

# A randomised control study comparing the Infant Flow Driver with nasal continuous positive airway pressure in preterm infants

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## Abstract

**Objective**—To compare the effectiveness of the Infant Flow Driver (IFD) with single prong nasal continuous positive airway pressure (nCPAP) in preterm neonates affected by respiratory distress syndrome.

**Design**—Randomised controlled study.

**Patients**—Between September 1997 and March 1999, 36 preterm infants who were eligible for CPAP treatment were randomly selected for either nCPAP or IFD and studied prospectively for changes in oxygen requirement and/or respiratory rate. The requirement for mechanical ventilation, complications of treatment, and effects on mid-term outcome were also evaluated.

**Results**—Use of the IFD had a significantly beneficial effect on both oxygen requirement and respiratory rate ( $p < 0.0001$ ) when compared with nCPAP. Moreover,  $\dot{V}_E$  requirement and respiratory rate were significantly decreased by four hours ( $p < 0.001$  and  $p < 0.03$  respectively). The probability of remaining supplementary oxygen free over the first 48 hours of treatment was significantly higher in patients treated with the IFD than with nCPAP ( $p < 0.02$ ). IFD treated patients had a higher success (weaning) rate (94% *v* 72%) and shorter duration of treatment (49.3 (31) *v* 56 (29.7) hours respectively; mean (SD)), although the difference was not significant.

**Conclusions**—IFD appears to be a feasible device for managing respiratory distress syndrome in preterm infants, and benefits may be had with regard to oxygen requirement and respiratory rate when compared with nCPAP. The trend towards reduced requirement for mechanical ventilation, shorter clinical recovery time, and shorter duration of treatment requires further evaluation in a multicentre randomised clinical trial.

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Keywords: Infant Flow Driver; continuous positive airway pressure; preterm; respiratory distress syndrome

Since the first description by Gregory *et al*,<sup>1</sup> continuous positive airway pressure (CPAP) has been widely used to manage respiratory distress syndrome (RDS) in newborn infants.<sup>2</sup>

During CPAP, the constancy of continuous distending pressure (CDP) levels throughout

the respiratory cycle is the fundamental requisite for restoring functional residual capacity (FRC) and reducing the work of breathing (WOB).<sup>3,4</sup> Unfortunately, to date, traditional CPAP systems have failed to achieve this goal. The Infant Flow Driver (Electro Medical Equipment Ltd, Brighton, Sussex, UK) has recently been proposed as a new system for administering CPAP in newborn infants. CPAP is generated in the vicinity of the nasal airways by converting kinetic energy from a jet of fresh humidified gas. A continuous flow rate of breathing gas of 5–11 litres/min generates a corresponding CPAP of 2–10 cm H<sub>2</sub>O. The theory behind the IFD is that the direction of the high pressure supply jet responds to pressures exerted in the nasal cavity by the patient's efforts.

Because of its design specificity, the IFD is claimed to be effective at reducing variations in airway pressure.<sup>5</sup> Whether this is of clinical relevance in terms of respiratory workload and efficacy of treatment remains to be confirmed. Although the IFD has gained widespread popularity in the treatment of RDS in newborns,<sup>6,7,8</sup> surprisingly few clinical data are available to substantiate its superiority over other devices.

Since January 1997, we have been using IFD as an alternative method of delivering CPAP to infants with RDS, obstructive/central apnoea, or recent extubation. About 100 neonates have been treated so far. Retrospectively, there are signs that respiratory recovery occurs earlier and the need for mechanical ventilation decreases when the IFD rather than traditional nasal CPAP (nCPAP) is used.

To test these findings, we performed a prospective, randomised, controlled trial comparing the IFD with conventional single prong nCPAP in preterm infants with RDS.

