www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2013;2(2):e020211
doi: 10.7363/020211 Advance publication: 2013 Aug 13

Original article

Flow-synchronized nasal intermittent positive pressure ventilation in the preterm infant: development of a project

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Proceedings

Proceedings of the 9th International Workshop on Neonatology · Cagliari (Italy) · October 23rd-26th, 2013 ·
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Abstract

This manuscript describes the experience of our team in developing a flow-triggered nasal respiratory support for the neonate and its related clinical applications. Although mechanical ventilation (MV) via an endotracheal tube has undoubtedly led to improvement in neonatal survival in the last 40 years, the prolonged use of this technique may predispose the infant to the development of many possible complications, first of all, bronchopulmonary dysplasia (BPD). Avoiding mechanical ventilation is thought to be a critical goal, and different modes of non invasive respiratory support may reduce the intubation rate: nasal continuous positive airway pressure (NCPAP), nasal intermittent positive pressure ventilation (NIPPV) and its more advantageous form, synchronized nasal intermittent positive pressure ventilation (SNIPPV). SNIPPV was initially performed by a capsule placed on the baby's abdomen. To overcome the disadvantages of the abdominal capsule, our team decided to create a flow-sensor that could be interposed between the nasal prongs and the Y piece. Firstly we developed a hot-wire flow-sensor to trigger the

ventilator and we showed that flow-SNIPPV can support the inspiratory effort in the post-extubation period more effectively than NCPAP. But, although accurate, the proper functioning of the hot-wire flow-sensor was easily compromised by secretions or moisture, and therefore we started to use as flow-sensor a simpler differential pressure transducer. In a following trial using the new device, we were able to demonstrate that flow-SNIPPV was more effective than conventional NCPAP in decreasing extubation failure in preterm infants who had been ventilated for respiratory distress syndrome (RDS). More recently we used flow-SNIPPV as the primary mode of ventilation, after surfactant replacement, reducing MV need and favorably affecting short-term morbidities of treated premature infants. We also successfully applied SNIPPV to treat apnea of prematurity (AOP). Finally, we developed a new shaped flow-sensor, which is smaller and lighter of the previous one and its reliability was tested using a simulated neonatal model.

Keywords

Respiratory distress syndrome, synchronized nasal intermittent positive pressure ventilation, noninvasive ventilation, nasal continuous positive pressure ventilation, bronchopulmonary dysplasia, mechanical ventilation.

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How to cite

Moretti C, Papoff P, Gizzi C, Montecchia F, Giannini L, Fassi C, Midulla F, Agostino R, Sanchez-Luna M. Flow-synchronized nasal intermittent positive pressure ventilation in the preterm infant: development of a project. J Pediatr Neonat Individual Med. 2013;2(2):e020211. doi: 10.7363/020211.

Introduction

NCPAP was the earliest form of non-invasive respiratory support used in infants with respiratory failure and its use goes back to the early seventies. In the following years the use of NCPAP as a primary mode of respiratory support has become standard practice in order to avoid invasive ventilation and to facilitate weaning from the ventilator but, despite its considerable efficacy, this technique cannot always prevent intubation or extubation failure. The failure rate of NCPAP is inversely correlated to the gestational age (GA) of the newborn and the more immature infants are the ones at higher risk of developing complications associated with invasive MV. NIPPV or nasal intermittent mandatory ventilation (NIMV) are more effective forms of respiratory support that provide CPAP plus superimposed ventilator mandatory breaths and are identified as SNIPPV/SNIMV when the ventilator pressure waves are synchronized with the spontaneous efforts of the patient. These techniques are being increasingly used in preterm infants with respiratory failure in order to further decrease the percentage of patients who need invasive MV or who fail extubation.

