Ventilatory Management of Infant Baboons with Hyaline Membrane Disease: The Use of High Frequency Ventilation¹

R. A. DELEMONS, J. J. COALSON, D. R. GERSTMANN, D. M. NULL, JR., N. B. ACKERMAN,
M. B. ESCOBEDO, J. L. ROBOTHAM, AND T. J. KUEHL

Department of Physiology and Medicine, Southwest Foundation for Biomedical Research; Department of Pathology and Pediatrics, University of Texas Health Science Center; Department of Pediatrics, Wilford Hall USAF Medical Center, San Antonio, Texas

ABSTRACT. We tested the hypothesis that high frequency oscillatory ventilation (HFOV) would result in decreased pulmonary barotrauma in infants with hyaline membrane disease by comparing HFOV at 10 Hz to conventional positive pressure ventilation with continual distending airway pressure (PPV/PEEP) in premature baboons with hyaline membrane disease. Nineteen baboon fetuses were randomized to one of two treatment groups, delivered at 140 ± 2 days, and, after stabilization and instrumentation of PPV/PEEP, placed in their respective ventilator group. Animals on conventional ventilation were managed by adjustment of tidal volume and frequency (to 1 Hz) to keep PaCO_2 below 55 and by adjustment of the mean airway pressure. One of the "HFOV" group died of cardiovascular complications before going on HFOV and was eliminated from data analysis. The remaining HFOV baboons survived the 11-day experimental period without evidence of airleak. Six of the 11 prematures treated with PPV/PEEP developed pulmonary interstitial emphysema and/or pneumothorax and five of the animals died within 48 h. The intergroup differences in airleak were significant ($p < 0.05$). Mean airway pressure (measured at the proximal airway) was higher initially with HFOV but then was lowered more rapidly than in the PPV/PEEP animals. The arterial to alveolar oxygen ratio rose and the FIO_2 could be lowered more rapidly with HFOV than with conventional ventilation. These differences reached significance by 20 h. After 60 h there were no significant differences between HFOV and the PPV/PEEP survivors. HFOV resulted in more uniform saccular expansion, higher arterial to alveolar oxygen ratio, less oxygen exposure, and decreased acute barotrauma when compared to PPV/PEEP. Although initially mean airway pressure was in the HFOV animals this was not associated with measurable baroinjury. These data support the efficacy of HFOV in the treatment of prematures with hyaline membrane disease. (*Pediatr Res* 21: 594-602, 1987)

Abbreviations

PPV/PEEP, positive pressure ventilation with continual distending airway pressure

HFOV, high frequency oscillatory ventilation
 $\bar{P}_{aw}$, mean airway pressure
HMD, hyaline membrane disease
 Pa/A O_2 , arterial to alveolar oxygen ratio
HFV, high frequency, low volume ventilation
 FawO_2 ,
 FawCO_2 ,
I:E, inspiratory:expiratory ratio
ANOVA, analysis of variance
PIE, pulmonary interstitial emphysema

HFV has been proposed as an alternative to conventional PPV/PEEP in the management of infants with HMD (1-4). Interest in this technique has been generated by the observation that, with an appropriate strategy, HFV can accomplish gas exchange at lower intrapulmonary intraluminal distending pressures, thus potentially reducing the risk of baroinjury (5-8).

The mechanisms of lung injury in infants with HMD are incompletely understood. Although most investigators believe that pulmonary immaturity, baroinjury, oxygen toxicity, and infection play a role in the pathogenesis of bronchopulmonary dysplasia, there is no general agreement about the relative importance of each factor (9-13). The premature baboon, delivered at 140 days gestation, develops HMD clinically, pathologically, and biochemically similar to that in man. When treated with positive pressure ventilation and exposed to 100% oxygen for periods from 8-14 days, these animals develop bronchopulmonary dysplasia (14, 15). Because of its reproducibility and homogeneity this model offers the opportunity to explore potential therapeutic interventions directly in the premature and to assess both physiologic and pathologic endpoints. The purpose of these studies was to compare HFOV to PPV/PEEP in the management of premature baboons with HMD. We hypothesized that HFOV would result in diminished barotrauma and by so doing might substantially alter the short-term and long-term course of this disease.

MATERIALS AND METHODS

Nineteen premature baboons were delivered by hysterotomy at 140 ± 2 days gestation. After timed pregnancy had been confirmed by ultrasound, the unborn fetuses were assigned, using a system of random numbers, to a specific ventilator treatment group. After delivery, all animals (regardless of assignment) were intubated with a 2.5-mm endotracheal tube and placed on a time-cycled, pressure limited neonatal ventilator (Bear Cub, Bournes Inc., Riverside, CA). An umbilical artery catheter with a continually recording PO_2 electrode (Invivox catheter, Critikon,

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Correspondence R. A. deLemos, M.D., Southwestern Foundation for Biomedical Research, Department of Physiology and Medicine, P.O. Box 28147, San Antonio, TX 78284.