## Patients and methods

The study was performed between September 1997 and March 1999 at the Department of Pediatrics, Neonatal Intensive Care Unit, Gaslini Children's Hospital, University of Genova, Italy. The local research ethics committee approved the study. All infants less than 12 hours old, with a gestational age below 36 weeks who were eligible for CPAP (clinical distress,  $P_{CO_2} < 65$  mm Hg, oxygen requirement greater than 30%, radiological finding of poor lung expansion) were considered suitable for the study. Respiratory distress was clinically defined as: sternal retraction, intercostal and

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Table 1 Baseline characteristics at trial entry of infants assigned to nasal continuous positive airway pressure (nCPAP) and the Infant Flow Driver (IFD)

	nCPAP (n=18)	IFD (n=18)	p Value
Birth weight (g)	1735 (473)	1706 (459)	0.85
Gestational age (weeks)	33 (1.4)	32 (1.2)	0.08
Number VLBW	7 (38%)	6 (33%)	0.97
Number SGA	5 (27%)	4 (22%)	0.96
M/F	7/11	11/7	0.32
Age (hours)	6 (5.2)	7 (5.8)	0.59
RR (breaths/min)	62.5 (8.57)	63.6 (7.66)	0.71
Saturated O <sub>2</sub> (%)	94 (4)	96 (2.1)	0.07
O <sub>2</sub> requirement	38.6 (9.2)	41.2 (8.3)	0.38
Pco <sub>2</sub> (mm Hg)	51 (11.08)	57.4 (10.17)	0.08

Unless otherwise indicated, values are mean (SD). VLBW, Very low birth weight; SGA, small for gestational age; RR, respiratory rate.

subcostal recession, grunting, tachypnoea. Babies were excluded if they had major congenital malformations, neuromuscular disease, severe birth asphyxia (Apgar score at five minutes of less than 4, serum bicarbonate < 12 mmol/l in the first hour), overwhelming infections, severe apnoea (more than three apnoeic episodes/hour requiring stimulation or bag ventilation), or evidence of patent ductus arteriosus with continuous left-right shunting. To obtain a homogeneous population, we also excluded a priori patients who had received antenatal steroids or intubation at delivery.

DELIVERING CDP

Over the last two decades, we have routinely delivered nCPAP through a single nasal catheter inserted deep into the pharynx, as previously described.<sup>9</sup> The nCPAP system consists of an oxygen blender with a flow meter, a heated humidifier, a respiratory circuit (inspiratory and expiratory tubing), and a bottle containing sterile distilled water to a depth of 7 cm (threshold resistor). Provided that the rate of continuous flow is adequate to the patient's inspiratory flow demand (usually 4–7 litres/min), we achieve the desired distending pressure by immersing the expiratory tubing to the desired depth—that is, 5 cm H<sub>2</sub>O = 5 cm of depth.

The IFD includes a three way branched pipe. High pressure support is delivered through one branch, another is connected to the nasal prongs, and the remaining branch is left open to the atmosphere. The nasal prongs are fitted on the basis of the infant's size, as suggested by the manufacturer, and are positioned with a bonnet and foam strips. When a good seal is obtained, a flow rate of 6–8 litres/min generates a CDP of 4–5 cm H<sub>2</sub>O. Both devices were calibrated against an independent oxygen analyser to determine any differences in oxygen delivery.

PROTOCOL

When parental consent had been obtained, patients were randomly assigned (by drawing a sealed, numbered envelope) to either IFD or nCPAP treatment. Cards for randomisation were prepared in blocks of six to ensure approximately equal numbers in each treatment group.

