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Ventilatory Response to Combined High Frequency Jet Ventilation and Conventional Mechanical Ventilation for the Rescue Treatment of Severe Neonatal Lung Disease

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Summary. High frequency jet ventilation (HFJV) was used to treat 176 infants who were either failing to respond to conventional mechanical ventilation (CMV) or demonstrating pulmonary air leak. The median birthweight for infants treated with HFJV was 1530 g, median gestational age was 31 weeks. Median duration of therapy with HFJV was 3.0, with a range of 0.1 to 27 days. During the first 24 hours of treatment, mean airway pressure decreased from 16.2 ± 0.3 (Mean ± SEM) cmH_2O to 12.2 ± 0.3 cmH_2O, while mean Pa_{O_2} increased from 65.3 ± 3.0 torr to 93.3 ± 3.0 torr during the same time period. Simultaneously, mean Pa_{CO_2} decreased from 46.4 ± 1.5 torr to 36.6 ± 1.0 torr, although peak inflating pressure decreased from 34.3 ± 0.7 cmH_2O to 30.1 ± 0.8 cmH_2O. Ninety-five (54%) infants treated with HFJV survived. Of 123 infants with RDS 75 (61%) survived. The rate of complications for HFJV patients was similar to that seen with CMV in our nursery. This study suggests that HFJV provides improved oxygenation and ventilation of infants at lower mean and peak pressures compared to conventional mechanical ventilation. HFJV combined with CMV may be a valuable adjunct to therapy in infants with severe lung disease. **Pediatr Pulmonol 1989; 7:244–250.**

Key words: Mean airway pressure, peak inflation pressure Pa_{O_2}, Pa_{CO_2}, pH; survival, complications.

INTRODUCTION

The introduction of mechanical ventilation for the treatment of respiratory failure represents one of the major advances in newborn intensive care during the past two decades. Lung diseases which were previously fatal are often successfully treated with techniques such as continuous positive airway pressure (CPAP)[1] and positive pressure mechanical ventilation.[2] Unfortunately, these therapies have been accompanied by the emergence of problems that were not seen prior to the use of neonatal mechanical ventilation, particularly in the low birthweight infant. Pulmonary interstitial emphysema (PIE) and other air leak syndromes, as well as bronchopulmonary dysplasia (BPD), a chronic lung disease first described by Northway et al. in 1967,[3] have become commonplace complications of ventilatory therapy. These problems have been associated with significant long term morbidity and mortality in afflicted infants.[4]

Because the use of mechanical ventilation has been associated with these undesirable problems, alternative approaches to the management of severe lung disease in newborn infants have been advocated. High frequency ventilation (HFV), involving the use of respiratory rates above 150 breaths per minute, is one of the most interesting new therapeutic approaches. At the present time, two primary forms of high frequency ventilators[5] exist for use in neonates: high frequency oscillatory ventilation (HFOV), usually generated by a piston or a vibrating diaphragm that provides a continuous sine wave movement of gas within the airway, and flow interrupter/jet ventilators, which interrupt a positive pressure gas flow to the patient followed by passive expiratory relaxation of the lung.

The purpose of this paper is to report the experience with high frequency jet ventilation (HFJV) at the Children's Hospital of Philadelphia during the past 5 years. High frequency jet ventilation during this period of time has been primarily used in a rescue mode in conjunction with conventional mechanical ventilation (CMV) to treat respiratory failure in infants who either had severe pulmonary air leaks or who were no longer responsive to treatment with conventional mechanical ventilation. The present report examines the response to treatment with

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combined HFJV and CMV in infants with severe neonatal lung disease.

MATERIALS AND METHODS

All infants enrolled in this study were outborn patients who were transferred to the Infant Intensive Care Unit of The Children's Hospital of Philadelphia during the period of time from January 1983 to September 1987. Each child began ventilatory therapy with a trial of conventional mechanical ventilation (rates less than 150 breaths per minute). Infants were considered as candidates for high frequency jet ventilation under a protocol approved by the Institutional Review Board of The Children's Hospital of Philadelphia and an investigational device exemption approved by the Food and Drug Administration of the United States. Because of the experimental nature of this therapy, infants were not treated with high frequency jet ventilation until they were extremely ill, with high expectation of mortality or major morbidity on conventional ventilation. Informed parental consent was obtained in every instance prior to initiation of HFJV.

