

# Nasal High Frequency Percussive Ventilation Versus Nasal Continuous Positive Airway Pressure In Transient Tachypnea of the Newborn: A Pilot Randomized Controlled Trial (NCT00556738)

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**Summary.** Objective: To determine whether nasal high frequency percussive ventilation (NHFPV) would decrease duration of transient tachypnea of the newborn (TTN) compared to nasal continuous positive airway pressure (NCPAP) in newborn infants. Methods: A prospective, unmasked, randomized, controlled clinical trial was conducted in 46 eligible newborn infants who were hospitalized for TTN in the University Hospital of Bordeaux (France) between 2007 and 2009. Infants born by cesarian section  $\geq 37$  GA,  $\geq 2,000$ g with diagnosis of TTN and with a transcutaneous saturation  $< 90\%$  at 20 min after birth were eligible. Infants were randomized to either NHFPV or NCPAP. The primary endpoint was a reduction of the duration of TTN. Secondary endpoints were the duration of oxygen therapy and the minimal level required to obtain a saturation between 90% and 96% integrated into an index which included a time factor:  $[(\text{FiO}_2 - 21)/\text{time of O}_2 \text{ therapy}]$ . Results: In the NHFPV group the duration of TTN was half the time of NCPAP group (105 min  $\pm$  20 and 377 min  $\pm$  150, respectively;  $P < 0.0001$ ). There was a significant decrease in duration of oxygen supplementation in the NHFPV group (6.3 min  $\pm$  3.3) compared to the NCPAP group (19.1 min  $\pm$  8.1;  $P < 0.001$ ), and a significant decrease in level of oxygen supplementation  $[(\text{FiO}_2 - 0.21)/\text{time of O}_2 \text{ therapy}]$  in the NHFPV group (0.29 min<sup>-1</sup>  $\pm$  0.16) compared to the NCPAP group (0.46 min<sup>-1</sup>  $\pm$  0.50;  $P < 0.001$ ). There was no complication and NHFPV was as well tolerated as NCPAP. Conclusion: NHFPV is well tolerated and more effective than NCPAP in treatment of TTN. NHFPV might be a novel and safe tool to manage TTN. **Pediatr Pulmonol.** 2010; 00:1–6. © 2010 Wiley-Liss, Inc.

**Key words:** Transient tachypnea of the newborn; respiratory distress; intensive care; newborn; randomized trial; continuous positive airways pressure; high frequency ventilation; non-invasive ventilation.

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## INTRODUCTION

Transient tachypnea of the newborn (TTN) is, with more than 40% of cases, the most common cause of neonatal respiratory distress.<sup>1,2</sup> TTN occurs when residual pulmonary fluid remains in lungs after delivery. Prostaglandins and catecholamines released during and after delivery induce lung fluid clearance as pulmonary circulation increases with the first breath. The persistence of lung fluid despite these mechanisms can induce TTN. The pathophysiology involves a lack of appropriate catecholamine release and/or the inability of fetal lung to switch from fluid secretion to fluid absorption and this is related to insufficiency and/or dysfunction of the epithelial Na<sup>+</sup> channel.<sup>3–5</sup> Risk factors include maternal asthma, male sex, macrosomia, maternal diabetes, and cesarean delivery.<sup>2,6</sup> The clinical presentation includes tachypnea and signs of respiratory distress immediately after birth or within 2 hr. Symptoms can last from a few hours to 3 days

with possible complications such as pneumothorax or pulmonary hypertension.<sup>2,6</sup> Treatment of neonatal respiratory distress is initially non-invasive ventilation with facial oxygen, nasal continuous positive airway pressure (NCPAP) eventually associated with oxygen therapy and mechanical ventilation in severe cases.<sup>6</sup> Oral furosemide

