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Patient-initiated, pressure-regulated, volume-controlled ventilation compared with intermittent mandatory ventilation in neonates: a prospective, randomised study

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Abstract *Objective:* To compare the effects of patient-initiated, pressure-regulated, volume-controlled ventilation (PRVC) with pressure-preset intermittent mandatory ventilation (IMV) in neonates with respiratory failure.
Design: Randomised, prospective study.
Setting: Intensive care unit (14 beds) in a 300-bed paediatric teaching hospital.
Patients: 60 neonates with respiratory distress syndrome (RDS) or congenital pneumonia, weighing < 2500 g and requiring mechanical ventilation.
Interventions: Ventilatory support until extubation via either IMV ($n = 30$) or PRVC ($n = 27$). In PRVC, the tidal volume (V_T) was preset and pressure-controlled breaths delivered with peak inspiratory pressure values adapted to achieve the preset V_T.
Measurements and results: Main outcome measures were duration of ventilation and incidence of bronchopulmonary dysplasia (BPD). Pulmonary air leaks and intraventricular haemorrhage (IVH) were considered major adverse effects. Demographic data, ventilation parameters and arterial/alveolar oxygen tension ratio were similar at randomisation. Duration of ventilation and incidence of BPD were not decreased by the use of PRVC. Air leaks occurred in 3 neonates in the PRVC group and in 7 babies treated with IMV (NS). The incidence of IVH grade > II was lower in babies treated with PRVC ($p < 0.05$). In a subgroup of neonates weighing < 1000 g, the duration of ventilation and incidence of hypotension were reduced in the PRVC group ($p < 0.05$).
Conclusion: Patient-initiated, pressure-regulated, volume-controlled ventilation can be safely used in neonates and may contribute to a lower incidence of complications.

Key words Neonate · Respiratory distress syndrome · Respiratory failure · Mechanical ventilation · Controlled clinical trial

Introduction

In the treatment of neonatal respiratory failure there is often a need for mechanical positive pressure ventilation (PPV) with positive end-expiratory pressure (PEEP) to increase lung volume and improve alveolar ventilation and the ventilation-perfusion relationship. Although PPV has substantially contributed to improved survival of critically ill newborn infants, its use has been responsible for acute and chronic complications. Despite adding exogenous surfactant, judiciously elevating fractional inspired oxygen (FIO_2) and using the lowest possible peak inspiratory airway pressure (PIP), pulmonary, air leaks may occur in up to 21% of neonates with respiratory distress syndrome (RDS) [1] and bronchopulmonary dysplasia (BPD) may oc-

cur in 17 to 49 % of babies with a birthweight < 1751 g [2].

Pressure-preset (pressure-limited) intermittent mandatory ventilation (IMV), provided by continuous flow, time-cycled ventilators, has become a standard technique of ventilatory support in neonatal intensive care. The main drawbacks of this method are poor control over volume delivered, with the danger of under- or overdistending the lungs, and difficulty in synchronising respiratory efforts with PPV. The latter problem has been partly solved with patient-initiated modes such as patient-triggered ventilation [3, 4] or synchronised IMV [5].

Pressure-regulated, volume-controlled (volume-preset) ventilation (PRVC) has been recently proposed as a new mode in which the smallest level of positive pressure required to deliver the preset tidal volume (V_T) is provided by the ventilator [6]. Mechanical breaths are in fact pressure-controlled; the level of PIP is regulated by microprocessor on a breath-by-breath basis to maintain the preset tidal and minute volumes. During inspiration a square pressure wave and decelerating flow are present and PIP never differs more than 3 cm H_2O between consecutive breaths. It is also a patient-initiated mode, and the ventilator can cycle in response to either a pressure decrease in the circuit or to a change in flow.

The aim of our study was to compare the immediate and outcome for neonates ventilated for the respiratory distress syndrome or congenital pneumonia by means of patient-initiated PRVC ventilation or conventional pressure-limited IMV.

