

Comparison of conventional and high-frequency ventilation: oxygenation and lung pathology

PHILIP P. HAMILTON, ADEBUSOLA ONAYEMI, JOHN A. SMYTH, JOHN E. GILLAN, ERNEST CUTZ, ALISON B. FROESE, AND A. CHARLES BRYAN
Respiratory Physiology, Research Institute, Hospital for Sick Children, Toronto, Ontario M5G 1X8, Canada

HAMILTON, PHILIP P., ADEBUSOLA ONAYEMI, JOHN A. SMYTH, JOHN E. GILLAN, ERNEST CUTZ, ALISON B. FROESE, AND A. CHARLES BRYAN. *Comparison of conventional and high-frequency ventilation: oxygenation and lung pathology*. *J. Appl. Physiol.: Respirat. Environ. Exercise Physiol.* 55(1): 131-138, 1983.—Oxygenation and lung pathology were compared during conventional (CMV) and high frequency (HFO) ventilation in an animal model of pulmonary injury. Adult rabbits (2-4 kg) were studied under general anesthesia. Following tracheostomy, pulmonary injury was induced by saline lavage. During 5 h of either HFO or CMV, HFO produced a marked improvement in oxygenation (407, 407, and 409 Torr at 1, 3, and 5 h, respectively) compared with CMV (98, 129, and 87 Torr; $P < 0.005$). After 5 h each animal was killed and the lungs were fixed for microscopy. All CMV animals developed diffuse hyaline membranes, whereas the HFO animals did not. In a second series of experiments, HFO and CMV were attempted for 20 h. All CMV animals died before 20 h, [mean time of death = 10.6 h, final arterial blood O_2 partial pressure $Pa_{O_2} = 56$ Torr, arterial blood CO_2 partial pressure ($Pa_{CO_2} = 56$ Torr, pH = 7.15], whereas 4 of 5 HFO animals completed the 20-h protocol (final Pa_{O_2} and Pa_{CO_2} , 403 and 37 Torr, respectively, pH = 7.29). Again, the CMV animals developed diffuse hyaline membranes, whereas the HFO animals did not. This study confirms our previous findings (Kolton et al., *Anesths. Analg. Cleveland* 61: 323-332, 1982) that HFO improves gas exchange in the acutely injured lung. Furthermore, the lower lung volume and/or larger phasic pressure-volume fluctuations associated with CMV can induce pulmonary damage. Avoidance of low lung volume and large pressure-volume changes through the use of HFO results in reduced pulmonary damage.

high frequency oscillation; mechanical ventilation; pulmonary lavage; hyaline membranes

THE VALUE OF CONVENTIONAL mechanical ventilation (CMV) in the treatment of acute respiratory failure is undisputed. However, CMV often superimposes additional damage on the underlying disease process. The high peak airway pressures that are necessary to achieve adequate gas exchange in the failing lung frequently give rise to pulmonary barotrauma, particularly pneumothorax and pneumomediastinum. Some studies, although few in number, have demonstrated that barotrauma from CMV may also manifest itself in other ways. Schwieler and Robertson (29), Nilsson et al. (23), and Pesenti et al. (24) have shown that hyaline membranes can be produced by applying CMV to the abnormal lung. Rob-

ertson (27) has suggested that high peak airway pressures cause overdistension of terminal airways in atelectatic lung units, resulting in damage to the airway epithelium. This epithelial damage may then progress to hyaline membrane formation within a few hours (10). Furthermore, when superimposed upon the underlying pulmonary lesion, the epithelial lesion and hyaline membranes may worsen respiratory failure and prolong the period of dependence on CMV.

Mechanical ventilation by high frequency oscillation (HFO) has recently been shown to be a useful means of respiratory support in humans with pulmonary disease (7, 28) and in animal models of acute pulmonary injury (6, 17). Since the tidal volumes employed during HFO are smaller than during CMV, peak airway pressures and tidal fluctuations in alveolar volume and pressure should be reduced proportionately (6, 28, 30). This potential advantage of HFO suggests that HFO may be associated with a lower incidence of pulmonary barotrauma than CMV.

Because the application of high airway pressures to the injured lung is associated with hyaline membrane formation, we hypothesized that ventilatory support with HFO should be associated with a lesser degree of hyaline membrane formation than CMV. We have tested this hypothesis in an animal model of surfactant deficiency and pulmonary edema induced by pulmonary lavage, using a modification of the technique described by Lachmann et al. (17). Following pulmonary lavage, the animals were ventilated using either CMV or HFO, after which the nature and extent of hyaline membrane formation was evaluated by light microscopy.