Indications for initiation of treatment with HFJV included the following: 1) premature infants with severe hyaline membrane disease that required peak inflating pressures above 30 cmH_2O and mean airway pressures (MAP) above 12 cmH_2O; 2) infants with air leak syndromes including progressive PIE, recurring pneumothorax and pneumopericardium; 3) infants with severe meconium aspiration syndrome and or persistent pulmonary hypertension of the newborn (PPHN), who continued to demonstrate respiratory failure with conventional mechanical ventilation at a peak inflating pressure greater than 35 cmH_2O with an $F_{I_{O_2}}$ of 1.0; 4) critically ill infants with congenital diaphragmatic hernia or pulmonary hypoplasia who failed to respond to conventional ventilatory support; and 5) infants with severe parenchymal lung disease such as Group B streptococcal pneumonia, requiring unacceptably high ventilator settings. At the time of initiation of therapy, 143/176 infants (81%) were receiving an inspired oxygen concentration of 1.0, reflecting the critical nature of their illness. All patients who did not require 100% inspired oxygen had either severe PIE or recurring pneumothoraces.

The starting settings for initiation of mechanical ventilation with the Life Pulse Ventilator (Bunnell Inc., Salt Lake City, UT) were derived from animal studies and empirical observations[6] made on infants requiring therapy. Ventilator frequency throughout the course of care was 420 breaths per minute. Early trials indicated this frequency to be optimal for this ventilator. Jet valve on-time (T_I) was always left at the shortest available setting, which was 0.02 seconds, and peak inflating pressure was initiated at variable pressures, based upon the infant's presentation and clinical condition. In general, peak inflating pressure was placed at 75–80% of the peak inflating pressure that the baby required while being treated with conventional mechanical ventilation. When high frequency ventilation was initiated, end-expiratory pressure was not changed from the level required during conventional ventilation. PIP, MAP, and PEEP were measured in the same manner both prior to and following initiation of HFJV. The Hi-Lo ET (Mallinckrodt Inc., St. Louis, MO) tube pressure-sensing port, which measures distal tracheal pressure, was used for this purpose in conjunction with the pressure transducer of the Bunnell ventilator.

In the first five infants who were treated with HFJV it was noted that atelectasis was a common occurrence if only high frequency ventilation was provided. As a result, the combined use of high frequency jet ventilation with background CMV became the routine approach with this therapy. For safety reasons, the jet ventilator cuts off gas flow if pressures exceeding the set peak inflating pressure on the ventilator are sensed for longer than 0.5 seconds. Since it was observed[6] that total interruption of the high frequency mode of therapy by a conventional ventilator breath resulted in an ineffectual mode of ventilation, infants were treated with background CMV with a setting of 5–10 breaths per minute at a minimum peak inflating pressure differential of 3–5 cmH_2O below that of the high frequency jet ventilator. The duration of conventional ventilator breaths was 0.5 seconds. This technique produced a waveform pattern in the airway that never resulted in interruption of the jet ventilation, but nonetheless provided a sigh breath that was superimposed on the high frequency breaths. This approach to ventilation resulted in decreased atelectasis, and improved carbon dioxide elimination and oxygenation.[6]

Infants were monitored continuously for both transcutaneous oxygen and carbon dioxide tension as well as by pulse oximetry. Once a period of stability for infants had been achieved, arterial blood gases were obtained. With the technique of HFJV, there appeared to be a greater interrelationship between Pa_{O_2} and Pa_{CO_2} than is usually seen with conventional mechanical ventilation. Pa_{CO_2} levels were kept at the highest level that provided adequate oxygenation ($Pa_{O_2} > 60$ torr) by adjusting PIP. For the majority of infants, a Pa_{CO_2} of 30–45 torr was required to maintain oxygenation. PIP was changed to achieve the desired Pa_{CO_2}. In several cases, adequate oxygenation could be obtained only when Pa_{CO_2} levels decreased to 25–30 torr. Ventilator changes that were made in such instances to raise Pa_{CO_2} often resulted in much poorer Pa_{O_2} levels. Pa_{O_2} was kept between 60–80 torr and arterial pH between 7.35–7.50. In some instances of severe persistent pulmonary hypertension, intentional hyperventilation was utilized with Pa_{CO_2} low-