Materials and methods

Patient selection

Consecutive neonates transferred to the intensive care unit (ICU) of the paediatric hospital between 15 November 1994 and 15 March 1996 were considered for entry into this study. Infants were eligible if the following criteria were satisfied: (1) need for mechanical ventilation for lung disease; (2) birthweight < 2500 g; (3) age < 72 h at randomisation. Exclusion criteria included terminal state of the infant at admission, pneumothorax or other forms of air leak, congenital anomalies, sepsis and meconium aspiration. As one ventilator for PRVC was available, infants were randomised only if this ventilator was not in use.

The study was conducted according to the principles established in Helsinki and was approved by the Committee on Human Experimentation at the Medical University of Łódź, Poland. The Committee suggested that informed consent was unnecessary, as PRVC had already been in use for neonates for over 2 years at our institution [7].

Randomisation and end-points

Neonates were randomised by means of drawing cards from consecutive, sealed envelopes. Stratification into smaller birthweight groups was not performed. The primary study end-points were duration of mechanical ventilatory support and the incidence of BPD. We also wanted to compare the ventilation variables during the first 10 days of treatment. The major adverse effects considered were pulmonary airleaks and periventricular-intraventricular haemorrhage (IVH).

Duration of ventilation was defined as number of days on ventilatory support until successful extubation (> 24 h of breathing without an endotracheal tube). Diagnosis of RDS was confirmed at 7 days of age by review of the clinical course and analysis of chest radiographs. For the diagnosis of pneumonia, asymmetrical consolidation on the radiograph with positive culture of blood or tracheal aspirate was needed. The presence of BPD was defined as the requirement for supplemented oxygen or PPV on day 28 of life and a chest X-ray receiving a BPD score of at least 4 on the Edwards scale [8]. X-rays were taken once a day during the acute stage of respiratory insufficiency and then twice a week if the patient was still being ventilated.

Other end-points of the study included the incidence of arterial hypotension, necrotising enterocolitis, persistent ductus arteriosus (PDA) and the need for sedation. Hypotension was diagnosed when the mean blood pressure was < 10th centile for birthweight and age or < 30 mm Hg in neonates weighing > 1500 g [9]. Duration of hypotension was not recorded, as hypotension was immediately treated with fluids or catecholamines, or both. Diagnosis of PDA was based on clinical symptoms and was confirmed by pulsed Doppler echocardiography [10]. Necrotising enterocolitis was diagnosed when abdominal distension was present, accompanied by free air in the bowel wall on X-ray or blood in the stool. The extent of IVH was classified as subependymal (grade I IVH), intraventricular without ventricular dilatation (grade 2), IVH with ventricular dilatation (grade 3) and intraventricular haemorrhage with intraparenchymal haemorrhage (grade IV) [11].

Ventilator treatment

The infants were managed by the clinical team in the ICU, with no special involvement of the authors. After randomisation, neonates in the IMV group were ventilated with time-cycled, pressure-limited, continuous flow ventilators: Bear 2001 Cub (Bear Medical Systems, Riverside, Calif., USA) or Sechrist IV 100 B (Sechrist Industries, Anaheim, Calif., USA). Patients in the PRVC group were ventilated by means of the Servo Ventilator 300 (Siemens-Elema, Solna, Sweden). The ventilator strategy in both groups was similar: PIP level (or V_T in the PRVC group) minimal to provide normal excursion of the chest [12], PEEP 3 to 5 cm H_2O and an FIO_2 to achieve oxygen saturation (pulse oximeter, Oxypleth 520 A, Novametrix Medical Systems, Wallingford, Conn., USA) between 88 and 95 %. The ventilator setting was kept at the level where spontaneous unlaboured inspiratory efforts were present. The inspiratory time was fixed at 0.5 s and shortened when it caused discomfort to the patient on a rate over 60 beats/min was used. PEPP was not allowed to drop to < 3 cm H_2O.

In the PRVC mode, initial V_T was based on the infant's average V_T (5–6 ml/kg) augmented by 4 to 5 ml of compressible volume and dead-space compensations. In the immediate period after admission, the V_T was adapted to the babies' chest movement and CO_2 elimination. The flow trigger in the Servo Ventilator was always active, with the sensitivity set at a high level (border between green and red fields on the scale) and the value of PIP was limited by the high pressure limit, usually set at 5 to 7 cm H_2O above the actual PIP value.