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has not been shown to significantly improve status and should not be given.<sup>7</sup> High-frequency percussive ventilation (HFPV) is a pressure limited, time-cycled, high-frequency mode of ventilation that delivers subphysiologic tidal volumes at rapid rates and that can be used via an endotracheal tube, a nasal probe, or a face mask.<sup>8–10</sup> In the endotracheal mode, in adults it has been shown to provide the same or improved oxygenation and ventilation at lower peak, mean, and end-expiratory pressures when compared with conventional ventilation.<sup>11,12</sup> In neonates, HFPV has been described in hyaline membrane disease and acute respiratory failure ventilation with improvement in oxygenation, significant decrease in PCO<sub>2</sub> and no change in central hemodynamics.<sup>13,14</sup> In the non-endotracheal mode it has the potential to improve secretion clearance and has been used in stable patients with cystic fibrosis<sup>15–20</sup> and more recently as a therapeutic option in exacerbations of patients with chronic obstructive pulmonary disease.<sup>21–23</sup> We hypothesized that the use of nasal HFPV may be well-tolerated and effective in TTN thus reducing the duration of respiratory distress when compared with the conventional NCPAP mode.

## METHODS

### Patients, Randomization, and Study Criteria

A prospective, unblinded, randomized controlled trial of NCPAP versus nasal high-frequency percussive ventilation (NHFPV; Percussionaire Corp., Sandpoint, ID) in TTN was initiated in 2007 in consecutive eligible newborn infants in the maternity intensive care nursery at Pellegrin University Hospital of Bordeaux in France. Between November 2007 and September 2009, 46 newborns infants were assigned using a table of random numbers and sealed opaque envelopes to either NCPAP or NHFPV. Randomization occurred after written informed consent had been obtained from the infant's parent or legal guardian. The primary endpoint was the duration of respiratory distress. Secondary endpoints were the duration and level of oxygen supplementation, and the incidence of pneumothorax, and pulmonary infections. Study entry criteria were infant newborns born by cesarian section  $\geq 37$  week gestational age (GA) and of  $\geq 2,000$ g birth weight, transcutaneous oxygen saturation  $< 90\%$  on room air, simplified Silverman score: (chest movement, expiratory grunt, and nares dilation)  $\geq 5$ , neonates managed within 20 min of birth. Before randomization infants were filmed and the

inclusion criteria were checked by an independent observer. Prior to cesarean section parents were informed of the protocol and when necessary the consent and the randomization were obtained between birth and initiation of respiratory support. Exclusion criteria included major congenital malformation or pulmonary malformation; meconium aspiration; neonatal infection with hemodynamic alteration; neonatal asphyxia (pH  $< 7.1$ ); clinical signs of chest wall retraction (that could be a differential diagnosis of TTN such as a hyaline membrane disease (HMD)). Newborn infants with secondary diagnosis of HMD were discontinued from the study. The clinical symptoms of the neonates included were evaluated every 5 min by an independent observer. Respiratory and cardiac monitoring (oxygen saturation, respiratory rate, heart rate) were continuously recorded and the endpoints were evaluated secondarily by an independent observer. The fraction of inspired oxygen (FiO<sub>2</sub>) was adjusted continuously to keep saturations at 90–96%. The newborns were monitored during 72 hr following birth in order to record eventual complications (pneumothorax and pulmonary infection).