TABLE 1—Characteristics of Infants Treated With HFJV (n = 176)

	Median	Range
Birthweight (g)	1,530	590–5,280
GA (wk)	31	24–43
Age at start HFJV (days)	1.8	0.2–90
Total time on HFJV (days)	3.0	0.1–27
Pre-HFJV time on CMV (days)	1.6	0.2–62
Post-HFJV time on CMV (days)	4.5	0–536

GA, gestational age; HFJV, high frequency jet ventilation; CMV, conventional mechanical ventilation.

ered to the highest level that allowed adequate oxygenation. Once infants began to show signs of improvement, weaning from jet ventilation was achieved primarily by decreasing F_{IO_2} as oxygenation improved and by decreasing PIP when Pa_{CO_2} decreased below the desired level. Infants were returned to conventional mechanical ventilation at an F_{IO_2} below 0.5 and peak inflating pressure below 15–25 cmH_2O. The rate of the jet ventilator was not varied during the course of any infant's care. Two infants were weaned directly to CPAP from HFJV.

Statistical analysis used to evaluate the clinical data included paired t testing, chi-square analysis, and an analysis of variance with repeated measures (ANOVA). The ANOVA used a parametric analysis, examined whether data samples taken sequentially over a period of time were statistically different or not.

RESULTS

Medians and ranges of characteristics describing infants enrolled in this study are presented in Table 1. These 176 infants represent 10.5% of all infants (N = 1,680) ventilated at The Children's Hospital of Philadelphia during this time period. The age at which HFJV was begun as well as total time on HFJV, time prior to HFJV on CMV, and time on CMV post HFJV are also noted in Table 1. Primary diagnoses of the 176 infants treated in this study were: respiratory distress syndrome (RDS) (131), persistent pulmonary hypertension of the newborn (23), Group B sepsis pneumonia (11), congenital diaphragmatic hernia (8), pulmonary hypoplasia (2), and BPD (1). In addition, 95 of the 176 infants (54%) had either PIE or a tension pneumothorax prior to initiation of HFJV. Among the 95 patients with pulmonary air leaks, 76 had hyaline membrane disease. Twenty-four (25%) either had persistence of air leak or died with continued air leak while on HFJV. Only two infants (1%) who had a tension pneumothorax developed it after initiation of HFJV; in the rest it was present prior this therapy.

The responses of all infants treated with HFJV can be seen in Figures 1 and 2, which illustrate changes in ventilatory support and changes in blood gases. F_{IO_2} decreased within the first 6 hours on HFJV therapy, from a mean of 0.96 to a mean of 0.91 ($P<0.001$) during the