Hypoxaemia [partial pressure of oxygen in arterial blood (PaO_2) < 50 mm Hg] was treated initially by increasing FIO_2, then PEEP and then PIP (V_T in the PRVC group). Hypercapnia [arteri-

al carbon dioxide tension ($PaCO_2$) > 55 mm Hg] was treated first by increasing the rate and later by elevating PIP (V_T in the PRVC group). During PRVC, the ventilator rate was usually regulated by the patients' own inspiratory activity, and only a backup rate (usually 20 % less than observed) was set on the ventilator. During weaning, PIP and V_T values were reduced first, there the FIO_2 and the set ventilator rate. When the patient's clinical status improved and FIO_2 < 0.25, PIP < 12 cm H_2O and set rate < 12 beats/min in both groups were required, a trial of continuous positive airway pressure (CPAP) was performed for 30–60 min, and, when tolerated, extubation was undertaken. In babies weighing < 1500 g, nasal CPAP was used after extubation until full stabilisation of gas exchange.

Surfactant was given only to neonates with RDS who were admitted to the ICU in the first 12 h of life and required an FIO_2 > 0.4 after the initial 4 h of treatment, according to the ICU policy at the time of the study. Neonatal medical management was provided uniformly for all infants according to the ICU's guidelines. For agitated patients, midazolam or pethidine was used for sedation and, in difficult cases, short-term muscle relaxation with pancuronium.

Monitoring

Infants were monitored by means of echocardiography, respirogram, pulse oximetry and blood pressure (measured directly when an FIO_2 > 0.4 was needed or the patient's clinical status was unstable). Values for airway pressure (P_{aw}) were calculated with a square respiratory pressure waveform assumed [13].

The values of PIP, P_{aw}, FIO_2 and ventilator rate were recorded every 6 h in the first 10 days of study, data were averaged over 24-h periods and median values were compared between groups. The amount of fluids received in the first 10 days of life was also compared. The arterial/alveolar oxygen tension (Pa/AO_2) ratio was calculated according to the formula:

$$Pa/AO_2 = PaO_2/ (713 \times FIO_2) - PaCO_2.$$

The patients had cranial sonography in the first 5 days after admission and then at least once a week until discharge. This was performed by a physician unaware that the babies were in the study.

Trial size

Using the results from the year 1993, when the mean ventilation time for infants in our ICU was 12 (± 6) days, we calculated that to detect a 5-day difference in favour of a new method of ventilation with 85 % power at the 5 % level, a sample size of 27 patients per group was needed. Anticipating some possible exclusions, we decided to include 30 patients in each group.

Statistical analysis

The comparability of study groups was tested by means of chi-square or two-tailed Fisher's exact tests for categorical variables and Student's *t*-test for continuous variables. Efficacy outcomes and comparisons of major adverse effects were made with the use of chi-square or two-tailed Fisher's exact tests. The mean values of PIP, P_{aw}, FIO_2, fluid intake and rate of mechanical ventilation in each of the first 10 days of study were compared between groups by means of the Mann-Whitney test. Duration of ventilation was displayed graphically with the Kaplan-Meier procedure and compared by means of the log rank test. SPSS for Windows 6.1 statistical package was used. Differences were considered significant at $p < 0.05$.

Table 1 Patient population and ventilation variables at randomisation to IMV and PRVC ventilation groups. Values are expressed as mean ± SD (*IMV* intermittent mandatory ventilation, *PRVC* pressure-regulated, volume-controlled ventilation, *CPAP* continuous positive airway pressure, *Pa/AO*$_2$ arterial/alveolar oxygen tension ratio, *PIP* peak inspiratory pressure)

	IMV	PRVC	*p*
Total number	30	27	
Boys/girls (*n*)	18/12	16/11	1.00
Birthweight (g) (range)	1137 ± 500 (600–2500)	1239 ± 436 (620–2450)	0.99
Gestational age (weeks)	30 ± 2.8	29 ± 3.2	0.88
Caesarean delivery (*n*)	9	12	0.22
Apgar score at 1 min	4.3 ± 2.5	4.0 ± 2.3	0.68
Apgar score at 5 min	5.5 ± 1.8	4.2 ± 1.8	0.02
Diagnosis of RDS	25	23	1.00
Age (h)	12.1 ± 12.3	15.6 ± 19.3	0.41
CPAP before randomisation (*n*)	12	12	0.66
Duration of ventilation before randomisation (days)	3.4 ± 2.2	5.5 ± 5.9	0.08
FIO_2	0.68 ± 0.27	0.62 ± 0.31	0.46
Pa/AO_2	0.32 ± 0.22	0.25 ± 0.11	0.26
PIP	18.6 ± 6.6	16.2 ± 5.7	0.15