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Tampa, FL) was inserted and positioned above the diaphragm. Baseline studies were performed as previously described (11).

During the instrumentation period, the ventilator was then adjusted according to the following protocol: PaO_2 was maintained between 50 and 80 torr by adjustment of the level of PEEP and inspiratory pressure at a fixed inspiratory duration (0.5–0.6 s) and/or by adjustment of the FIO_2 . All animals were initially started on 4 cm H_2O PEEP. Initially the strategy was to raise the $\bar{P}_{\text{aw}}$ until a rapid increase in PaO_2 was observed on the continually recording O_2 electrode. Subsequent decisions as whether to alter FIO_2 and $\bar{P}_{\text{aw}}$ were in general made with the experimental goal of reducing the FIO_2 below 0.8 as soon as possible. PaCO_2 (measured by intermittent arterial sampling) was kept between 35 and 55 torr by adjustment of the ventilator frequency (up to 60 breaths per min) or inspiratory pressure. If oxygenation was adequate, the PaCO_2 above 55 torr, and the maximum frequency had not been reached, frequency was adjusted preferentially. If these changes did not result in a PaCO_2 within the protocol guidelines, inspiratory pressure was increased.

Airway pressure was measured at the proximal airway using a Validyne pressure transducer (model DP 45, Validyne, Northridge, CA) with linear calibration to 40 Hz. Airway pressure, blood pressure, FawO_2 and FawCO_2 were continually recorded. A central venous catheter was inserted into the internal jugular vein for fluid administration. After all procedures had been completed, a set of blood gases and a chest radiograph were obtained and the animal was placed on the ventilator appropriate to the group to which they had been randomized.

A fixed frequency of 10 Hz was used during HFOV. The initial $\bar{P}_{\text{aw}}$ was determined by that used at the end of the instrumentation period. Thereafter oxygenation was optimized by adjustment of the $\bar{P}_{\text{aw}}$ and/or FIO_2 with the goal being to maximize the Pa/A O_2 ratio. PaCO_2 was kept within the range of 35 to 55 torr by adjustment of the delivered tidal volume. HFOV was provided using a piston oscillator powered by a linear motor (model SS-1, Texas Research Co., San Antonio, TX). This device can deliver a frequency between 1 and 50 Hz and has a variable I:E ratio. An I:E ratio of 1:2 was used in these studies. All HFOV baboons were sighed using the time cycled ventilator for 1 min of each hour at 30 breaths per min. The pressures initially utilized were those used at the end of the instrumentation period. As the mean airway pressure subsequently could be reduced, the $\bar{P}_{\text{aw}}$ during the sigh period was reduced an equivalent amount.

Ventilator management of the PPV/PEEP animals continued as it had in the instrumentation period. Since, in general, animals whose PaCO_2 exceeded 55 torr also had a low Pa/A O_2 , inspiratory pressure (rather than ventilator frequency) was initially increased to improve ventilation. Frequency was preferentially altered (to a maximum of 60/min) when the PaCO_2 exceeded protocol guidelines while oxygenation was adequate or when it was believed that an increase in inspiratory pressure would be deleterious.

Animals were paralyzed with pancuronium bromide and sedated with ketamine hydrochloride throughout the first 48 h of the experiment. They then were allowed to breathe spontaneously. Sedation with ketamine and local anesthesia were administered for any invasive procedures.

Weaning was attempted after 48 h by decreasing the ventilatory rate and pressure in the PPV/PEEP animals and by decreasing $\bar{P}_{\text{aw}}$ and tidal volume during HFOV. Extubation was attempted if an animal had a PCO_2 less than 50 torr and a PaO_2 greater than 50 torr in FIO_2 0.5. Animals were then kept on supplemental oxygen until they could maintain a PaO_2 over 50 torr in room air or until sacrifice.

All baboons were initially begun on an intravenous solution of 5% dextrose with 500 mg of calcium gluconate per 250 ml and 2 U sodium heparin per ml at a rate of 150–200 ml/kg/day. NaCl and KCl were added as indicated by measurement of serum electrolytes. After 48 h animals received total parenteral nutrition

from a solution of amino acids, glucose, electrolytes, vitamins, and trace minerals calculated to deliver 2.25 g amino acids and 82 kcal/kg/day by the end of the 1st wk.

Arterial blood gases were measured hourly for the first 24 h, every 2 h between 24 and 48 h, every 4 h from 48 to 96 h, and every 8 h after 96 h until the animal was sacrificed. Serum electrolytes, blood urea nitrogen, and creatinine were measured daily. Dextrostix, urine specific gravity, and urine glucose were measured every 4 h. Hematocrit was determined every 4 h during the first 24 h and every 8 h thereafter. Blood was replaced volumetrically with either fresh citrate phosphate dextrose or heparinized blood from adult donors. Chest radiographs were obtained at 1, 2, 6, 12, 18, 24, 36, 48, 60, 72, and 96 h and daily thereafter. These were read by two observers without knowledge of the treatment group. Single shot angiograms were preformed at 1 h and as indicated thereafter by clinical signs of patent ductus arteriosus or by presence of retrograde flow in the femoral artery by continual wave Doppler ultrasound.