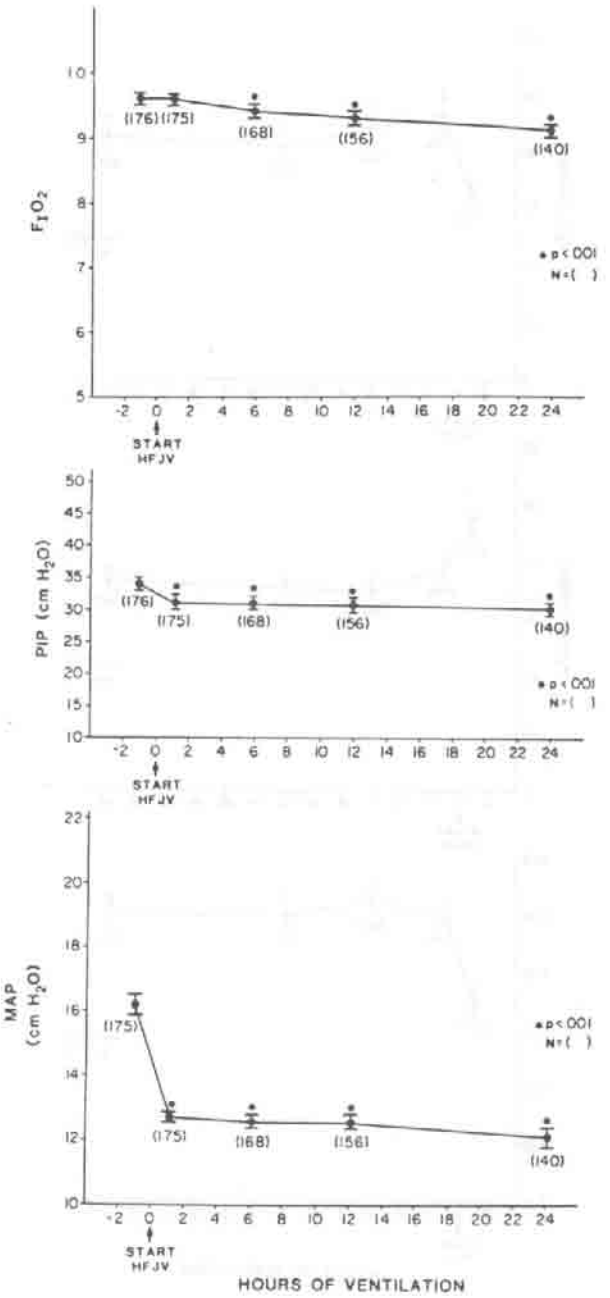

Fig. 1. Changes in F_{IO_2}, PIP, and MAP immediately prior to the initiation of HFJV/CMV therapy and for the first 24 hours following treatment. *P* values compare values following initiation of HFJV to pre-HFJV ventilatory support. Vertical bars indicate SEM. Numbers in parentheses indicate patients with measurements at those times. F_{IO_2}, fractional concentration of inspired oxygen; PIP, peak inflating pressure; MAP, mean airway pressure; HFJV, high frequency jet ventilation; CMV, conventional mechanical ventilation.