A brief history of the first trials of non-invasive nasal ventilation

Following the initial description of nasal prongs by Kattwinkel et al. [1] and Caliumi-Pellegrini et al. [2] to deliver NCPAP, in 1981 our group of "La Sapienza" University of Rome described the first successful application of NIPPV with short bi-nasal prongs in 10 preterm neonates with a birth-weight ranging between 800 and 1,200 g and who were affected by severe apnea spells in spite of administration of NCPAP and methylxantines [3]. In most cases the underlying clinical problem was sepsis and the NIPPV treatment was performed for 5 to 14 days. In that trial ventilator-patient synchrony was optimized as much as possible by monitoring the thoracic impedance and the ventilator pressure and then by setting ventilation parameters similar to the spontaneous breathing rhythm of the neonate. However NIPPV was judged of very limited use in patients with severe respiratory distress, as the surfactant era had not yet begun. The very simple pressure-limited ventilator employed, MOG® 80 (Ginevri, Rome, Italy), was developed in our unit and the nasal prongs used were the ones described by Caliumi-Pellegrini, a neonatologist in our staff.

The widespread use of NIPPV was blocked in 1985 by Garland et al. [4] who reported that newborns ventilated with nasal support were 30 times more likely to develop gastrointestinal perforation than were mechanically ventilated neonates.

In 1999, after a paper by Friedlich et al. [5] who first successfully used SNIMV to treat 22 very low birth-weight infants (VLBW) after extubation,

neonatologists became interested in using this technique again; following clinical trials [6, 7] confirmed its efficacy and the absence of the risk of gastrointestinal perforation. The trigger device employed in most SNIMV trials was the Graseby abdominal pneumatic capsule, a sensor that, during spontaneous inspiration of the neonate, detects the outward movements of the abdomen due to the contraction of the diaphragm.

Physiological effects of synchronization during nasal ventilation

In the mid-nineties a new system was developed in our unit which allowed flow-SNIPPV by nasal prongs. The device was made up of a hot-wire flow-sensor interposed between the Y piece and the nasal cannula and connected to a time-cycled, pressure-limited neonatal ventilator (MOG® 2000, Ginevri, Rome, Italy). We chose to develop a flow-sensor because the abdominal capsule, although highly sensitive, has several disadvantages. First, positioning the capsule requires considerable skill. For example, when the capsule is stuck too close to the rib margin of an infant with respiratory distress, subcostal retractions can cause asynchrony because the abdomen expands during expiration rather than inspiration. Secondly, when the capsule is placed too high on the abdomen, especially in an agitated infant with active expiration, inspiratory and expiratory movements can both stimulate the capsule inappropriately. Although uncommon, even associated diseases such as patent ductus arteriosus (PDA) may produce artifacts and mimic respiratory efforts [8]. Under all these circumstances the neonate's respiratory conditions can deteriorate because of asynchrony. Asynchrony, however, is not the only disadvantage of the Graseby capsule. Respiratory assistance may also diminish as a result of abdominal distension due to feeding intolerance or the nasal ventilation itself. During these events poor abdominal excursions may result in low detection of respiratory efforts.

A flow-sensor used with nasal prongs also has an important drawback: it is hard to analyze the flow-signal because of the large and variable leaks from the mouth and the nostrils of the patient [9, 10]. We were able to overcome this problem by using software to remove the continuous component of the flow signal, the leaks, while the fast variation of the signal, the patient's spontaneous inspiration, was recorded and used to trigger the ventilator. Another possible disadvantage is the increase of dead volume but, in our experience, this is only a theoretical problem since expiratory flow vents mainly from the patient's mouth. With this device we studied the physiological effects of SNIPPV in 11 VLBW infants after extubation, comparing them with NCPAP [11]. The parameters simultaneously recorded during treatment were: tidal volume (Vt) estimated as volume changes of the chest and measured by jacket plethysmography; esophageal pressure (Pe) determined by an air-filled balloon catheter; airway pressure (Paw); transcutaneous (Tc) PO_2 and $TcPCO_2$. The study protocol for each infant consisted of two 60-min periods of ventilation in NCPAP and in SNIPPV applied in random order immediately after extubation. During SNIPPV, $TcPCO_2$ and the infant's mean respiratory rate were significantly lower than during NCPAP, while Vt and Ve were significantly greater. Moreover recording of Pe during both modes of ventilation indicated significant differences between the two techniques, with the lowest values consistently observed during SNIPPV as a result of the unloading provided by the ventilator. The mean trigger response time was 65 ± 12 ms and the ventilator triggered successfully on more than 90% of the infant's breaths. One of most the important criticisms of this trial is that the PEEP/CPAP set was low (+ 3 cm H_2O) and that this factor could have positively influenced the physiological effects of SNIPPV on lung mechanics. But in the following years several papers confirmed that, compared to NCPAP, SNIPPV was able to reduce the patient's work of breathing and the chest wall distortion [12-14]. More recently some of our results were also confirmed by Chang et al. [15] and Owen et al. [16]. The first studied the effects of nasal ventilation in clinically stable preterm infants and concluded that synchronization reduces the breathing effort of the patient and results in better infant-ventilator interaction than non-synchronized nasal ventilation. The second, studying the effects of NIPPV on spontaneous breathing in preterm infants, concluded that only when pressure peaks occur during spontaneous inspiration, tidal volume increases suggesting that synchronization is beneficial. These favorable effects are probably due to the fact that, during SNIPPV, the mean Paw is higher than with NCPAP and the pressure waves are effectively transmitted to the lungs because mechanical inflations are timed with spontaneous efforts, when the glottis is open. Moreover, the flow delivery to the lungs is facilitated by the fast rise of the pressure that pushes the soft palate against the tongue sealing the oral cavity. Despite the