Results

During the 18 months of the study a total of 122 potentially eligible neonates were admitted to our ICU. Of these, 51 could not be randomised because the Servo Ventilator was in use and 11 because they met the exclusion criteria. Sixty neonates entered the study, but 3 had to be excluded later, all from the PRVC group: 1 patient because of pneumothorax and another because of sepsis, not diagnosed at randomisation. The third patient was excluded after being inadvertently randomised when the ventilator for PRVC was in use. Finally, 57 neonates were available for analysis: 27 ventilated with the use of PRVC and 30 by means of IMV.

Patient population, pre-treatment variables and ventilation parameters did not differ between the groups at admission, apart from the Apgar score at 5 min (data from 41 neonates only), which was lower in the PRVC group (Table 1). Prenatal steroids were used in 5 neonates from the IMV group and in 3 from PRVC group (NS). During the study, 2 neonates in each group received surfactant. PRVC proved to be feasible even in babies weighing < 750 g, and no technical problems were encountered. Autocycling was occasionally ob-

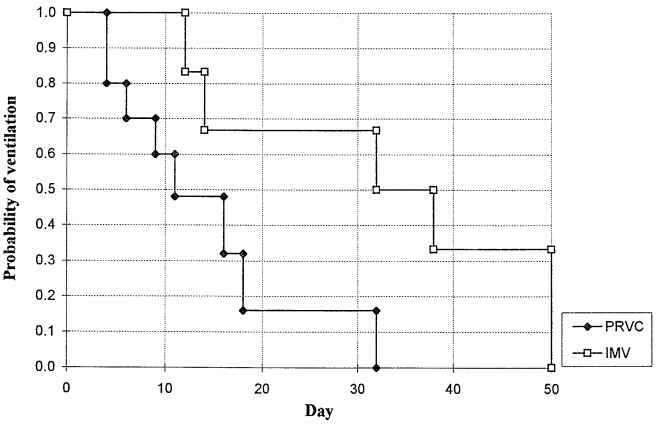

Fig. 1 Kaplan-Meier plot showing duration of ventilation in babies weighing < 1000 g. The *p* value (log-rang test) was 0.025

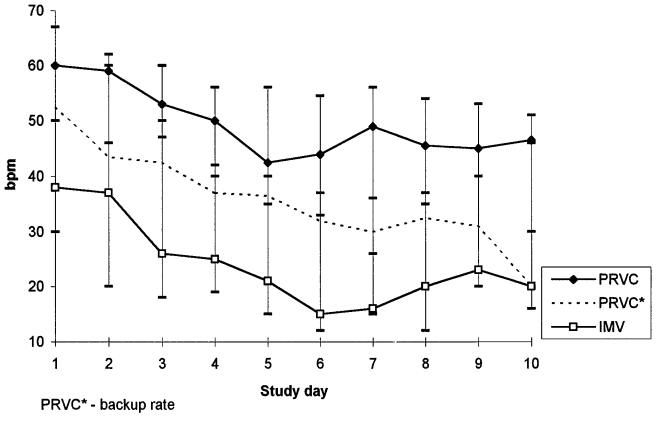

Fig. 2 Ventilator rate in patients treated with PRVC and IMV. Values are medians with 25th and 75th percentiles. There was a significant difference in rate throughout the whole initial 10-day period of ventilation ($p < 0.05$)

served, mostly due to movement of excessive water condensed in the tubing and was immediately eliminated.

Duration of ventilation did not differ significantly between the IMV (median 8 days, 95 % confidence interval (CI) 2 to 14 days) and PRVC groups (median 8 days, 95 % CI 5 to 11 days); it was significantly shorter in the subgroup of neonates weighing < 1000 g ventilated with PRVC (median 11 days, 95 % CI 3 to 19 days) compared with patients ventilated with IMV (median 32 days, 95 % CI 3 to 61 days, $p = 0.025$) (Fig. 1).