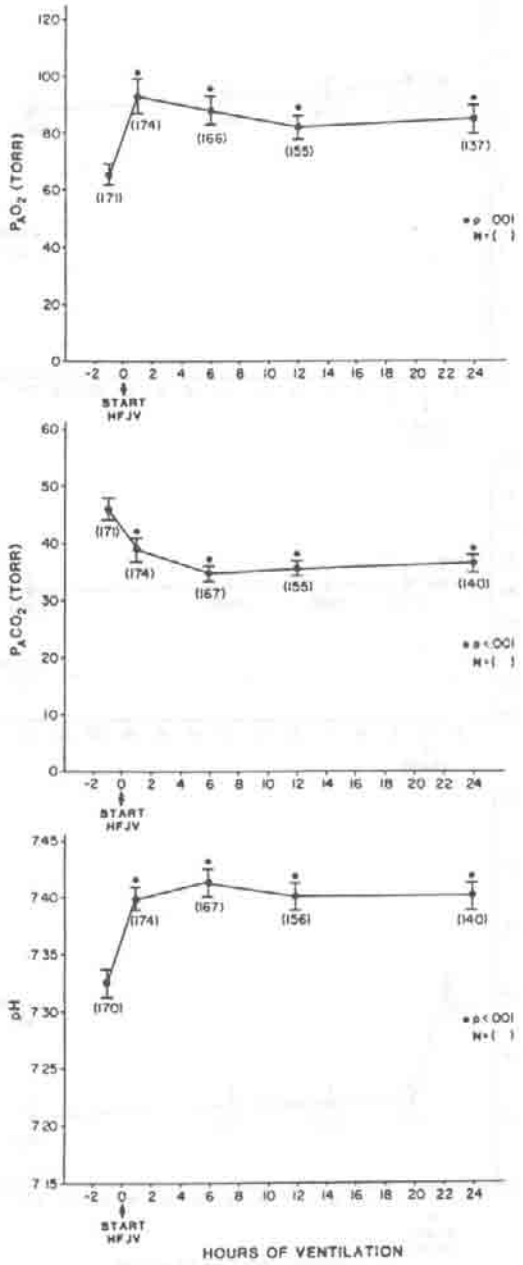

Fig. 2. Changes in Pa_{O_2}, Pa_{CO_2}, and pH immediately prior to the initiation of HFJV/CMV therapy and for the first 24 hours following treatment. *P* values compare values following initiation of HFJV to pre-HFJV ventilatory support. Vertical bars indicate SEM. Numbers in parentheses indicate number of patients with measurements at those times. HFJV, high frequency jet ventilation; CMV, conventional mechanical ventilation.

first 24 hours. Peak inflating pressure decreased from a mean of 34.3 ± 0.7 cmH_2O to a 30.1 ± 0.8 cmH_2O ($P<0.001$), a decrease of 12.5%. Mean airway pressure decreased from 16.2 ± 0.3 cmH_2O to 12.2 ± 0.3 cmH_2O ($P<0.001$), a decrease of 24.7%. Mean arterial Pa_{O_2} improved from 65.3 ± 3.0 torr to a 93.3 ± 3.0 torr ($P<0.001$) 1 hour after initiation of therapy and averaged 22 torr higher following 24 hours of treatment. The most dramatic response to treatment was seen as Pa_{CO_2} decreased from a pre-HFJV level of 46.4 ± 1.5 torr to 36.6 ± 1.0 torr ($P<0.001$) following 24 hours of treatment. As expected, mean pH increased from 7.33 ± 0.01 prior to treatment, to 7.40 ± 0.01 ($P<0.001$) after 24 hours. The significant improvements in ventilator settings and blood gases are similar if one compares the 157 infants who survived longer than 6 hours and the total group of 176 infants.

The findings in infants with RDS, which comprised the largest number of infants treated with HFJV, was examined by ANOVA to determine if trends in repeated measures could distinguish survivors from non-survivors over the course of the first 24 hours of treatment. Results of this analysis are presented in Figures 3 and 4. The response of the RDS group was similar to the overall group of infants regarding changes in inspired oxygen concentration, peak and mean airway pressures, and blood gas values. There were statistically significant differences between survivors vs. non-survivors during the first 24 hours of treatment with HFJV. Improvement in F_{IO_2} ($P = 0.03$) and PIP ($P = 0.007$) was significantly greater in the survivors compared to the non-survivors. MAP decreased in both groups at the initiation of HFJV and continued to decrease in the survivors as compared to the infants who subsequently died. Because of the similarity in change during the early part of therapy, this trend analysis could not demonstrate statistical significance. Pa_{O_2} increased substantially more ($P = 0.002$) in the group of survivors than did pH ($P = 0.05$). Pa_{CO_2} showed a significant improvement ($P = 0.05$) in survivors compared to nonsurvivors.

The results of this study indicate that 95 of the 176 infants (54%) referred to The Children's Hospital of Philadelphia survived with HFJV treatment. Survival by diagnosis is seen in Table 2. It should be noted, however, that 15 of the 176 infants transported to this hospital arrived in a severely moribund condition (pH≤6.9) and survived for less than 6 hours. In addition, four infants who survived treatment with HFJV received it for less than 6 hours duration. These four infants were removed from the high frequency ventilator because of mechanical difficulties involving humidification of the ventilator unit. For the 157 infants who were treated for longer than 6 hours by HFJV, 91 (58%) survived and 66 (42%) died. Survival in these 157 infants, by diagnosis, is seen in Table 3. Table 4 demonstrates survival of the same infants by birthweights.

