.[20–23]

There were several limitations to the present study. First, it was a retrospective study. Second, it was a single center study. Third, the PLV mode of a Servo ventilator 300 was used for all ventilated preterm infants during period 1, whereas the VTV mode of a Babylog VN 500 ventilator was used for all ventilated preterm infants in period 2. This procedure lacks consistency and could be improved upon in future studies.

In conclusion, in the present study, VTV resulted in lower rates of hypercarbia, mortality, and a combined outcome of death or BPD, compared with PLV in preterm infants. Therefore, the authors suggest that using this new lung protection strategy could reduce VILI in preterm infants.

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