There was a significantly lower incidence of IVH grade III or IV in infants ventilated by means of PRVC ($p = 0.03$) (Table 2). A multivariate logistic regression technique was used to ascertain whether the use of PRVC promotes the development of severe IVH. This analysis adjusted for confounding factors which might affect the development of IVH, i. e. gestational age,

Table 2 Clinical results and major adverse effects in neonates undergoing IMV and PRVC ventilation modes

	IMV ($n = 31$)	PRVC ($n = 27$)	p
BPD	6	6	0.79
Any form of air leak	7	3	0.31
Pneumothorax	6	2	0.26
Interstitial emphysema	1	1	1.00
IVH (all grades)	15	6	0.07
IVH (III–IV)	11	3	0.03
Deaths during the study	8	4	0.30
Persistent ductus arteriosus	3	3	1.00
Necrotising enterocolitis (*n*)	7	6	0.97
Hypotension	14	14	0.79
Sepsis acquired during the study	8	5	0.51
Patients requiring sedation	27	22	0.72
Duration of sedation (days) (mean ± SD)	4.2 ± 6.9	4.2 ± 3.6	0.96
Patients requiring muscle relaxants	7	2	0.15

postnatal age, birthweight, Apgar score, sex, development of an air leak syndrome. The only factors which correlated with the increased risk of severe IVH were lower gestational age and the use of IMV.

There were no differences in overall mortality, incidence of air-leak syndromes, PDA, necrotising enterocolitis, hypotension and sepsis acquired during the study. There were more cases of pneumothorax in neonates ventilated by IMV (6 vs 2, NS). The need for sedation was similar in the groups; for muscle relaxation it was slightly less in the PRVC group (NS).

In the first 10 days of treatment the ventilator rate was significantly higher in the PRVC group ($p < 0.05$) (Fig. 2). This was due to the ventilator response to the infants' own breathing activity. The values of FIO_2, PIP, PEEP and P_{aw} were not significantly different during the first 10 days in the ICU. At extubation from PRVC, the mean PIP value was 9.66 (± 1.73) cm H_2O, at extubation from IMV, 10.95 (± 2.42) cm H_2O ($p = 0.052$). Fluid intake was not significantly different in the first 10 days of life between the groups.

The post hoc analysis of the results in the subgroup of neonates with birthweight < 1000 g is presented in Table 3. In this population, the mean birthweight was 764 (± 111) g in the IMV group and 850 (± 113) g in the PRVC group ($p = 0.1$); the gestational age was 26.5 (± 1.9) weeks and 26.3 (± 2.3) weeks, respectively ($p = 0.72$). There were fewer incidences of hypotension among babies weighing < 1000 g ventilated by PRVC.

Table 3 Patients' characteristics and results in the subgroup of infants with birthweight below 1000 g. Values are mean ± SD or numbers of patients

	IMV (n = 10)	PRVC (n = 10)	p
Boys/girls	4/6	5/5	1.00
Birthweight (g)	764 ± 111	850 ± 113	0.10
Gestational age (weeks)	26.5 ± 1.9	26.3 ± 2.3	0.72
Apgar score at 1 min	3.2 ± 2.4	3.6 ± 2.1	0.70
Apgar score at 5 min	4.8 ± 2.3	5.0 ± 1.2	0.87
Age at randomisation (h)	11.3 ± 12.9	19.3 ± 24.9	0.38
BPD	5	3	0.65
Any form of air leak	2	0	0.47
Pneumothorax	1	0	1.00
Intestinal emphysema	1	0	1.00
IVH (all grades)	7	3	0.18
IVH (III–IV)	6	2	0.17
Deaths during the study	4	1	0.30
Hypotension	10	5	0.03
Persistent ductus arteriosus	2	2	1.00
Necrotising enterocolitis	5	5	1.00
Sepsis during the study	5	3	0.65
Patients requiring sedation	10	9	1.00
Duration of sedation (days)	6.4 ± 10.7	4.8 ± 4.6	0.68

Discussion

The use of pressure-preset modes of ventilation may result in unnecessary high volumes delivered to the lungs when pulmonary compliance improves, or in low volumes when airway resistance rises or compliance decreases. Volume-controlled mode may be chosen for ventilatory support in preterm infants and its use might prevent the episodes of hypoxaemia due to the sudden decrease of V_T [14]. The drawback of standard volume ventilation is that the preset V_T is delivered independently of actual pulmonary compliance and airway resistance and high inspiratory pressures may occur [15].