Table 5 demonstrates the effect of initial PIP on subsequent survival. The higher was the PIP on CMV prior to initiation of HFJV, the less the chances for survival once HFJV was initiated. Complications from this form of mechanical ventilation as shown in Table 6 were relatively low given the degree of illness at the time of

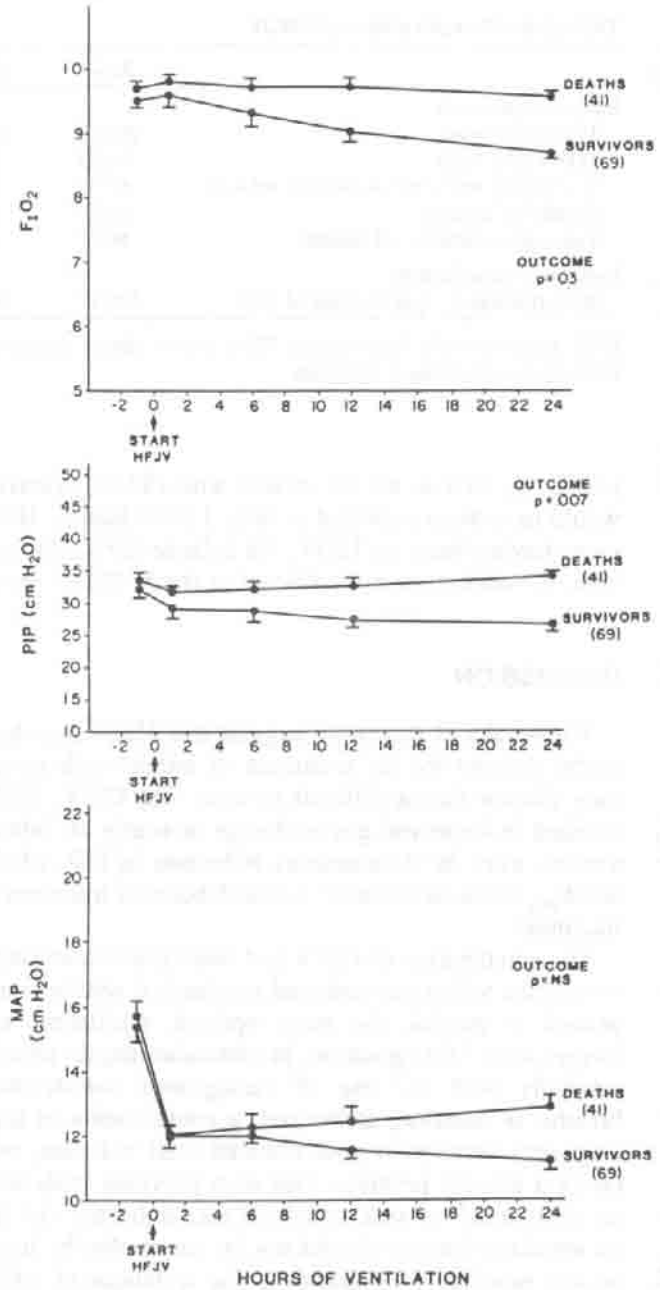

Fig. 3. Comparison of survivors and non-survivors with RDS treated with HFJV/CMV therapy immediately prior to and for the first 24 hours following treatment demonstrating changes in F_{IO_2}, PIP, and MAP. Vertical bars indicate SEM. *P* values indicate ANOVA analysis of curves comparing the two groups. F_{IO_2}, fractional concentration of inspired oxygen; PIP, peak inflating pressure; MAP, mean airway pressure; HFJV, High frequency jet ventilation; CMV, Conventional mechanical ventilation.