According to a preset protocol, CDP was initially set to 4 cm H<sub>2</sub>O in both groups. It was increased by steps of 1 cm H<sub>2</sub>O up to a

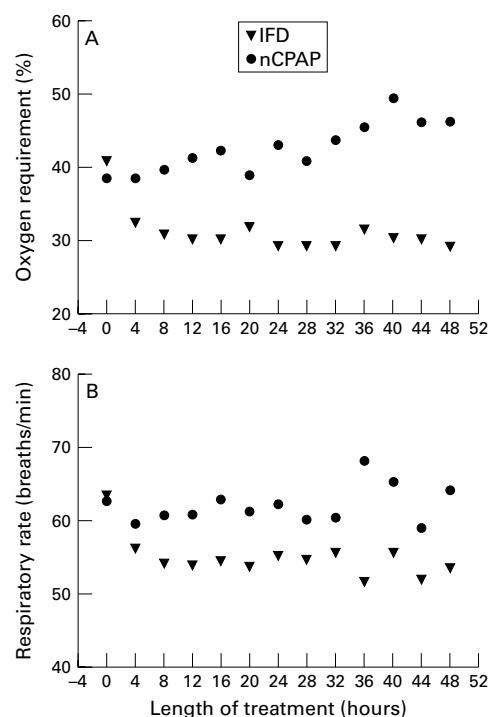


Figure 1 Averaged curves of changes in fraction of inspired oxygen (F<sub>IO</sub>) (A) and respiratory rate (RR) (B) during the first 48 hours of treatment using the Infant Flow Driver (IFD) or nasal continuous positive airway pressure (nCPAP). Univariate repeated measures analysis showed a significant difference between the two systems for F<sub>IO</sub> and RR (p < 0.0001). A paired t test showed that F<sub>IO</sub> and RR values in the IFD group became significantly different from the baseline at four hours (p < 0.001 and p < 0.03 respectively).

maximum of 6 until depth of retraction decreased. Likewise, CDP was increased if a fraction of inspired O<sub>2</sub> (F<sub>IO</sub>) ≥ 0.6 was required to keep saturated O<sub>2</sub> in the range 90–95% depending on gestational age. Conversely CDP was reduced by steps of 1 cm H<sub>2</sub>O to 4 when F<sub>IO</sub> < 0.5 was required (for more than four hours consecutively) to keep saturated O<sub>2</sub> as defined above.

At enrolment, caffeine citrate was started with a loading dose of 20 mg/kg given intravenously, followed by a daily maintenance dose of 5 mg/kg given intravenously. Oxygen requirements, respiratory rate (RR), heart rate (HR), and saturated O<sub>2</sub> by pulse oximetry were monitored continuously and recorded every four hours. To achieve a reliable estimate, the average of a complete two minute count of RR, HR, and saturated O<sub>2</sub> from each patient was recorded as a single measurement and subsequently processed. Blood gases were determined on capillary blood every four hours during the first 24 hours of treatment and every eight hours thereafter or at the discretion of the health care team. Non-invasive blood pressure was obtained by oscillometry every eight hours during the first 24 hours of treatment and every 12 hours thereafter (only mean values were analysed statistically). All infants underwent an ultrasound cerebral scan at enrolment and at least three times subsequently. Periventricular intraventricular haemorrhage was classified as described by Papile *et al.*<sup>10</sup> Any adverse clinical events (abdominal distension, pulmonary air

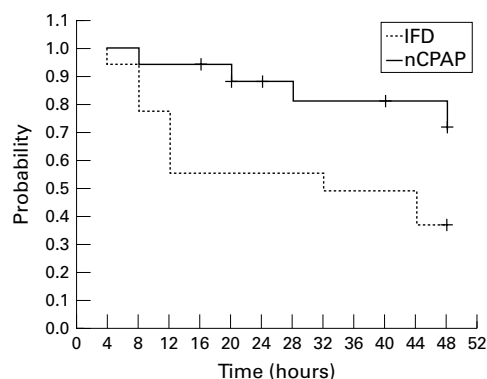


Figure 2 Kaplan-Meier curves. Assuming the fraction of inspired oxygen ( $F_{iO_2}$ ) = 0.21 as the event, the probability of remaining supplementary oxygen free over the first 48 hour period is significantly higher ( $p < 0.02$ ) with the Infant Flow Driver (IFD) than with nasal continuous positive airway pressure (nCPAP).

leaks, nasal injury, damage to septal mucosa) were also prospectively recorded. We strongly suggest the use of a pacifier to optimise CDP. Surfactant treatment was not used in these patients until failure criteria were reached.

