

# High-Frequency Jet Ventilation and Surfactant Treatment of Newborns With Severe Respiratory Failure

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**Summary.** Twenty-eight newborn infants (birthweight,  $2.4 \pm 1.1$  kg; gestational age,  $34.6 \pm 6.1$  weeks) with respiratory distress syndrome (RDS), meconium aspiration syndrome, or pneumonia who deteriorated in spite of optimal conventional mechanical ventilation (CMV) and exogenous surfactant therapy were treated with high-frequency jet ventilation (HFJV) and continued surfactant therapy. For enrollment, infants had to have a limited response to surfactant therapy and conventional ventilation, and meet clinical criteria that confirmed clinical deterioration and severity of illness. Study infants had received exogenous calf lung surfactant extract (CLSE) and conventional ventilation prior to the start of HFJV at  $46.3 \pm 8.2$  hours of age. Patients initially responded to HFJV alone with significant improvement in several respiratory variables, but deteriorated subsequently and received additional doses of exogenous surfactant on HFJV. Exogenous surfactant and HFJV resulted in significant and sustained improvement in several respiratory variables. Only ten patients deteriorated to meet criteria for a second surfactant dose on HFJV, and two patients received a third dose. Twenty-five of the 28 patients studied survived (89%). No patients received extracorporeal membrane oxygenation or were discharged home on oxygen. The results of this pilot study suggest that the combination of HFJV and exogenous surfactant replacement may be effective in treating infants with more severe respiratory failure, and indicate the need for more extensive controlled investigations. *Pediatr Pulmonol.* 1992; 13:108-112. © 1992 Wiley-Liss, Inc.

**Key words:** Calf lung surfactant extract; respiratory distress syndrome; pneumonia; meconium aspiration; BPD; mean and inspiratory pressure; blood gases; outcome.

## INTRODUCTION

Surfactant replacement therapy for the respiratory distress syndrome (RDS) is now widespread, and improvements in neonatal morbidity and mortality have been reported for a variety of clinical trials using this intervention.<sup>1-6</sup> In addition, surfactant treatment may also provide therapeutic benefits to full-term infants with respiratory failure due to meconium aspiration syndrome (MAS) or pneumonia.<sup>7</sup> However, in spite of the overall success of surfactant therapy in neonates with respiratory failure, many ventilated infants still have significantly impaired respiratory function, despite exogenous surfactant therapy and will die or develop significant chronic lung disease due to complications of respiratory failure. In some series, this represents up to 50% of all enrolled infants.<sup>1,5,7</sup> Detailed information about the numbers and characteristics of these infants is still being developed,<sup>8</sup> but it is clear that optimizing treatment to reduce morbidity and mortality will be an important concern in clinical neonatology.

The majority of premature infants who require ventilatory support for RDS are treated initially with exogenous surfactant replacement therapy and conventional me-

chanical ventilation (CMV).<sup>9</sup> Full-term infants with respiratory failure are treated with CMV, extracorporeal membrane oxygenation (ECMO), and high frequency ventilation.<sup>10-12</sup> Little quantitative information is currently available about the comparative benefits of surfactant therapy in patients receiving other modes of assisted ventilation, such as high-frequency jet ventilation (HFJV).<sup>13-15</sup> HFJV has been of particular interest because it allows adequate gas exchange at reduced mean

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airway or peak inspiratory pressures.<sup>15,16</sup> Because of these characteristics, HFJV is particularly applicable to critically ill neonates who continue to require ventilatory support despite surfactant therapy and CMV. Although the use of HFJV has not been found to result in improved survival, compared to CMV in infants treated without surfactant replacement therapy,<sup>16</sup> this mode of ventilation has not been well tested when used together with exogenous surfactant.

This report examines a pilot group of 28 infants over a 2 year period who received exogenous surfactant therapy first on CMV and then again while on HFJV. The patients were enrolled in on-going clinical trials of surfactant therapy for RDS and for treatment of full-term infants with respiratory failure. Infants failed to respond sufficiently to initial exogenous surfactant given with CMV. After meeting defined criteria, patients were then rescued with HFJV, and subsequently received at least one dose of exogenous surfactant in order to determine if infants would have a better physiologic response to surfactant with HFJV compared to surfactant with CMV.