### Study Definitions

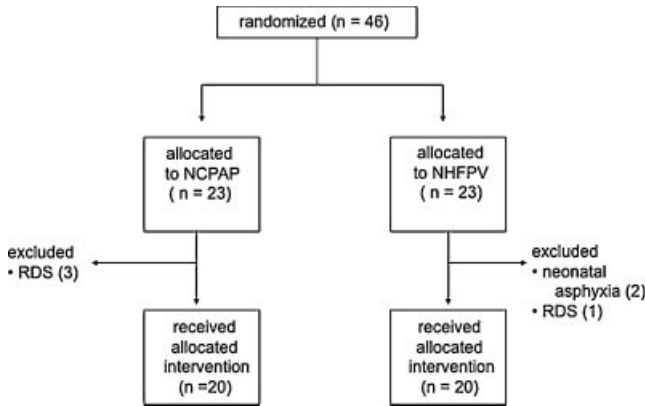
We undertook a “simplified Silverman score” defined by the Silverman score without the item regarding chest wall retraction (chest movements, expiratory grunting, and nasal flaring) in order to avoid the inclusion of patients presenting with another diagnosis such as HMD.<sup>24</sup> HMD was defined in the presence of clinical features and a positive chest X-ray (atelectasis, air bronchograms, diffuse reticular-granular pattern). Air leaks were documented by clinical features and a positive chest X-ray evidence of pneumothorax. Sepsis was diagnosed by a positive blood culture or suggestive clinical and laboratory presentation. Recovery of the TTN was defined by absence of clinical sign of respiratory distress (modified Silverman score equal to zero), arterial transcutaneous oxygen saturation  $> 90\%$  without oxygen, respiratory rate  $< 60$ /min, without any respiratory support. For the quantification of oxygen supplementation without invasive measurement, we used the level of FiO<sub>2</sub> adjusted to keep saturations at 90–96% (FiO<sub>2</sub>—0.21) related to time: [(FiO<sub>2</sub>—0.21)/time of O<sub>2</sub> therapy].<sup>25</sup>

### High-Frequency Percussive Ventilation (HFPV)

The high-frequency percussive ventilator (VDR3, Percussionaire, Bird technologies, Sandpoint, ID) is a pneumatically powered, time cycled, and pressure limited ventilator (Fig. 2A). It is a ventilatory technique that delivers small bursts of high-flow respiratory gas into the lung at high rates. Unique to the HFPV is the presence of a sliding venturi system (phasitron, Fig. 2B,C), powered by compressed gas that generates the oscillations in the range

#### ABBREVIATIONS

NHFPV	Nasal high frequency percussive ventilation
NCPAP	Nasal continuous positive airway pressure
GA	gestational age
HMD	hyaline membrane disease
FiO <sub>2</sub>	fraction of inspired oxygen
SEM	standard error of the mean.



**Fig. 1.** Flow diagram of infants who were screened and randomly assigned to the NHFPV and NCPAP groups. Three infants in the NHFPV group were excluded because of secondary diagnosis of HMD. Two infants in the NCPAP group were excluded because of diagnosis of neonatal asphyxia and one infant because of secondary diagnosis of HMD.

of 80–650 cycles/min.<sup>8,22</sup> Airway pressures oscillates between 2 and 35 cmH<sub>2</sub>O and the airway walls vibrate in synchrony with these oscillations. In non-endotracheal mode, HFPV can be delivered via a facial mask or a nasal probe<sup>9,10</sup> (Fig. 2B).

**Respiratory Management**

CPAP or NHFPV were delivered via a heated humidified nasal probe. In the CPAP group, the PEEP was delivered via a conventional time cycled, pressure limited ventilator (Babylog 8000; Drager, Telford, PA). NCPAP setting was 5 cmH<sub>2</sub>O and FiO<sub>2</sub> adjusted to keep saturations at