All animals were treated with ampicillin (200 mg/kg/day) and gentamycin (5 mg/kg/day) for the duration of the experiments.

Based on our previous data (14, 15), pathologic changes of bronchopulmonary dysplasia appear within 8–10 days of treatment with positive pressure ventilation and hyperoxia. We therefore chose 11 days as the endpoint in these studies. However, since pathologic endpoints were a critical factor in our study design, the level of supportive care in the event of catastrophic deterioration was limited. If, prior to the completion of the designated study period, an animal in either group developed cardiopulmonary complications which could not be reversed by simple resuscitative maneuvers as defined in the protocol, the experiment was terminated. Animals were sacrificed by an overdose of anesthesia.

Pathologic methods. Lung fixation consisted of perfusion of quarter-strength Karnovsky's fixative through the pulmonary vascular system, while maintaining lung inflation at a constant transpulmonary pressure of 20 cm H_2O (16). After opening the thorax and examining the lungs grossly, the ductus arteriosus was located and tied off. The right ventricle was opened and a catheter placed in the main pulmonary artery and secured. The left auricle was opened to allow the perfusate to escape. The lungs were slowly inflated using 20 cm H_2O pressure and the trachea was then cross-clamped. Lungs were flushed of blood with an iso-osmotic/iso-oncotic Hanks' balanced salt solution for approximately 1 min at 30–40 mm Hg perfusion pressure, followed immediately by the infusion of Karnovsky's fixative for a minimum of 20 min. After the perfusion, the entire heart-lung preparation was removed *en bloc* from the chest and floated in additional fixative until the lungs were cut and embedded for light and electron microscopy studies 24 h later. All other organs were examined and fixed for microscopic study. Necropsy was performed at the time of sacrifice or within 30 min of death.

Statistical methods. Physiologic data collected on each animal every hour during the first 20 h was analyzed by ventilator group and by survivors using analysis of variance for repeated measures. The 20-h time point was chosen as the endpoint for this analysis because the first death in the PPV/PEEP group occurred at 21 h and all data sets were complete prior to this point. For FIO_2 and Pa/A O_2 , linear regression analysis of the data during the instrumentation period and for the first 3 h after assignment to a specific ventilator yielded slopes for each animal which were compared between groups by unpaired *t* test.

Longitudinal data, including only surviving animals, was compiled using the physiologic data collected every hour during the first 24 h and every 2 h from this point until death or completion of the experiment. These data were averaged over 6- and 8-h intervals, respectively. If more than 50% of the data points were missing for any interval, the interval calculation was considered a missing value for each animal. Interval means were pooled by group at each time point for statistical analysis. Analysis of variance of repeated measures was used to determine the signif-

ificance of intergroup differences in the longitudinal data. Group means at specific time points were also compared by unpaired *t* test.

Specific clinical endpoints (airleak, mortality) were compared among groups using either Fisher's exact test or the variable χ^2

Table 1. FIO_2 , peak airway pressure, mean airway pressure, PaO_2 , $PaCO_2$, and $Pa/A O_2$ in PPV/PEEP and HFOV baboons at end of instrumentation period (mean $\pm$ SE)

	PPV/PEEP	HFOV	
<i>n</i>	11	7	
FIO_2	0.68 ± 0.04	0.65 ± 0.05	NS
P peak (cm H ₂ O)	32.6 ± 1.3	30.3 ± 1.0	NS
$\bar{P}aw$ (cm H ₂ O)	14.3 ± 0.9	14.6 ± 0.8	NS
PaO_2 (torr)	104.5 ± 13.9	107.4 ± 20.1	NS
$PaCO_2$ (torr)	35.5 ± 2.9	31.1 ± 3.0	NS
$Pa/A O_2$	0.27 ± 0.05	0.27 ± 0.04	NS

Fig. 1. FIO_2 , $\bar{P}aw$, $Pa/A O_2$ (mean $\pm$ SE) by ventilator group over the first 20 experimental h. Note that the $\bar{P}aw$ was higher early in the HFOV animals. There was a significant intergroup difference in FIO_2 and $Pa/A O_2$ by the end of this period.

Fig. 2. pHa , $PaCO_2$, and mean blood pressure (measured in the abdominal aorta) over the first 20 h. Despite high peak distending pressures in the PPV/PEEP baboons $PaCO_2$ remained higher in this group throughout this period. Air leaks were first detected at 21 h in the PPV/PEEP animals. The fall in mean blood pressure in both groups coincided with evidence for left to right shunting through a ductus arteriosus.

with the Yates' correction for small numbers. All tests were considered significant for $p < 0.05$.