#### CLASSIFICATION OF WEANING OUTCOMES

Success was defined as the ability to remain CPAP free and to achieve goal criteria as follows: medically stable with  $PCO_2 < 60$  mm Hg, saturated  $O_2 > 95\%$  without supplementary  $O_2$  requirement, and CDP  $\leq 4$  cm  $H_2O$  for four hours consecutively.

Failure to wean was defined by (a) an increase in  $PCO_2$  above 65 mm Hg and/or pH  $< 7.25$  on two consecutive occasions,  $O_2$  requirement  $\geq 60\%$  at CDP of 6 cm  $H_2O$  to keep saturated  $O_2 > 90\%$  for more than four hours consecutively; (b) more than three apnoeic episodes/hour requiring stimulation or bag ventilation; (c) adverse events as described above that appreciably affect the clinical course. In such cases, further management was at the discretion of the health care team.

#### STATISTICAL DESIGN AND DATA ANALYSIS

This was a randomised controlled study. The sample size was estimated from a previous pilot study using a power of 85% and a significance level of 0.05. The primary objective was to assess the effects of IFD as compared with nCPAP in short term outcome (changes in oxygen requirements and/or respiratory rate within 48 hours). The secondary variable was to assess the success rate of weaning, the potential complications of treatment, and the effects on mid-term outcome (death, intraventricular haemorrhage, oxygen dependency at 28 days of life). Differences between the two groups were evaluated by Fisher's exact test for each categorical variable and by Student's  $t$  test

for each continuous variable. The paired Student's  $t$  test was used to investigate changes in the clinical variables. Univariate repeated measures analysis was used to compare the oxygen requirement and respiratory rate between methods. Survival rates were calculated by the Kaplan-Meier method for analysis of data. Clinical comparison of oxygen delivery was assessed by the Bland-Altman method. Data were processed by the SPSS software package (Chicago, Illinois, USA).

## Results

A total of 36 infants were enrolled in our study and randomly assigned to one of the two treatment groups. Data were normally distributed. Table 1 summarises the clinical data at the time of enrolment. Calibration against an independent oxygen analyser showed that the IFD delivered 0.5% more oxygen than nCPAP.

Use of the IFD had a significantly advantageous effect on both oxygen requirement ( $p < 0.0001$ ) and respiratory rate ( $p < 0.0001$ ) when compared with nCPAP (fig 1). The difference in mean oxygen requirement and respiratory rate over the first 48 hour period was statistically significant in the IFD group starting from the fourth hour (fig 1). Moreover, the probability of remaining supplementary oxygen free over the first 48 hours of treatment was significantly higher in IFD treated patients than in nCPAP treated ones ( $p < 0.02$ ) (fig 2). No statistically significant difference was found for the following: saturated  $O_2$ ,  $PCO_2$ , HR, mean non-invasive blood pressure, and CDP.

Table 2 shows the characteristics of the patients according to the secondary outcomes. Successful weaning occurred in 17/18 patients in the IFD group and in 13/18 in the nCPAP group (success rate 94% *v* 72%;  $p = 0.17$ ). The reasons for failure were respiratory acidosis in four cases (one patient in the IFD group (gestational age 32 weeks) and three in the nCPAP group (gestational age 30, 33, and 33 weeks)) and hypoxaemia in the remaining two (both in the nCPAP group; gestational age 33 and 32 weeks).

The four patients whose failure was due to respiratory acidosis underwent mechanical ventilation. The two babies on nCPAP who showed failure because of hypoxaemia were changed to the IFD, and were successfully weaned after 32 and 44 hours. Data from these patients were subsequently withdrawn from the study and excluded from analysis. There were no significant differences between duration of treatment, although patients in the IFD group spent a shorter time on support than those randomised to nCPAP (49.3 (31) *v* 56 (29.7) hours respectively; mean (SD)). No adverse events occurred that required discontinuation of treatment. However, there was a complication rate of 27% in the IFD group (one pneumothorax, three hyperaemia of the nasal mucosa, one bleeding of the nasal mucosa). No deaths, intraventricular haemorrhages, or oxygen dependence at 28 days of life were observed in either of the groups.