## MATERIALS AND METHODS

The 28 infants enrolled in this pilot study were participants in on-going randomized and open-labelled surfactant replacement trials, conducted at the University of Rochester Medical Center (Strong Memorial Hospital, Rochester, NY). Infants reported in this HFJV pilot study included only those who had received at least one rescue dose of exogenous surfactant and CMV. In order to receive exogenous surfactant as an initial rescue or as a repeated dose in the premature trials, infants had to be ventilated with a mean airway pressure (MAP) of at least 7 cmH<sub>2</sub>O and/or a fraction of inspired oxygen (FiO<sub>2</sub>) ≥ 0.40.<sup>17</sup> Full-term infants required an FiO<sub>2</sub> ≥ 0.50 and a MAP ≥ 7.0 cmH<sub>2</sub>O.<sup>7</sup>

If infants deteriorated clinically despite surfactant replacement therapy and optimal conventional ventilation, [multiple adjustments of inspiratory pressure (IP), positive end-expiratory pressure (PEEP), ventilator rate, and inspiratory time], they were eligible to enter the pilot study of HFJV and additional exogenous surfactant. The eligibility criteria used for initial HFJV included two of the following five: MAP ≥ 12 cmH<sub>2</sub>O, IP ≥ 30 cmH<sub>2</sub>O, arterial/alveolar oxygen ratio < 0.1, arterial P<sub>CO<sub>2</sub></sub> ≥ 55 torr, and pH ≤ 7.20. The study was approved by the Institutional Review Board of the University of Rochester, and informed consent was obtained. Infants were reintubated with a triple lumen "hi-lo" endotracheal tube and placed on a Life Pulse High-Frequency Jet Ventilator (Bunnell Inc., Salt Lake City, UT). The rate was set at 420 breaths/min with an inspiratory time of 0.02 seconds, which has been shown to provide adequate gas exchange while minimizing air trapping.<sup>15</sup> FiO<sub>2</sub>, IP, and PEEP

(measured distally just before and during HFJV) were varied to keep Pa<sub>CO<sub>2</sub></sub> between 40 and 50 torr and Pa<sub>O<sub>2</sub></sub> between 60 and 70 torr. A background sigh rate of 4 breaths per minute was provided by the conventional ventilator to prevent atelectasis.<sup>15</sup> IP on the background rate was maintained at 2–5 cmH<sub>2</sub>O below that of the HFJV to prevent overdistention and additional barotrauma.

If infants continued to require at least 40–50% inspired oxygen and a MAP ≥ 7 despite HFJV, they received at least one dose of exogenous surfactant while HFJV was maintained. The surfactant used was a calf lung surfactant extract (CLSE), prepared at Rochester as described previously.<sup>2,13,19</sup> CLSE, containing 98% lipid and 1–2% hydrophobic surfactant SP-B and C apoproteins, was dispersed at a concentration of 30 mg/mL in 0.15 M NaCl after organic solvent extraction, and was then autoclaved for sterility. The CLSE dose was 90 mg of surfactant in 3 mL saline for premature infants or 90 mg (3 mL)/kg for full-term infants. Surfactant was administered via a feeding tube placed in the distal portion of the endotracheal tube. The surfactant dose was divided into two aliquots and administered 2–3 minutes apart while the jet ventilator was operating. One to two conventional sigh breaths were given rapidly just after surfactant administration to clear the endotracheal tube and prevent plugging.

## Physiological Variables and Statistical Analysis

The acute effects of HFJV and exogenous surfactant therapy were evaluated in terms of MAP, IP, arterial partial pressure of oxygen and carbon dioxide (Pa<sub>O<sub>2</sub></sub> and Pa<sub>CO<sub>2</sub></sub>), arterial/alveolar oxygen ratio (a/A ratio), oxygenation index (OI = MAP × FiO<sub>2</sub> × 100/Pa<sub>O<sub>2</sub></sub>), and arterial pH. Statistical analyses were performed using the Student's paired *t*-test.