A panel of standards was derived from the study animals and represented the spectrum of changes from the most normal or mild to the most severe abnormal change. Five panels, representing grade 1–grade 5, mild to severe, respectively, were chosen. A Zeiss photomicroscope fitted with a $1\times$ objective was used to photograph the entire cross-section of a lobe or an area most representative of a given lobe of all five lobes of each animal in the study. The 35 mm negatives were photographically enlarged to yield 8×10 black and white photographs. Each photograph was graded independently by three different observers using the panel of standards. This method has been described previously (17, 18). Agreement between observers was measured by the Chronbach's α test. The *t* test was used to test for any ventilator

effect among groups. The mean of the raters' scores was calculated and the lobe scores were summed for each animal.

RESULTS

One of the baboons assigned to the HFOV group died with cardiovascular complications during the instrumentation period. Since it was never actually placed on the oscillator, data from this animal have been excluded from analysis.

Mean birth weight was 533 ± 27 g in the PPV/PEEP and 575 ± 26 g in the HFOV animals. The instrumentation period lasted between 1.8 and 2.6 h (mean 2.3 h). There were no significant differences in FIO_2 , peak airway pressure, mean airway pressure, PaO_2 , PaCO_2 , or Pa/A O_2 between the two groups of animals prior to placement on their designated ventilators at the end of the instrumentation period (Table 1).

Fig. 3. FIO_2 , $\bar{P}_{aw}$, and Pa/A O_2 (mean $\pm$ SD) for all surviving animals. The open circle represents the end of the instrumentation period and the first data is plotted at the midpoint of the first averaged interval. Note that at 42 h significant recovery occurred in both ventilator groups. After 60 h there were no significant differences among survivors.

Fig. 4. PaO_2 and PaCO_2 (mean $\pm$ SD) among survivors.

Mean airway pressure (measured at the proximal airway) was initially higher with HFOV but stabilized after 8 h at a slightly lower level (Fig. 1). In contrast, PPV/PEEP-treated prematures started at lower mean pressures but required an increase in $\bar{P}_{aw}$ between 4 and 10 h to maintain their PaO_2 in the desired range. Between 10 and 60 h there was a consistent trend towards higher mean airway pressures in the surviving PPV/PEEP as compared to the HFOV animals. These intergroup differences did not reach statistical significance. Peak airway pressures for the PPV/PEEP group had to be increased from 32 to 39 cm H_2O between 4 and 10 h in order to keep the PaCO_2 below 55 torr. The requirement for increased mean and peak airway pressures in this time frame occurred in all but one of the animals on conventional ventilation. After 24 h of age there was a progressive decrease in the requirement for peak airway pressure in the surviving PPV/PEEP baboons.

FIO_2 remained high in the PPV/PEEP animals and could be lowered only from 0.68 to 0.65 over the first 20 h. In contrast, there was a significant decrease in FIO_2 within 3 h of institution of HFOV with an overall decrease from 0.65 to 0.38 by 20 h. Both the differences in slope and in FIO_2 by 20 h were statistically significant ($p < 0.05$). There were no intergroup ventilator-associated differences in PaO_2 during this period (Fig. 2). The Pa/A O_2 of the conventionally ventilated baboons remained essentially unchanged over the first 20 h (Fig. 1). Within 3 h of initiating HFOV, there was a significant increase in Pa/A O_2 in these animals compared with controls. Pa/A O_2 continued to improve in this group, with the intergroup difference by ANOVA reaching significance by 20 h.

Between 42 and 60 h, there was marked improvement in oxygenation and a concurrent reduction in mean airway pressure in the surviving PPV/PEEP animals (Fig. 3). This was manifested by a significant rise in Pa/A O_2 and fall in FIO_2 and $\bar{P}_{aw}$ over time. There were similar trends in the HFOV animals but, because at 42 h they already had significantly lower Pa/A O_2 and FIO_2 , only the decrease in $\bar{P}_{aw}$ after 42 h reached statistical significance compared with the previous time interval. After 48 h, there were no significant intergroup differences (by ANOVA or t test) in FIO_2 , Pa/A O_2 , PaCO_2 , or $\bar{P}_{aw}$ between the HFOV and the surviving PPV/PEEP prematures (Figs. 3 and 4). All of

the animals surviving over 46 h were extubated prior to sacrifice at 11 days.

Five of the 11 baboons treated with positive pressure ventilation developed massive air leak and died between 21 and 46 h (Table 2). Although in each animal death resulted from cardiopulmonary failure, radiographic and clinical evidence of PIE/pneumothorax preceded that of hypotension and shock, and cardiovascular collapse appeared to be related to unsuccessful attempts to maintain satisfactory ventilation at high ventilation pressures. At necropsy their lungs showed hyaline membrane disease, poor saccular aeration, airway dilatation, pulmonary interstitial emphysema and pseudocyst formation (Fig. 5 *A* and *B*). The remaining animals in the PPV/PEEP group survived the entire experimental period. Those that ultimately survived had a strong trend toward higher Pa/A O₂ and lower FIO₂ after 10 h of age (Fig. 6) than did those who later died with air leak. These intragroup differences were apparent well before any of the animals developed radiographic evidence of PIE or pneumothorax. There were, however, no significant differences in mean or peak airway pressures between subsets prior to the recognition of radiographic changes.