We compared the use of patient-initiated, pressure-regulated, volume-controlled ventilation with unsynchronised, pressure-preset IMV in neonates. We found a significantly lower incidence of severe IVH in patients ventilated by means PRVC. It may be in part the result of stable volume delivered to the lungs of babies treated with PRVC. Excessive V_T high PIP and pneumothorax are the well-known factors in the aetiology of intracranial haemorrhage in neonates [16–18]. The wide variation in V_T is known ot occur during pressure-preset IMV [19]. In volume-control mode, the changes in lung compliance do not influence V_T. Under- or overdistension is avoided. This should provide faster recruitment of lung volume in the early stages of treatment and a diminished negative effect on circulation later, which might be reflected in fewer episodes of hypotension in the smallest babies. The tidal and minute volumes guaranteed during PRVC could result in a lower incidence of arterial desaturations, but this should be confirmed in a further study.

In the PRVC mode, apart from stable volume, the value of PIP is kept 5 cm H_2O below the preset high pressure limit. Such control over PIP is not available in Bear and Sechrist ventilators, which are known to produce "pressure overshoot" in response to flow increase in the breathing circuit [20].

The large alterations in intrathoracic and arterial pressure which occur when babies "fight" with the ventilator may result in the development of IVH [21, 22]. Synchronisation achieved due to patient-initiated breaths during PRVC should decrease the number of episodes of "fighting". Synchronous ventilation was found to reduce fluctuations in blood pressure [23] and variations in cerebral blood flow velocity in neonates [24] – the suggested risk factors for IVH among newborn preterm infants. The use of another patient-initiated method has been found advantageous in terms of progression from IVH grades I/II to IVH grades III and IV [25]. Less overdistension of the lungs with the synchronised mode might hasten the healing process and lessen the need for ventilatory support. Duration of mechanical ventilation was significantly shorter in a subgroup of our patients weighing < 1000 g. The similar result was obtained by Visveshwara et al. in babies weighing < 850 g, with a patient-initiated mode [25].

The overall incidence of oxygen dependence at 28 postnatal days in our patients was low and less than in the study of de Boer et al., where long-term pressure-preset triggered ventilation was used [26]. This may be the result of the low volume and pressure approach used in our groups and restrictive fluid therapy [2]. There was no difference in the incidence of BPD between the groups.

As the PRVC is also a patient-triggered mode, the rate of mechanical breaths was regulated by the breathing activity of the infants. The high sensitivity of this ventilator flow-triggering enables most of the inspiratory efforts to be picked up [27, 28]. Flow systems are also prone to autocycling, because the leaking flow is recognised as initiation of a breath by the patient [29]. High rate PPV is known to be advantageous in terms of pulmonary complications in comparison to low rate ventilation [30, 31]. It may result in better protection of distal airways and alveoli in the surfactant-deficient lung, because small airways are not allowed to collapse at end-expiration and avoid being ripped apart with each inspiration [32].

Although surfactant was used in only 5 of our patients, we think that our results are applicable to neonates treated with surfactant. As changes in compliance occur

rapidly after its administration, excessive tidal volumes may be delivered if conventional time-cycled, pressure-limited ventilators are used [33]. Volume-preset modes like PRVC might be considered with reduction in PIP, signalling the onset of surfactant action. Also, not all patients respond favourably to surfactant treatment [34, 35], and its use has not resulted in a significant decrease in the incidence of intracranial haemorrhages [36].

We conclude that patient-initiated PRVC ventilation is a safe technique for long-term ventilatory support in neonates with low birthweight and may contribute to decreasing the incidence of complications. Further studies are needed to establish the place of this method in neonatal intensive care.

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