Table 2 Outcomes for infants assigned to nasal continuous positive airway pressure (nCPAP) and the Infant Flow Driver (IFD)

	nCPAP	IFD	<i>p</i> Value
Successful weaning	13/18 (72%)	17/18 (94%)	0.17
Need for mechanical ventilation	3 (17%)	1 (5%)	0.59
Duration of treatment (hours)*	56.5 (29.7)	49.3 (31)	0.48

\*Values are mean (SD).

## Discussion

The main purpose of this study was to investigate whether the IFD was superior to traditional nCPAP. We hypothesised that the IFD would facilitate respiratory recovery of patients with moderate RDS because of its technical specificity. This seemed to be the case.

In our study, IFD treated patients showed a lower oxygen requirement, a decreased respiratory rate, and, although not statistically significant, a higher rate of successful weaning and a shorter duration of treatment. To our knowledge, this is the first study to report these findings.

In a previous cross over study, Ahluwalia *et al*<sup>11</sup> showed no clear improvement in oxygenation using the IFD compared with nCPAP. No differences in any other clinical variables or clinical comfort were reported either. No data on the duration of treatment were provided. The authors concluded that no data were available to suggest any clear clinical superiority of the IFD. However, a possible bias of the study was that the period of observation was too short to produce any statistically significant results. Kavvadia *et al*<sup>12</sup> failed to show any IFD related short term advantages over the single nasal prong system. However, only infants who had been extubated were studied, and no randomisation was performed. In our opinion, it would be more effective to test the IFD in the acute stage of RDS when respiratory distress first appears and FRC is low.

Applying CPAP mainly results in an increase in FRC and an improvement in static lung compliance. Oxygenation consequently increases because the ventilation/perfusion mismatch is reduced. In addition, CPAP allows a greater tidal volume for each alveolar unit, leading to adequate minute ventilation and a decrease in WOB and RR.

However, the prerequisite for successful recruitment of adequate FRC remains the constancy of CDP during the breathing cycle.<sup>3,4</sup> The theory behind the IFD is that the direction of the high pressure supply jet responds to pressures exerted in the nasal cavity by the patient's efforts by means of the so-called "Coanda effect".<sup>5-7</sup> On inspiration, the low pressure in the nasal cavity gives a positive pressure gradient between the jet supply and the nasal cavity, and the jet flows towards the patient, aiding the respiratory effort. On exhalation, the build up of pressure in the nasal cavity alters the detailed structure of the jet mixture and the fluid from the jet flows down the expiratory branch. By these changes in the flow, the device follows the breathing requirements of the baby allowing spontaneous inhalation and exhalation with only a minimal variation in CDP during the respiratory cycle. Our results suggest that this achieves clinical relevance.

A striking finding in our study was the significant decrease in both the oxygen requirement and the respiratory frequency that occurred in the IFD group (fig 1). The positive bias in oxygen delivery by the IFD was considered clinically negligible. It is noteworthy that the IFD group showed a significant decrease in

its oxygen requirement and stabilisation of the respiratory rate earlier than the nCPAP group. Furthermore, the probability of remaining supplementary oxygen free at 48 hours was significantly higher with the IFD than with nCPAP (fig 2). Assuming that infants requiring the highest  $F_{IO_2}$  are likely to have a low FRC,<sup>13</sup> we would argue that FRC is restored more efficiently in patients on the IFD.