One of the 11-day PPV/PEEP survivors was found to have pseudocysts at necropsy. The overall difference in the incidence of air leak between the two ventilator groups was significant (p

< 0.05). The five remaining surviving animals in this group had no evidence of airway disruption or bronchopulmonary dysplasia. Varying degrees of focal atelectasis were present. Bronchoalveolar hemorrhages were seen in two of the PPV/PEEP baboons at 11 days. All seven HFOV animals survived the 11-day experimental period. None had evidence of BPD at necropsy (Fig. 7). Bronchoalveolar hemorrhages were found in three of the seven HFOV animals.

Analysis of data derived from the panel of standards grading method revealed a high degree of interobserver reliability with $\alpha = 0.9732$. There were no significant differences in lung inflation pattern among lobes or between ventilator groups when comparing those animals surviving the entire experimental period.

DISCUSSION

In these studies premature baboons with HMD treated with HFOV had a significant decrease in acute baroinjury resulting in increased survival compared with those treated with PPV/PEEP. This appeared to correlate with more uniform lung inflation in the first 24 h. The differences in saccular expansion resulted, directly or indirectly, in higher Pa/A O₂ and lower oxygen exposure in the HFOV animals. Although initially higher, mean airway pressures could be reduced more rapidly during

Table 2. *Pathologic findings*

Animal	Ventilator	Survived (h)	Cause of death	Pathology
Q83	PPV/PEEP	264	Sacrificed	Mild pneumonia; focal hemorrhage; atelectasis
Y83	PPV/PEEP	264	Sacrificed	Pseudocysts; mild pneumonia; focal hemorrhage; atelectasis
F84	PPV/PEEP	23	Pneumothorax	PIE; pseudocysts; HMD; atelectasis
J84	PPV/PEEP	264	Sacrificed	ba hemorrhage; focal atelectasis
D85	PPV/PEEP	21	Pneumothorax	HMD; atelectasis; focal hemorrhage
F85	PPV/PEEP	264	Sacrificed	Atelectasis RUL, LLL due to mucous plugs; mild pneumonia
L85	PPV/PEEP	39	PIE	HMD; atelectasis; PIE; pseudocysts; bronchoalveolar hemorrhage
Q85	PPV/PEEP	32	PIE	HMD; atelectasis, PIE; bronchoalveolar hemorrhage
R85	PPV/PEEP	264	Sacrificed	Mild pneumonia
X85	PPV/PEEP	46	PIE	HMD; atelectasis; PIE; pseudocysts; bronchoalveolar hemorrhage
CC85	PPV/PEEP	264	Sacrificed	Focal atelectasis due to mucous plugs
S83	HFOV	264	Sacrificed	Focal atelectasis due to mucous plugs; bronchoalveolar hemorrhage
B84	HFOV	264	Sacrificed	Bronchoalveolar hemorrhage; focal atelectasis
D84	HFOV	264	Sacrificed	Bronchoalveolar hemorrhage
C85	HFOV	264	Sacrificed	Normal
G85	HFOV	264	Sacrificed	Focal atelectasis RUL
K85	HFOV	264	Sacrificed	Normal
P85	HFOV	264	Sacrificed	Mild bronchopneumonia

Fig. 5. Dilation of the airways (*A*) and distal saccular atelectasis are evident in a 24 h PPV/PEEP ventilated animal. In *B*, multiple pseudocysts (*p*), several filled with blood, are present. The airways (*A*) are overly distended with saccular atelectasis. *V*, vessel. Hematoxylin and eosin, $\times 20$, respectively.

HFOV, supporting our previous 24-h morphologic observations that there were ventilator-related structural and functional pulmonary differences (18).

These experiments gave us a unique opportunity to correlate morphologic and physiologic findings in an animal model closely

resembling human HMD. We have previously shown that, by 24 h of age, baboons with HMD ventilated with PPV/PEEP had striking maldistribution of intrapulmonary gas with poorly expanded saccules and dilated, overdistended distal conducting airways. In contrast, prematures treated with HFOV had more

Fig. 6. F_{IO_2} , $\bar{P}_{aw}$, and $Pa/A O_2$ ratio during the first 20 h in the PPV/PEEP animals who survived compared to those who died. Note a trend toward lower $Pa/A O_2$ ratio and F_{IO_2} before there was any radiographic evidence of air leak.