## RESULTS

The clinical characteristics of the 28 infants studied are given in Table 1. Fifteen infants were born at term (2 with group B streptococcal pneumonia, 13 with meconium aspiration syndrome) and 13 at preterm with RDS (≤ 35 weeks gestational age). The infants had been treated before study entry with 1.9 ± 0.2 doses of exogenous surfactant and CMV. Physiologic parameters were analyzed just before and 1 hour after the last dose of surfactant and CMV, prior to study entry. No significant changes were noted in MAP, pH, Pa<sub>CO<sub>2</sub></sub>, or OI following surfactant administration. The IP increased from 28.1 ± 1.7 cmH<sub>2</sub>O before surfactant to 31.0 ± 1.2 cmH<sub>2</sub>O after surfactant administration (*P* < 0.05). The a/A ratio did improve significantly from 0.11 ± 0.01 to 0.18 ± 0.02 following surfactant administration (*P* < 0.05), but the duration of response was short. The latter was defined as the time following surfactant administration until infants

**TABLE 1—Clinical Characteristics of 28 Infants Treated With Surfactant and HFJV<sup>a</sup>**

Birthweight (kg)	2.4 ± 1.1 <sup>b</sup> (0.69-4.13)
Gestational age (wks)	34.6 ± 6.1 <sup>b</sup> (25-41)
Surfactant doses before HFJV	1.9 ± 0.2 <sup>c</sup> (1-4)
Surfactant doses on HFJV	1.6 ± 0.2 <sup>c</sup> (1-3)
Age HFJV started (hours)	46.3 ± 8.2 <sup>c</sup> (1-48)
Total time on HFJV (hours)	50.2 ± 6.9 <sup>c</sup> (2-240)
Time on HFJV before surfactant (hours)	11.1 ± 1.7 <sup>c</sup> (1-36)
Survival % (n/28)	89 (25/28)
BPD % (n/28)	14 (4/28)
Discharged on O <sub>2</sub>	0
ECMO	0
IVH % (n/28)	21 (6/28)

<sup>a</sup>HFJV, high-frequency jet ventilation; BPD, bronchopulmonary dysplasia (defined by O<sub>2</sub> requirement at 28 days); ECMO, extracorporeal membrane oxygenation; IVH, intraventricular hemorrhage.

<sup>b</sup>Mean ± SD (range).

<sup>c</sup>Mean ± SEM (range).

had clinically deteriorated to pre-surfactant values (FiO<sub>2</sub>, ventilator settings, and arterial blood gases). Following surfactant and CMV, the duration of response was only 6.8 ± 0.9 hours. All 28 study patients were then treated with HFJV alone, following enrollment at a mean postnatal age of 46.3 ± 8.2 hours. As shown in Table 2, infants (both preterm and term) were in severe respiratory distress accompanied by marked abnormalities in arterial blood gases 1 hour before the start of HFJV, requiring significant ventilatory support. Preterm infants were having difficulty oxygenating and ventilating, while the term infants were having difficulty primarily with oxygenation. One hour after the start of HFJV (Table 2), statistically significant improvements were noted in IP, MAP, a/A ratio, OI, PaCO<sub>2</sub>, and arterial pH. However, this initial favorable response was not sustained, and respiratory status worsened over several hours. One dose or more of exogenous surfactant were then given while HFJV was continued.

Table 3 shows the acute response of respiratory variables to the first dose of exogenous surfactant given on HFJV. This initial surfactant dose was administered an average of 11.1 ± 1.7 hours after patients were placed on HFJV. Table 3 demonstrates that the respiratory improvement noted immediately after initiation of HFJV (Table 2) had diminished by the time exogenous surfactant was given. The data in Table 3 also show that exogenous surfactant delivery resulted in further improvement in respiratory status. Preterm infants again had significant improvements in oxygenation and ventilation following surfactant, while term infants sustained improvements primarily in oxygenation. This beneficial response to surfactant and HFJV was sustained for 17.7 ± 4.7 hours ( $P < 0.05$ , compared to duration of response for the prior dose of surfactant while on CMV). A sustained response

for surfactant and HFJV was defined as the duration of time until clinical deterioration caused a return to pre-surfactant values of FiO<sub>2</sub>, ventilator settings, arterial blood gases, and another dose of surfactant was administered. More frequently, if infants clinically improved, sustained response was defined as the duration of time on HFJV until ventilator support was decreased enough for infants to tolerate ventilation again with CMV (IP generally ≤ 20 cmH<sub>2</sub>O, FiO<sub>2</sub> ≤ 0.5). Fifteen of 28 patients studied, received only a single dose of exogenous surfactant during jet ventilation. This sustained response of 15/28 patients to a single dose of exogenous surfactant during HFJV was in contrast to the pattern found for these same patients during earlier conventional mechanical ventilation. Three of these patients had failed to respond adequately to four doses of surfactant on earlier CMV and four had failed to respond to three doses. Only ten infants met criteria for a second dose of exogenous surfactant on HFJV, and three patients received a third dose. Jet ventilation was continued in the 28 infants for 50.2 ± 6.9 hours.