advantages of SNIPPV, the upper airways of infants treated with this technique require extra care. To facilitate airway opening, the infant must be properly positioned and regularly checked and the nose must be frequently inspected to keep it clear of secretions. In addition, to avoid autotriggering or low signal detection, the sensor must be checked so that the reading is not affected by the buildup of secretions and humidity.

Clinical experience with flow-synchronized nasal ventilation

SNIPPV can be used as a secondary or primary mode. The "secondary mode" refers to SNIPPV use following long-term invasive mechanical ventilation. The "primary mode" refers to SNIPPV use soon after birth and may or may not include intubation-surfactant-extubation (INSURE) technique for surfactant replacement. SNIPPV can be also used to treat apnea of prematurity.

SNIPPV "secondary mode"

Extubation following prolonged mechanical ventilation is frequently associated with post-extubation respiratory failure, due to hypoxemia, respiratory acidosis, atelectasis and apnea. It has been shown that SNIPPV was significantly better than NCPAP in preventing extubation failure in neonates recovering from RDS [5]. The efficacy and safety of this technique has also been reported by others [6, 7, 17]. In 2008 our group conducted an unmasked, prospective randomized controlled trial to compare the efficacy of flow-SNIPPV and NCPAP in increasing the likelihood for successful extubation in 63 VLBW infants [18]. In this trial SNIPPV was provided by a new ventilator expressly developed for "nasal ventilation" (Giulia®, Ginevri, Rome, Italy) and the flow-sensor employed was no longer the hot-wire flow-sensor, whose reliability was easily compromised by secretions or moisture, but a simpler differential pressure transducer. Each infant was randomized to receive either SNIPPV or NCPAP soon after extubation. The success rate of extubation was significantly higher in SNIPPV group (90%) compared to NCPAP group (61%). In this study the most striking effect of SNIPPV was that it stimulated breathing, as demonstrated by the absence of respiratory acidosis and apneic episodes as causes of failure. In fact, infants assigned to NCPAP failed extubation mainly because of apnea and hypercapnia; by contrast those assigned to SNIPPV mainly failed because of hypoxia. Although there were no statistically significant differences in secondary outcomes, the duration of MV using an endotracheal tube and the incidence of BPD were both lower in the SNIPPV group than in the NCPAP group. Neither procedure induced major adverse effects. An issue of our flow-SNIPPV technique was the weight of the flow-sensor: the load pushing on the nostrils may increase the risk of nasal damage. In our study nasal damage was not a major problem but attention was needed to lessen the weight of the flow-sensor by suspending the Y-piece.