We excluded preterm babies who had received antenatal steroids and/or intubation at delivery. Such treatments may significantly influence lung recruitment and consequently interfere with the quality of the data or the interpretation of the results. In our study, it was important to obtain a homogeneous sample size, in which the ability of the two devices to recruit the lung could be processed with no iatrogenic interference. In our opinion, the restrictive exclusion criteria improved the feasibility of the study. In addition, because of the restrictive exclusion criteria applied, only infants with a relatively mature mean gestational age were chosen (most infants with greater immaturity are treated with antenatal steroids and consequently excluded from this study). Although we have no reason to believe that the changes we show would have been different, we realise that a new study may be warranted to broaden our observations to a wider spectrum of preterm infants.

Our results may, to some extent, be explained by the higher gas flow generated by the IFD. This is an important point that requires some consideration. The flow rate is important in keeping CDP stable, and it must be empirically set to meet the infant's inspiratory demands. However, increasing the flow rate to achieve "stable" pressure may not always be the best choice. If the flow rate is set high, it makes it difficult for the patient to exhale and may cause increased WOB.<sup>14</sup> Furthermore, in continuous flow systems, even the design of the expiratory valve is crucial in keeping CDP stable. From this point of view, the two devices are not comparable. Because of its unusual fluidic circulation, IFD shows a near linear relation between flow rate and CDP.

In contrast, a threshold resistor exhalation valve, as in our "bubble" nCPAP, offers little resistance to flow, and adequate CDP could be maintained regardless of respiratory alterations in the rate of continuous flow.<sup>14</sup> On this basis, provided that the patient's inspiratory demands are met, it is our opinion that the difference in flow between the two devices is unlikely to affect the results appreciably.

Our study also suggests that IFD may be beneficial in reducing the need for mechanical ventilation. Furthermore, it is noteworthy that two patients who failed to improve with nCPAP because of poor oxygenation were rescued by use of the IFD and successfully weaned without mechanical ventilation. However, this should be interpreted with caution, and, whether use of the IFD is an effective "rescue" method in patients for whom traditional nCPAP failed, remains to be confirmed.

The reported tendency towards an increase in adverse events when using the IFD is of concern.<sup>15 16</sup> We feel that nursing care is critical to the handling of the IFD to avoid such problems. The main point is to ensure a gentle seal when the device is applied. IFD prongs are slightly flared at the end and fit comfortably into the infant's nares, so no major pressure is needed to achieve a good seal. If the device is fitted too tightly, trauma is inevitably a risk. The gas mixture must be warmed and humidified to prevent damage to the mucosa. We routinely ensured that inspired gases were delivered at body temperature (37°C) and that they achieved near total saturation with water vapour (44 mg/l). This policy resulted in only minor nasal trauma (oedema and a small amount of bleeding) and these healed with no complications or discontinuation of treatment. At the beginning of the study, some concerns were expressed by the nursing staff over difficulties in correct insertion of the prongs (because they are being attached to an active infant and not a fixed surface, they are easily dislodged), but confidence and skill with the device progressively improved with training and handling.

Our study provides no data on major adverse events such as pulmonary air leaks. One baby on IFD treatment experienced a mild pneumothorax, which spontaneously recovered without any intervention or discontinuation of treatment. A possible explanation is that limiting CDP to 6 cm H<sub>2</sub>O incurs a low risk of serious complications.

Lastly, babies randomised to the IFD group spent about seven hours less time on respiratory support than those in the nCPAP group. We argue that this did not result in a significant difference because of the relatively small number of patients. However, it may be of clinical relevance with respect not only to patient comfort but also the cost of care and total hospital stay. Moreover, the additional costs of the specific equipment needed for the IFD have to be taken into consideration. Studies are therefore warranted to investigate further whether the potential clinical benefits outweigh the additional costs.

To conclude, the IFD appears to be a feasible device for managing RDS in preterm

infants, and, compared with nCPAP, benefits may be accrued in lower oxygen requirement and respiratory rate. Moreover, a trend towards a lower rate of mechanical ventilation, shorter clinical recovery time, and shorter duration of treatment has been shown. A multicentre randomised controlled trial is needed to confirm these findings.

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