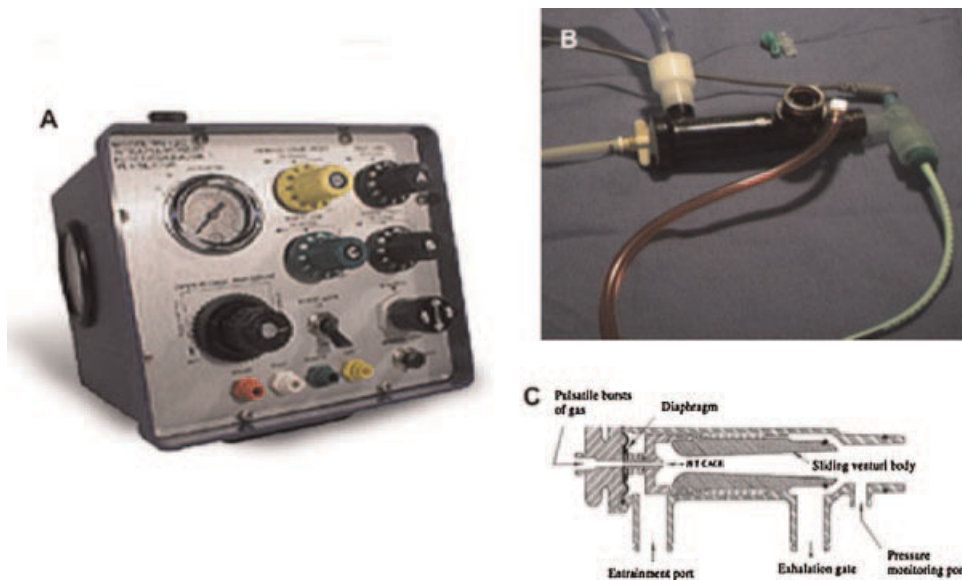
90–96%. The setting of NHFPV was as follows: pressure of 5 cmH<sub>2</sub>O, high-frequency ventilator at 5 Hz as previously described for non-endotracheal respiratory support<sup>9,26</sup> and FiO<sub>2</sub> adjusted to keep saturations at 90–96% (Fig. 2). The O<sub>2</sub> saturation probe placement was standardized on preductal location. The HFPV and NCPAP setting were not changed during the procedure. There was no systematic control of the PCO<sub>2</sub>, but infants who exhibited a deterioration of the respiratory distress under nasal ventilation were monitored by blood gas analyses, X-ray, blood testing, in order to look for a differential diagnosis of TTN (HMD, infection, pneumothorax, etc.).

**Statistical Methods and Data Analysis**

Patient characteristics were summarized using observed proportions, means and standard error of the mean (SEM), medians and quartiles for discontinuous variables. Using a preliminary cases series, we calculated our sample size to detect a 20% reduction of the respiratory distress duration with HFPV compared with NCPAP. With  $\alpha = 0.05$  and a power of 80%, we estimated that 20 infants were needed in each group. Comparisons between the two groups were tested using the Mann–Whitney test or  $\chi^2$ -test, as appropriate. A *P*-value of <0.05 was considered to indicate statistical significance.

**Ethics**

The research protocol for this study was approved by the institutional review board of the University Hospital of Bordeaux (France). The research protocol was registered in ClinicalTrials.gov (NCT00556738).



**Fig. 2.** Intrapulmonary percussive ventilation device (Percussionaire IPV-3; Percussionaire Corp.; Fig. 2A). Image (Fig. 2B) and schematic (Fig. 2C) of the phasitron: the sliding venturi body moves back and forth to open and close the phasitron exhalation gate by an orificed diaphragm. Burst of air are delivered to the patient during forward movement of the phasitron.

TABLE 1—Maternal and Infant Baseline Characteristics

Characteristics	NCPAP (n = 20)	HFPV (n = 20)	P-value
Preeclampsia (n)	0	0	ns
Antenatal steroids (n)	0	0	ns
Chorioamnionitis (n)	0	0	ns
Anesthesia (n; spinal/epidural/general)	18/1/1	15/2/3	ns
Cesarean section (n)	20	20	ns
Male sex (n)	6	8	ns
Birth weight (g; mean $\pm$ SEM)	3,004 $\pm$ 116	3,375 $\pm$ 160	ns
Gestation age (wk; mean $\pm$ SEM)	38 $\pm$ 0.5	37 $\pm$ 0.4	ns
1-min Apgar score (median Q1–Q3)	7.5 (4–8)	8 (7–9)	ns
5-min Apgar score (median Q1–Q3)	9 $\pm$ (8–9)	9 $\pm$ (8–9)	ns
Initial modif. Silverm. score (median Q1–Q3)	5 $\pm$ (5–6)	5.5 $\pm$ (5–6)	ns
Initial art. sat. (%; mean $\pm$ SEM)	77 $\pm$ 3	76 $\pm$ 4	ns