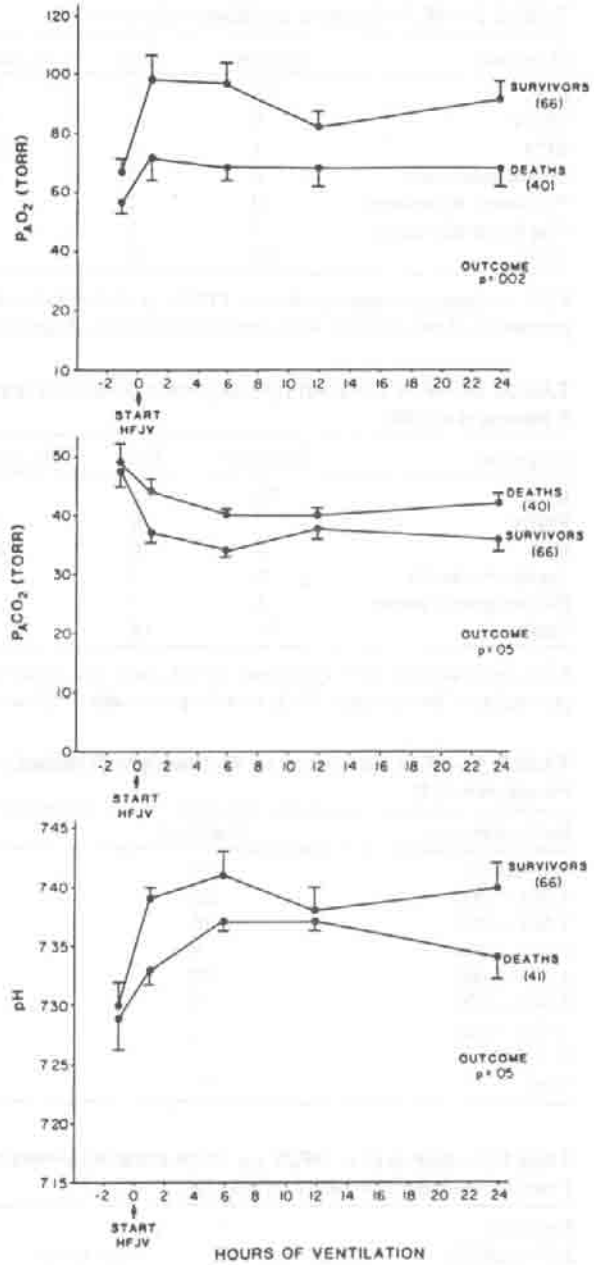

Fig. 4. Comparison of survivors and non-survivors with RDS treated with HFJV/CMV therapy immediately prior to and for the first 24 hours following treatment demonstrating changes in Pa_{O_2}, Pa_{CO_2}, and pH. Vertical bars indicate SEM. *P* values indicate ANOVA analysis of curves comparing the two groups. HFJV, high frequency jet ventilation; CMV, conventional mechanical ventilation.

transfer of these infants to our nursery. Necrotizing tracheobronchitis, a significant concern during treatment, occurred in only six infants. It was diagnosed clinically by cessation of chest movement and emergency bronchoscopy. Bronchoscopy was also performed in any infant who demonstrated increased secretions and hemorrhagic or other changes of secretions in appearance, but not routinely on all babies.

The severity of the lung disease and the effect of HFJV upon survival in infants enrolled in this study can be ascertained from the following findings. Of 96 infants with RDS who presented with a $P_{(A-a)}O_2$ greater than 600

TABLE 2—HFJV Survival by Diagnosis (n = 176)

Diagnosis	Survived	Died	(% survivors)
RDS	76	55	58
PPHN	9	14	39
BPD	1	0	100
Sepsis/pneumonia	6	5	55
Pulmonary hypoplasia	0	2	0
Diaphragmatic hernia	3	5	38
Total	95	79	

RDS, respiratory distress syndrome; PPHN, persistent pulmonary hypertension of the neonate; BPD, bronchopulmonary dysplasia.

TABLE 3—HFJV Survival by Diagnosis (Infants Treated > 6 hours; n = 157)

Diagnosis	Survived	Died	(% survivors)
RDS	75	48	61
PPHN	7	9	44
BPD	1	0	100
Sepsis/pneumonia	5	5	50
Diaphragmatic hernia	3	4	43
Total	91	66	

RDS, respiratory distress syndrome; PPHN, persistent pulmonary hypertension of the neonate; BPD, bronchopulmonary dysplasia.