uniform saccular inflation and less small airway dilatation. The similarities between the clinical course, $Pa/A O_2$, F_{IO_2} , and $\bar{P}_{aw}$ in the first 24 h in these experiments and those earlier data suggest that the morphology at 24 h was similar in both studies. Therefore, nonuniform lung inflation appears to be characteristic of hyaline membrane disease during treatment with conventional positive pressure ventilation. Hawker *et al.* (19) described similar pathology in human infants dying after ventilator treatment of severe HMD. Nilsson and coworkers (20, 21) noted that the high airway pressures needed to ventilate the preterm rabbit lung resulted in nonhomogeneous expansion with overinflation of the more compliant segments. From our observations it is clear that pathologic small airway overdistension occurs during PPV/PEEP in baboon prematures with HMD and it is our notion that further dilatation of these airway segments leads to loss of structural integrity and pulmonary interstitial emphysema, pseudocyst formation and pneumothorax (22).

We found a high incidence of airleak associated with high

mortality in the baboon prematures ventilated with PPV/PEEP. The peak ventilation pressures in these animals were high but still did not result in adequate alveolar ventilation prior to development of air leak. In contrast, HFOV resulted in more uniform lung inflation, less acute baroinjury, and better survival. The mechanisms underlying these intergroup differences are complex.

Early interest in HFOV centered on its ability to accomplish adequate gas exchange with low tidal volumes and presumably less risk of baroinjury. Although we did not measure intrapulmonary pressures in these studies, there is no question that the intrapulmonary peak to peak pressure swings during HFOV at 10 Hz were lower than those during PPV/PEEP (23). While this could account in part for the difference in acute air leak between the two ventilator groups, it cannot explain all of the observations.

Initially, animals on HFOV were subjected to higher $\bar{P}_{aw}$ than were those on conventional ventilation. This resulted from an experimental design which was aimed at comparing the effects of an "optimal" HFOV strategy to one commonly used during conventional ventilation of human prematures. After the initiation of HFOV, $\bar{P}_{aw}$ was set at a level which resulted in a rapid increment in oxygenation. Further adjustment of the $\bar{P}_{aw}$ was dependent on the $Pa/A O_2$ response during the sigh maneuver. This strategy, while leading to initially higher mean airway pressures during HFOV, did not result in detectable airway disruption or significant intergroup differences in blood pressure or metabolic acidemia. The rapid increase in $Pa/A O_2$ seen early in the HFOV animals may well have resulted from the higher $\bar{P}_{aw}$ and is consistent with the hypothesis that the ideal ventilatory support in HMD is one in which a high, near constant, airway pressure is applied (24). With the strategy used, PPV/PEEP animals had relative hypoventilation and a high incidence of acute baroinjury and it is unlikely that they would have tolerated $\bar{P}_{aw}$ at the levels used during HFOV. These observations suggest that peak distending pressure rather than mean airway pressure is the critical factor in the development of PIE in infants with HMD and that one advantage of HFOV is the ability to safely use a high mean airway pressure.

After 10 h animals on HFOV achieved higher $Pa/A O_2$ at lower proximal $\bar{P}_{aw}$. This would appear to contradict extensive data relating oxygenation in diffuse alveolar disease to the $\bar{P}_{aw}$. Since we measured mean pressure only at the proximal airway, it is possible that this measurement was not representative of distal mean pressure and that the intrapulmonary pressures were considerably higher (25). This would be unlikely with the HFOV strategy used since the I:E ratio was 1:2 and the frequency was only 10 Hz. Even if there were an increase in $\bar{P}_{aw}$, it did not appear to be of significance since there was no baroinjury in this group and no radiographic evidence of hyperinflation.

When the data were examined over time, we found that from 10 to 20 h, the ratio of $Pa/A O_2$ to $\bar{P}_{aw}$ rose significantly in the HFOV animals suggesting that their lungs were functionally improving. During the same interval, $\bar{P}_{aw}$ in the PPV/PEEP treated prematures had to be increased to maintain the same $Pa/A O_2$. This is similar to the findings of Nilsson and others (20, 21, 26) and suggests that positive pressure ventilation results in additive lung injury in the surfactant deficient lung. In addition, the observation that the ratio between $Pa/A O_2$ and $\bar{P}_{aw}$ increased with HFOV during this same period supports the possibility that HFOV (or the use of a high mean airway pressure) actually enhances functional development of the immature lung.

Kolobow and coworkers (27, 28) have described rapid improvements in lung compliance in immature lambs on partial bypass after keeping the lungs inflated at constant pressure. It is possible that HFOV acts like constant pressure at the saccular level and improves alveolar stability by some combination of enhanced surfactant synthesis, decreased turnover or prevention of additive lung injury (29, 30). Lastly, the study design utilized PPV/PEEP in both treatment groups during the initial stabili-

Fig. 7. Section of lung of 11 day PPV/PEEP survivor. There was no significant morphologic differences between the HFOV and the 11 day PPV/PEEP survivors.

zation period in order to allow us to compare disease severity prior to ventilator assignment. Had we compared PPV/PEEP to the immediate institution of HFOV, the morphologic and physiologic differences between ventilator groups may have been more striking. Additional experiments using HFOV as the sole mode for ventilatory support and focusing on this critical early window will help to further define the relative role of each of these potential mechanisms.