## RESULTS

Between November 2007 and September 2009, 46 infants were enrolled in the study. Four infants were excluded after randomization because of secondary diagnosis of HMD and two because of diagnosis of neonatal asphyxia associated with TTN (Fig. 1). There were no statistical differences between the two groups with regard to any of the baseline maternal and infant characteristics (Table 1). There was no complication (pneumothorax, pulmonary infection, local intolerance) in infants studied. The two modes of ventilation were clinically well tolerated without need for sedation. All infants improved clinically on the given form of support, without necessitating formal mechanical ventilation. The respiratory distress duration was significantly decreased in the NHFPV group (105 min  $\pm$  20) compared with the NCPAP group (377 min  $\pm$  150;  $P < 0.001$ ; Fig. 3). The duration of

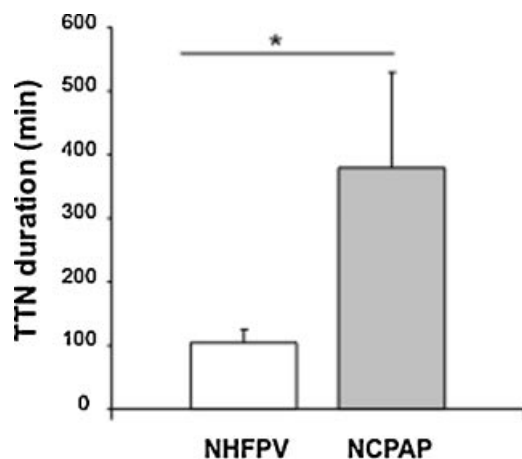


Fig. 3. Duration of TTN between the NHFPV and NCPAP groups. The duration of TTN was significantly reduced in the NHFPV group compared with the NCPAP group ( $P < 0.001$ ). Error bars represent standard error of the mean.

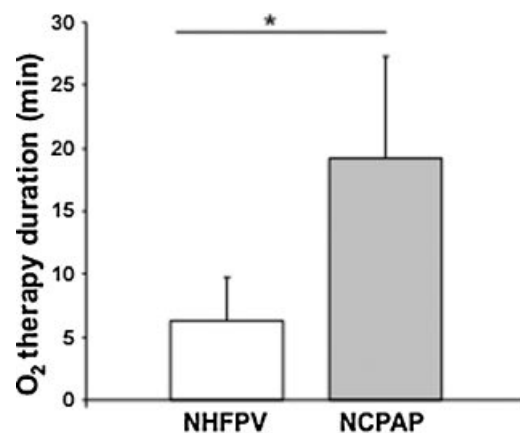


Fig. 4. Duration of oxygen therapy between the NHFPV and NCPAP groups. The duration of oxygen therapy was significantly reduced in the NHFPV group compared with the NCPAP group ( $P < 0.001$ ). Error bars represent standard error of the mean.

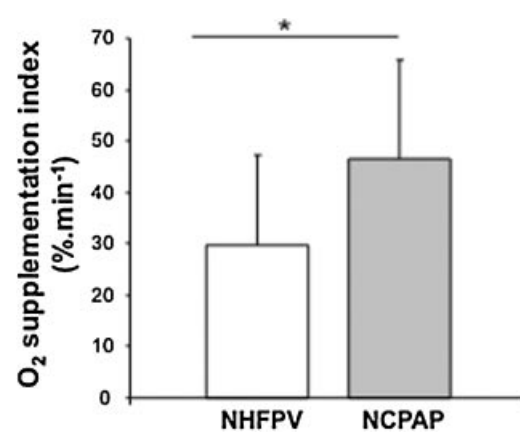


Fig. 5. Level of oxygen supplementation between the NHFPV and NCPAP groups. The level of oxygen supplementation was significantly reduced in the HFPV group compared with the NCPAP group ( $P < 0.001$ ). Error bars represent standard error of the mean.



oxygen supplementation was significantly decreased in the NHFPV group ( $6.3 \text{ min} \pm 3.3$ ) compared with the NCPAP group ( $19.1 \text{ min} \pm 8.1$ ;  $P < 0.001$ ) (Fig. 4). The level of oxygen administered during the treatment was significantly decreased in the NHFPV group ( $0.29 \text{ min}^{-1} \pm 0.16$ ) compared with the NCPAP group ( $0.46 \text{ min}^{-1} \pm 0.50$ ;  $P < 0.001$ ; Fig. 5).