Twenty-five of the 28 infants studied survived to discharge home (89%). The one premature infant who died weighed 630 g and had severe RDS, a patent ductus arteriosus, and necrotizing tracheobronchitis (grade II) on pathologic examination. Two full-term infants had overwhelming group B streptococcal sepsis and died primarily of cardiovascular failure (poor cardiac contractility and hypotension). No infant received ECMO. Four of the 13 preterm infants had oxygen requirement at 28 days and an abnormal chest radiograph consistent with bronchopulmonary dysplasia (BPD). None of the 15 term infants developed BPD. None of the 28 infants were discharged home on oxygen. Six premature infants developed an intraventricular hemorrhage (two, grade I; two, grade II and two, grade IV).

## DISCUSSION

This study showed that HFJV acutely improved oxygenation and ventilation in infants with RDS, pneumonia, and meconium aspiration syndrome who had failed to respond adequately to optimal conventional mechanical ventilation and exogenous surfactant therapy. Although acute improvements were present after HFJV was initiated in these patients (Table 2), the effects of jet ventilation alone were transitory. Patients subsequently deteriorated and were given additional exogenous surfactant on HFJV within an average of 11.1 hours (Table 3). Clinical deterioration may have occurred on HFJV due to excessively rapid weaning of inspiratory pressure (due to hypocarbia and adequate oxygenation) with resultant decreases in MAP. When MAP decreased, some atelectasis may have occurred with worsening arterial blood gases. Inspiratory pressure and PEEP could have been increased

TABLE 2—Physiologic Changes Before and 1 Hour After HFJV<sup>a</sup>

	Preterm (n = 13)		Term (n = 15)		All infants (n = 28)	
	Pre	Post	Pre	Post	Pre	Post
Inspiratory pressure (cmH <sub>2</sub> O)	30.4 ± 1.5	27.0 ± 1.6**	35.2 ± 1.9	27.9 ± 1.6	33.0 ± 1.6	27.7 ± 1.2
Mean airway pressure (cmH <sub>2</sub> O)	12.7 ± 0.8	9.7 ± 0.4	16.4 ± 0.6	14.3 ± 0.7**	14.8 ± 0.6	12.2 ± 0.6
pH	7.23 ± 0.04	7.33 ± 0.03	7.39 ± 0.04	7.52 ± 0.03	7.32 ± 0.03	7.43 ± 0.03
Pa <sub>CO</sub> <sub>2</sub>	63.0 ± 7.6	38.1 ± 4.3	37.0 ± 5.2	24.0 ± 2.6**	49.1 ± 5.1	30.5 ± 2.9
Oxygenation index	23.5 ± 3.2	11.1 ± 2.5	29.0 ± 2.9	16.2 ± 3.0	26.5 ± 2.1	13.6 ± 1.9
a/A ratio	0.13 ± 0.02	0.26 ± 0.05	0.10 ± 0.01	0.19 ± 0.04	0.11 ± 0.01	0.22 ± 0.03

<sup>a</sup>Values are mean ± SEM, all pre-post differences statistically significant except those marked by \*\*.