After 42 h, there was a significant decrease in requirement for $\bar{P}_{aw}$ and a rise in $Pa/A\ O_2$ in the HFOV and the surviving PPV/PEEP animals. By 96 h, there were no longer any intergroup differences in lung inflation patterns, $Pa/A\ O_2$, or $\bar{P}_{aw}$. This recovery presumably was associated with the appearance of functionally adequate levels of alveolar surfactant, was independent of ventilator mode, and occurred despite substantial differences in the magnitude and duration of oxygen exposure between the two ventilator groups. It is also consistent with our previous experience (17). From this we can conclude that the relative hyperoxia in the PPV/PEEP animals did not result in additive lung injury. We have previously shown that the premature baboon (140 ± 2 days) with HMD is susceptible to oxygen injury and develops bronchopulmonary dysplasia after prolonged treatment with positive pressure ventilation and FI_{O_2} 1.0 (14, 15). With the degree of oxygen exposure obtained in these experiments, recovery in the surviving PPV/PEEP animals occurred early and the changes of BPD were not seen. This observation has important clinical and physiologic implications. Most investigators have implicated oxygen injury or pulmonary barotrauma in the pathogenesis of bronchopulmonary dysplasia. The results of these studies and others (31) suggest that chronic pulmonary baroinjury may not occur except in the presence of persistent parenchymal pulmonary disease. It further suggests the possibility that the major benefit of HFOV in the treatment of infants with HMD occurs early in the course of the illness and that there may be no particular advantage to its continued use once there has been significant resolution of the underlying disease process.

The physiologic findings in these experiments are consistent with those previously reported using HFOV in the premature rabbit and human (1) (Froese A, personal communication) but not with that recently described by Solimano *et al.* (32) in premature lambs. The apparent discrepancy may lie, as suggested by those authors, in species differences in animal models or in the use of lower mean airway pressures during their studies. There would appear, based on our data and that of others (1, 24), to be a critical relationship among mean airway pressure, alveolar volume, and the efficacy of HFOV in the management of diffuse alveolar disease. The use of intermittent sighs in the initial phase of these experiments allowed us to find the appropriate $\bar{P}_{aw}$ and lung volume. Once this was reached, large volume inflations resulted in no improvement or a decrement in oxygenation and could no longer be shown to be of clinical benefit.

These studies clearly support clinical trials of the use of HFOV in the management of infants with HMD. Not only does the appropriate use of HFOV result in lower intraluminal distending pressures and a reduced risk of structural disruption, but it appears to favorably alter the "natural" progression of HMD as seen during treatment with conventional ventilation. Additional studies are necessary both to define the mechanisms of the apparent "protective" effect of HFOV and to develop the most efficacious clinical strategy for its use.

REFERENCES

1. Hamilton PP, Onayemi A, Smyth JA, Gillan JE, Cutz E, Froese AB, Bryan AC 1983 Comparison of conventional and high-frequency ventilation: oxygenation and lung pathology. *J Appl Physiol* 55:131-138
2. Heijman K, Sjostrand U 1974 Treatment of respiratory distress syndrome—a preliminary report. *Opusc Med* 19:235
3. Bland RD, Kim MH, Light MJ, Woodson JL 1980 High-frequency mechanical ventilation in severe hyaline membrane disease. An alternative treatment? *Crit Care Med* 8:275-280
4. Bland RD, Sedin EG 1983 High-frequency mechanical ventilation in the treatment of neonatal respiratory distress. *Int Anesthesiol Clin* 21:125-147
5. Bohn DJ, Miyasaka K, Marchak BE, Thompson WK, Froese AB, Bryan AC 1980 Ventilation by high-frequency oscillation. *J Appl Physiol* 48:710-716