## DISCUSSION

In this prospective, randomized controlled study, we showed that NHFPV is a well-tolerated mode of nasal ventilation for neonates. Moreover, we showed a superiority of NHFPV for ventilation care of TTN in comparison to NCPAP. There was a significant decrease of respiratory distress and oxygen therapy duration and a significant decrease of oxygen therapy level in the NHFPV group. NHFPV is a new approach to ventilation assistance of respiratory distress and in our knowledge this is the first prospective randomized controlled study of HFPV in the newborn population.

To date, few studies have been published on the use of HFPV in pediatric patients with pulmonary disease. HFPV has been used in a non-endotracheal mode for the treatment of atelectasis and retained secretions in cystic fibrosis or neuromuscular diseases.<sup>15–18,20</sup> Pfenninger et al. described endotracheal use of HFPV in two studies of neonates with hyaline membrane disease and acute respiratory failure. They showed improvement in oxygenation, a significant decrease of  $\text{PcO}_2$  and no change in central hemodynamics.<sup>13,14</sup>

TTN is a self-limited disease which is common in infants and may be prolonged over a 24–72 hr period with few potential complications including hypoxia, respiratory fatigue, or air leaks (pneumothorax, pneumomediastinum).<sup>6</sup> This usually benign respiratory distress was studied as a proof of concept of the usefulness of HFPV in neonates.

TTN is the result of a delay in clearance of fetal lung liquid. For effective gas exchange to occur, alveolar spaces must be cleared of excess fluid and the pulmonary blood flow increased to match ventilation with perfusion. Failure of these events can cause the infant to develop respiratory distress.<sup>27–29</sup> An additional proposed benefit of HFPV is the generation of intrapulmonary mechanical percussive waves, which may aid in the lysis and clearance of airway mucus and secretions.<sup>10,30–34</sup> The increase of the fetal lung liquid clearance by HFPV could explain in part the results of our study.

The significant decrease of duration and level of oxygen delivered in the NHFPV group was hardly of clinical importance but this result confirms an effective and well-tolerated mode of ventilation. Moreover, respiratory distress could induce excess cost<sup>35</sup> and NHFPV could be significant in term of workload and cost reduction for respiratory distress care in this population.

This ventilation mode is a low-cost device and is easily used. It was well-tolerated by the infants with no complication observed even if the small sample size of our study do not allow a full safety evaluation. No serious adverse effects of HFPV have been reported in previous adult or infant studies.<sup>10,13–17,34,36,37</sup>

Our study has several limitations. Firstly, this is not a blinded study, secondly, the inclusion criteria and primary endpoint were defined by clinical criteria like Silverman score. It could have induced bias of interpretation by minimizing the severity of infants included or modify the interpretation of respiratory distress recovery. To correct this bias, the inclusion criteria were reinforced by oxygen saturation as objective element and a delay of 20 min after birth to evaluate the infant after the common birth transition period. Moreover, the neonate include were filmed before the randomization and the inclusion criteria were checked by an independent observer. At last, the respiratory distress recovery was also defined by a respiratory rate  $\leq 60$  per minute and a saturation  $\geq 95\%$  without oxygen, which are not compatible with persistence of respiratory distress. The results of this preliminary study done on a mostly benign kind of respiratory distress show a potential interest of this mode of ventilation in the treatment of more severe diseases.

In conclusion, we have shown that NHFPV is more effective than NCPAP in treatment of TTN. NHFPV may be a novel and safe tool to take care TTN. Additional studies are needed evaluating NHFPV in larger number of neonates with TTN and other respiratory distress conditions.

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