TABLE 3—Physiologic Changes Before and 1 Hour After Combined Surfactant and HFJV<sup>a</sup>

	Preterm (n = 13)		Term (n = 15)		All infants (n = 28)	
	Pre	Post	Pre	Post	Pre	Post
Inspiratory pressure (cmH <sub>2</sub> O)	28.0 ± 1.4	24.5 ± 1.5	29.0 ± 1.6	28.0 ± 1.6**	28.6 ± 1.1	26.1 ± 1.1
Mean airway pressure (cmH <sub>2</sub> O)	10.5 ± 0.4	9.3 ± 0.5	14.0 ± 0.8	13.6 ± 0.7**	12.4 ± 0.5	11.6 ± 0.6
pH	7.27 ± 0.03	7.41 ± 0.04	7.50 ± 0.03	7.51 ± 0.04**	7.39 ± 0.03	7.47 ± 0.03
Pa <sub>CO</sub> <sub>2</sub>	50.0 ± 5.6	33.3 ± 4.3	28.0 ± 2.3	27.0 ± 2.9**	38.3 ± 3.5	30.0 ± 2.5
Oxygenation index	16.9 ± 2.1	9.0 ± 1.7	23.6 ± 2.1	13.9 ± 2.5	20.6 ± 1.7	11.8 ± 1.7
a/A ratio	0.13 ± 0.02	0.26 ± 0.05	0.09 ± 0.01	0.21 ± 0.04	0.11 ± 0.01	0.22 ± 0.03

<sup>a</sup>Values are mean ± SEM, all pre-post differences statistically significant except those marked by \*\*.

significantly to recruit alveoli and improve oxygenation and ventilation. However, this increases the risk of complications of mechanical ventilation such as pneumothoraces. Surfactant administration may be a better alternative to recruit alveoli at lower ventilator pressures.

Exogenous surfactant was effectively given while patients were on HFJV, and acute improvements in respiratory function were associated with this combination therapy (Table 3). Fifteen of the 28 patients required only a single dose of exogenous surfactant during HFJV, while 10 required a second dose and 3 required a third. This pattern of response contrasted sharply with that exhibited earlier by these patients when they were given surfactant therapy during CMV. Thirteen patients in this study had MAS and responded well to exogenous surfactant and HFJV. Surfactant inactivation may play an important role in MAS, and infants may respond optimally to this combined form of therapy.<sup>7</sup> Full-term infants had improvements in oxygenation following exogenous surfactant administration similar to that seen in preterm infants with RDS. The improvements were immediate, sustained for several hours, and were reproduced with additional treatment.<sup>7</sup> No adverse effects were noted following exogenous surfactant administration when infants were simultaneously receiving HFJV.

The data reported here on HFJV and surfactant therapy are limited in that they represent a pilot experience without control patients. It is possible that since infants were

placed on HFJV at almost 2 days of life, they might have improved without HFJV or surfactant therapy. However, this seems unlikely since infants had continued to clinically deteriorate before and had such a rapid and prolonged improvement after the combination therapy. The results suggest that the combination of HFJV and exogenous surfactant may have benefits in some infants who have not responded to surfactant therapy and CMV. Further definition of potential benefits will require randomized controlled studies directly comparing surfactant therapy given with HFJV to surfactant therapy and conventional ventilation, and assessing outcome variables such as survival and incidence of chronic lung disease.

If exogenous surfactant therapy is found to be more beneficial to some patients when given with HFJV rather than with CMV, potential mechanisms will need to be better understood. While the mode of ventilation should not alter the underlying interfacial activity of exogenous surfactant, it may influence the expression of physiological activity. HFJV generates different ventilation pressure wave forms when compared to CMV.<sup>14</sup> These pressure effects might in turn generate differences in alveolar size-distribution and morphology during the breathing cycle that would influence the response to surfactant, although this has not been well studied. Another possibility is that in some patients, HFJV may lead to a better pulmonary distribution of tracheally instilled exogenous surfactant compared to CMV, and this would give an

overall improvement in pulmonary function. This theory has been studied in surfactant-deficient neonatal piglets given technetium-99m labelled exogenous surfactant.<sup>20</sup> Dynamic imaging was unable to demonstrate significant differences in the short-term distribution kinetics of surfactant in piglets ventilated with CMV or HFJV, although this methodology does not give detailed, quantitative assessments of pulmonary deposition. In another study by Walther et al.,<sup>21</sup> major differences in the pulmonary distribution of carbon-14-labeled exogenous surfactant in premature lambs ventilated with high-frequency oscillatory ventilation were not demonstrated when compared to CMV. Additional animal experiments that further define alveolar inflation and deflation patterns and surfactant distribution in HFJV compared to CMV would be very helpful in interpreting the results of clinical studies in infants.

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