6. Marchak BE, Thompson WK, Duffy P, Miyaki T, Bryan MH, Bryan AC, Froese AB 1981 Treatment of RDS by high-frequency oscillatory ventilation: a preliminary report. *J Pediatr* 99:287-292
7. Frantz ID III, Werthammer J, Stark AR 1983 High-frequency ventilation in premature infants with lung disease: adequate gas exchange at low tracheal pressure. *Pediatrics* 71:483-488
8. Ackerman NB Jr, deLemos RA 1984 High-frequency ventilation. *Adv Pediatr* 31:259-293
9. Northway WH Jr, Rosan RC, Porter DY 1967 Pulmonary disease following respiratory therapy of hyaline-membrane disease. *N Engl J Med* 276:357-368
10. Northway WH Jr 1979 Observations on bronchopulmonary dysplasia. *J Pediatr* 95:815-818
11. Tooley WH 1979 Epidemiology of bronchopulmonary dysplasia. *J Pediatr* 95:851-855
12. Bancalari E, Abdenour GE, Feller R, Gannon J 1979 Bronchopulmonary dysplasia: clinical presentation. *J Pediatr* 95:819-823
13. Phillip AGS 1975 Oxygen plus pressure plus time: the etiology of bronchopulmonary dysplasia. *Pediatrics* 55:44-50
14. Escobedo MB, Hilliard JL, Smith F, Meredith K, Walsh W, Johnson D, Coalson JJ, Kuehl TJ, Null DM Jr, Robotham JL 1982 A baboon model of bronchopulmonary dysplasia. I. Clinical features. *Exp Mol Pathol* 37:323-334
15. Coalson JJ, Kuehl TJ, Escobedo MB, Hilliard JL, Smith F, Meredith K, Null DM Jr, Walsh W, Johnson D, Robotham JL 1982 A baboon model of bronchopulmonary dysplasia. II. Pathologic features. *Exp Mol Pathol* 37:335-350
16. Coalson JJ 1983 A simple method of lung perfusion fixation. *Anat Rec* 205:233-238
17. Bell RE, Kuehl TJ, Coalson JJ, Ackerman NB Jr, Null DM Jr, Escobedo MB, Yoder BA, Cornish JD, Nalle L, Skarin RM, Cipriani CA, Montes M, Robotham JL, deLemos RA 1984 High-frequency ventilation compared to conventional positive-pressure ventilation in the treatment of hyaline membrane disease in primates. *Crit Care Med* 12:764-768
18. Langston C, Waszkiewicz E, Thurlbeck WM 1979 A simple method for the representative sampling of lungs of diverse size. *Thorax* 34:527-530
19. Hawker JM, Reynolds EOR, Taghizadeh A 1967 Pulmonary surface tension and pathological changes in infants dying after respiratory treatment for severe hyaline membrane disease. *Lancet* 2:75-77
20. Nilsson R 1982 The artificially ventilated preterm rabbit neonate as experimental model of hyaline membrane disease. *Acta Anaesthesiol Scand* 26:89-103
21. Nilsson R, Grossmann G, Robertson B 1980 Bronchiolar epithelial lesions induced in the premature rabbit neonate by short periods of artificial ventilation. *Acta Pathol Microbiol Immunol Scand [A]* 88:359-367
22. Ackerman NB Jr, Coalson JJ, Kuehl TJ, Stoddard R, Minnick L, Escobedo MB, Null DM, Robotham JL, deLemos R 1984 Pulmonary interstitial emphysema in the premature baboon with hyaline membrane disease. *Crit Care Med* 12:512-516
23. Bell RE, Yoder BA, Ackerman NB Jr, Null DM Jr, deLemos RA 1984 Comparison of high frequency ventilation by oscillator, jet, and flow interrupter to standard positive ventilation in oleic acid induced lung injury in dogs. *Crit Care Med* 12:321
24. Kolton M, Cattran CB, Kent G, Volgyesi G, Froese AB, Bryan AC 1982 Oxygenation during high-frequency ventilation compared with conventional mechanical ventilation in two models of lung injury. *Anesth Analg* 61:323-332
25. Simon BA, Weinmann GG, Mitzner W 1984 Mean airway pressure and alveolar pressure during high-frequency ventilation. *J Appl Physiol* 57:1069-1078
26. Lachmann B, Jonson B, Lindroth M, Robertson B 1982 Modes of artificial ventilation in severe respiratory distress syndrome. Lung function and morphology in rabbits after wash-out of alveolar surfactant. *Crit Care Med* 10:724-732
27. Kolobow T, Gattinoni L, Tomlinson T, Pierce JE 1978 An alternative to breathing. *J Thorac Cardiovasc Surg* 75:261-266
28. Solca M, Kolobow T, Huang H, Chen V, Buckhold D, Pierce J 1984 Respiratory distress syndrome in immature lambs. Prevention through antenatal accelerated conditioning of the lung. *Am Rev Respir Dis* 129:979-984
29. Mannino FL, McEvoy RD, Hallman M 1982 Surfactant turnover in high frequency oscillatory ventilation (HFOV). *Pediatr Res* 16:356A(1662)
30. Ennema JJ, Reijngoud DJ, Egberts J, Mook PH, Wildevuur CRH 1984 High-frequency oscillation affects surfactant phospholipid metabolism in rabbits. *Respir Physiol* 58:29-39
31. deLemos R, Wolfsdorf J, Nachman R, Block AJ, Leiby G, Wilkinson HA, Allen T, Haller JA, Morgan W, Avery ME 1969 Lung injury from oxygen in lambs: the role of artificial ventilation. *Anesthesiology* 30:609-618
32. Solimano A, Bryan C, Jobe A, Ikegami M, Jacobs H 1985 Effects of high-frequency and conventional ventilation on the premature lamb lung. *J Appl Physiol* 59:1571-1577