SNIPPV "primary mode"

In 2004 Santin et al. [19] conducted a pilot observational study using SNIPPV as a primary mode of ventilation in a group of larger premature neonates with RDS. The authors concluded that infants of 28 to 34 weeks GA requiring surfactant with early extubation to SNIPPV had a shorter duration of intubation and decreased need for oxygen as compared to MV. A following trial confirmed the beneficial effects of this mode of non invasive ventilation for VLBW infants with RDS [20]. Our group recently conducted a study using flow-SNIPPV as the primary mode of ventilatory support in < 32 weeks' gestation preterm infants with RDS [21]. The aim of the trial was to evaluate whether SNIPPV, used immediately after INSURE technique, was effective in further reducing the incidence of MV when compared to the conventional INSURE/NCPAP treatment. We had statistically significant results: 11 out of 31 (35.5%) infants in the NCPAP group and 2 out of 33 (6.1%) infants in the SNIPPV group failed the INSURE approach and underwent MV. Fewer infants in the INSURE/SNIPPV group needed a second dose of surfactant, a high caffeine maintenance dose, and pharmacological treatment for PDA. Differences in O_2 dependency at 28 days and 36 weeks of postmenstrual age were at the limit of statistical significance in favor of SNIPPV treated infants. We concluded that SNIPPV use, combined with surfactant, seems to be a promising strategy for treating infants in the acute phase of RDS.

SNIPPV for apnea of prematurity

AOP is a common problem in preterm infants which can be treated with NCPAP and NIPPV [22]. As it is unclear whether SNIPPV would be even more effective in treating this condition, we conducted a clinical crossover RCT to assess the

effects of NCPAP, NIPPV and flow-SNIPPV on the rate of apnea related desaturation events and bradycardias in very low birthweight infants and to evaluate the influence of these modes of ventilation on pattern of breathing and gas exchange [23]. Nineteen < 34 week's gestation preterm infants were allocated to receive NCPAP, NIPPV and flow-SNIPPV applied in random order for 4 h each. Throughout the study were simultaneously monitored and recorded: airway flow, airway pressure, standard thoracic impedance, ECG and beat-to beat HR, SpO_2 and pulse waveform, RR and transcutaneous PO_2 and PCO_2.We observed that the median rate of desaturations/h during NCPAP and NIPPV was significantly higher when compared with flow-SNIPPV (5, 5.15, and 2.9 respectively). There were no differences in bradycardias events between NIPPV and flow-SNIPPV, while they were significantly more frequent during NCPAP. Compared to NCPAP and NIPPV, central apneas were significantly less frequent during flow-SNIPPV (3.6, 4.8 and 1.6 respectively) and baseline HR significantly lower (median values: 159, 158 and 156 bpm respectively). No differences in baseline FiO_2, SpO_2, RR and transcutaneous blood gases were observed comparing the three ventilation modes. Our findings seems to indicate that flow-SNIPPV is more effective in treating AOP in preterm infants than NCPAP and NIPPV.

Validation of the flow-sensor used for SNIPPV with a simulated neonatal model

A common criticism of using a flow sensor for non-invasive ventilation is that its reliability can be altered by the continuous flow passing through it generated by the variable leaks from the infant's nostrils and mouth or by the variable expiratory flow. For this reason we decided to demonstrate, in a simulated neonatal model (**Fig. 1**), the reliability of our flow-sensor with different measured leaks through it and the performance of the Giulia® ventilator [23]. The flow-sensor used for test was the last model (**Fig. 2**), which is much smaller and lighter than the one used in the previous clinical trials but with the same fluidic characteristics. The standard circuit of the ventilator was completed with a high-precision, low-resistance flow-sensor (**Fig. 1-b**) placed between the Giulia® flow-sensor (**Fig. 1-a**) and the prongs (**Fig. 1-c**) to measure the total flow towards the patient. One of the two prongs was left completely open in order to create a large leak (**Fig. 1-d**), whereas the other was connected to a neonatal test-lung contained in a cylinder (**Fig. 1-e**). The inflation of the test lung was obtained using an electric engine that moved a syringe generating a negative pressure inside the cylinder (**Fig. 1-f**). The electric engine was programmed so as to generate, in 0.33 seconds, a tidal volume of 5 or 3 ml of air beyond the resting volume of the test lung, mimicking "high" and "low" spontaneous inspiratory flows respectively. The fixed parameters set on the Giulia® ventilator were: Ti 0.3 sec, PIP 20 cm H_2O, Trigger level 0.2 l/min. By contrast, in order to obtain different leak-flows, we tested the system with increasing PEEP (+5, +8, +10 cm H_2O) and set flow (8-10 l/min) levels. The resulting leak-flow using different PEEP and set