TABLE 4—HFJV Survivors by Birthweight (Treated > 6 hours; n = 157)

Birthweight (g)	Survived	Died
500–1,000	14	27
1,001–1,500	20	13
1,501–2,000	16	8
2,001–2,500	9	4
2,501–3,000	12	6
3,001–3,500	7	5
3,501–4,000	11	0
> 4,000	2	3
Total	91	66

TABLE 5—Survival of HFJV by Peak Inflating Pressures Prior to Initiation of HFJV (n = 157)

Pre-HFJV PIP (cmH_2O)	Total	%	Survivors	%
25–30	13	8	9	70
30–34	41	26	33	80
35–40	37	24	22	60
41–50	52	33	23	44
>50	14	9	4	29

HFJV, high frequency jet ventilation; PIP, peak inflating pressure.

torr, and with either a pulmonary air leak or PIP above 30 cmH_2O, 57 (59%) survived.

In infants with pulmonary hypertension, the scoring system described by Davis et al.,[7] devised at this institution, was used to evaluate the effectiveness of HFJV. Of the 38 infants with pulmonary hypertension (this number includes 5 with pneumonia/sepsis, 2 with pulmonary hypoplasia, and 8 with congenital diaphragmatic hernia, as well as the 23 infants with PPHN), survival would have been expected in only 3 (8%) babies. However, having been on HFJV, 15 infants (39%) did survive; the difference is significant at the $P<0.001$ level.

TABLE 6—Complications of HFJV

	Ratio	(%)
Early complications		
IVH (RDS only)	29/123	(24)
PDA (RDS only)	9/123	(7)
Necrotizing tracheobronchitis (all infants)	6/157	(4)
Sepsis (all infants)	5/157	(3)
Pneumopericardium (all infants)	5/157	(3)
Long term complications		
BPD (Increased O_2 at 28 days of life)	52/117	(44)

IVH, intraventricular hemorrhage; PDA, patent ductus arteriosus; BPD, bronchopulmonary dysplasia.

DISCUSSION

The results of this study suggest that HFJV may be a useful therapy for the treatment of infants with severe lung disease that is difficult to treat with CMV. HFJV resulted in improved gas exchange in nearly all infants treated, even as simultaneous reduction in PIP, MAP, and F_{IO_2} could be achieved within 6 hours of initiation of treatment.

The combination of HFJV and intermittent mandatory ventilation with a conventional mechanical ventilator appeared to provide the most optimal ventilation and oxygenation.[6] Oxygenation, in particular, improved substantially with the use of background conventional breaths; in addition, atelectasis, a complication of high frequency ventilation with reduced tidal volumes, was rarely a clinical problem. Our own previous trials with jet ventilation[6] as well as animal data indicated that the jet ventilator breaths should not be interrupted by intermittent mandatory inspirations. The technique of utilizing a PIP on the conventional ventilator that was 3–5 cmH_2O pressure below the PIP on the jet ventilator was most optimal for the large majority of infants that were treated. This technique resulted in the superimposition of a sigh on continuous HFJV, preventing atelectasis and increasing oxygenation.

The acute complication rate for this new combined form of mechanical ventilation appears to be acceptable when compared to conventional mechanical ventilation. Follow-up of surviving infants to date has not indicated any long term untoward effects.[8] Intraventricular hemorrhage did not appear to increase with this approach.[9] Unlike previous reports,[10] infants treated at our institution did not experience necrotizing tracheobronchitis to a significant degree. BPD (defined by oxygen dependency

at 28 days of age) was common, occurring in 44% of infants treated. It is difficult to determine, however, if chronic lung disease resulted from earlier treatment with CMV from treatment by HFJV, or from the severity of the underlying disease. Recent data from the National Collaborative Study on High Frequency Oscillatory Ventilation[11] suggest that the incidence of BPD in infants treated with either CMV or high frequency oscillatory ventilation initiated near the time of birth is approximately 40% in babies less than 2,000 g. Thus, the incidence of BPD in our study did not vary significantly from that reported by the National Collaborative Study for either form of ventilation. Other complications did not seem to occur with any greater frequency than that seen with CMV.

A combination of HFJV with CMV ventilation appears to be a useful approach to the treatment of severe lung disease in the neonate. Infants who are no longer responding to CMV may improve with HFJV when used selectively and appropriately. Further investigation into this form of therapy is justified, and expansion of our knowledge with regard to the mechanisms by which high frequency ventilation provides improved exchange of gases may be of great significance.

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