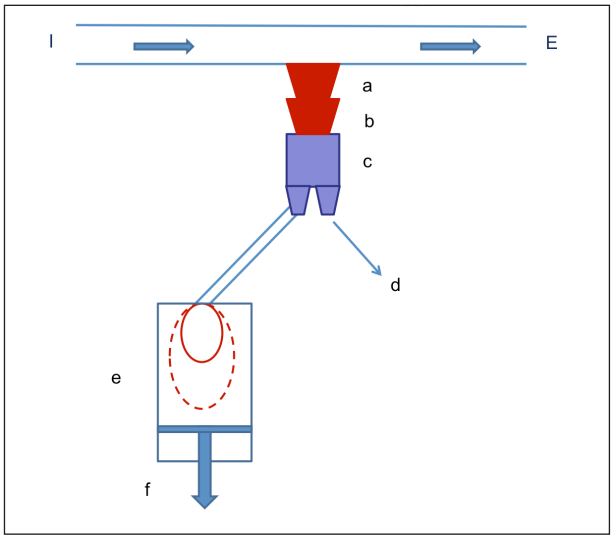

Figure 1. Diagram of the simulated neonatal model (see text).

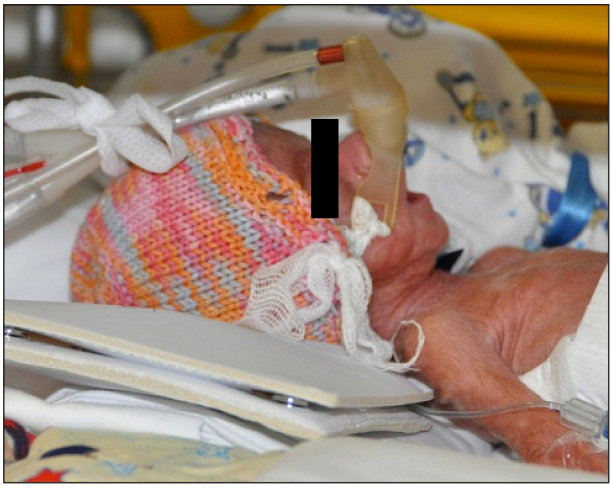

Figure 2. The Giulia® flow-sensor used in a VLBW infant of 700 g.

flow levels were in the range of 2.8-4 l/min (28 to 46% of the set flow). We took 10 measurements in each experimental condition, which were obtained by combining different PEEP and set flow levels with "high" and "low" spontaneous inspiratory flow. The Giulia® flow-sensor detected 100% of the simulated spontaneous breaths in presence of any tested amount of leak from the prongs. The mean response time, measured from the beginning of spontaneous inspiration to the beginning of the inspiratory pressure rise in the circuit was 64 ± (SD) 7 ms (range 46-77 ms). Considering all the experimental conditions, the minimum spontaneous inspiratory volumes detected by the Giulia® flow-sensor to trigger a mechanical breath were 0.021 ± (SD) 0.02 ml and 0.027 ± (SD) 0.04 ml with "high" and "low" spontaneous inspiratory flow respectively, while the minimum flow activating the trigger was 3 ml/sec. These data allow us to conclude that the Giulia® flow-sensor developed for non-invasive ventilation is capable of detecting very small "spontaneous" inspiratory volumes and flows and that its performance is not affected by the amount of leaks.

Conclusions

Our clinical observations [18, 21, 23] are consistent with laboratory data and show that our flow-sensor is reliable to perform SNIPPV for the treatment of neonatal respiratory failure. According to the evidence from clinical trials, SNIPPV seems more effective than NCPAP in reducing the need of intubation in RDS, in improving the success of extubation and in treating apnea, with a reassuring absence of side effects. Additional studies and more adequately powered RCT are needed to confirm these data and to survey the effects of SNIPPV on the incidence of the more severe forms of BPD.

Declaration of interest

C. Moretti is a consultant to Ginevri Medical Technologies. Ginevri Medical Technologies has not contributed any financial support for this paper or had any part in the authorship.

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