METHODS

Twenty adult male New Zealand White rabbits [2-4 kg in wt) were studied in pairs. Ten were studied during a 5-h protocol and 10 during a 20-h protocol. Anesthesia was induced with intravenous pentobarbital (8-12 mg/kg) and ketamine (3-5 mg/kg) and maintained with intermittent pentobarbitone (2-5 mg/kg) every 60-90 min. Five percent dextrose in Ringer lactate solution was infused at $5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. Tracheostomy was performed on each animal, and the trachea was cannulated with a 3- to 4-mm ID uncuffed endotracheal tube that was secured in place by two peritracheal sutures. Neuromuscular paralysis was initiated and maintained with intra-

venous pancuronium bromide (2–4 mg/h). A femoral arterial catheter was inserted by cutdown for continuous monitoring of systemic arterial pressure by a pressure transducer (Hewlett-Packard model 1280) and for intermittent determination of arterial blood gases by a pH/blood gas system (Corning model 175). Rectal temperature was maintained at $39 \pm 1^\circ\text{C}$ using an overhead radiant heater (Airshields model SC-78-2).

CMV was delivered by an infant ventilator (Bourns model BP200) that was used as a constant-pressure generator, time cycled. Peak-to-peak airway pressures were monitored at the proximal end of the endotracheal tube by a pressure transducer (Validyne model DP7, 40cmH₂O). Mean airway pressure (relative to atmosphere) was obtained by passing the raw pressure signal through two cascaded bipolar low-pass critically damped filters. This device was capable of integrating the pressure waveform signal over a range of frequencies from 0.05 to over 30 Hz.

HFO was delivered by a piston pump with an adjustable stroke driven by a variable-speed electric motor. This apparatus has been described in detail previously (7, 16). Mean and peak-to-peak airway pressures were monitored at the proximal end of the endotracheal tube. A pressure-limiting device was incorporated into the circuit so that if mean airway pressure exceeded a preset limit (e.g. by accidental occlusion of the gas exit port), the circuit would open to the atmosphere via a pressure-relief valve. The response time of this device was less than 250 ms.

Following anesthesia/paralysis and instrumentation, each animal was ventilated conventionally (Bourns BP200) with 100% O₂ and control measurements of heart rate, systemic arterial pressure, airway pressures, and arterial blood gases were made prior to pulmonary lavage. The lungs were then lavaged 6–8 times over a 15- to 20-min period with normal saline (25–30 ml/kg each wash, 39°C) at a pressure not exceeding 30cmH₂O. Following the lavage, conventional ventilation with 100% O₂ was continued in each animal for another 15–20 min. Mean airway pressure was adjusted to 15cmH₂O, peak and end-expiratory pressures to 25 ± 1 and 6 ± 1 cmH₂O, respectively, inspiratory-to-expiratory ratio to 1:1, and ventilatory rate such that normocapnia was maintained. The end-expiratory pressure was set using a pressure-limited valve. Adequate pulmonary lavage was considered to have been achieved if the arterial blood O₂ partial pressure (Pa_{O₂}) on CMV was 120 Torr or less after this 15- to 20-min postlavage control period.

Following the control period, one animal from each pair was randomly assigned to the CMV protocol and the other to the HFO protocol. Ventilator settings for the CMV animal remained at the values set during the control period. For the HFO animal, O₂ flow the fraction of inspired O₂ (Fi_{O₂} = 1.0) to the circuit was adjusted to deliver an identical mean airway pressure (15cmH₂O) as in the CMV animal. Since oscillatory frequency was maintained at 15 Hz, normocapnia was achieved by altering the stroke volume of the piston. Tidal volume delivered during HFO was measured using a hot-wire anemometer and ranged from 1.5- to 2.0 ml/kg.

After each animal had been stabilized on its respective

ventilatory mode (10–15 min) arterial blood gases were determined and then a sustained inflation (SI) at a pressure of 25–30cmH₂O and lasting for 15 s was performed in an attempt to recruit alveolar volume and thus increase Pa_{O₂} (17). Approximately 5–10 min after the SI, arterial blood gases were again determined. Ventilation by either CMV or HFO was then continued in the first 5 pairs of animals for 5 h; arterial blood gases, heart rate, systemic arterial pressure, and airway pressures were monitored intermittently throughout. In the other 5 pairs of animals the study period was extended to 20 h or until the animal died.

After completion of the protocol, each animal was killed with 3 ml of pentobarbitone (Euthanol, 240 mg/ml). The lungs were then carefully excised en bloc. The right main-stem bronchus was tied close to the carina and was cut distal to this tie. The left lung (LL) was then inflated through the trachea with formalin, at a pressure of 15–20cmH₂O, and was allowed to fix for 12–16 h. The right middle lobe (RML) was placed in formaldehyde solution, uninflated, and the right lower lobe (RL) was placed in Bouin's solution, uninflated.

Following fixation blocks of lung tissue were sectioned and stained with hematoxylin and eosin. Each section was examined under light microscopy by two pathologists, one of whom was not informed of the group to which each section belonged. Hyaline membrane formation was assessed in the Bouin's-fixed specimens according to the technique described by Lauweryns et al. (18). Sections were surveyed with a $\times 10$ objective, and the severity of hyaline membrane formation was graded 0 to 3+ (0, no hyaline membrane formation; 1+, occasional fields showing hyaline membrane formation; 2+, many, but not all fields showing hyaline membrane formation; 3+, hyaline membrane formation in all fields examined).

In their original description of this model, Lachmann et al. (17) noted that although the lavage induced surfactant deficiency, there was also considerable pneumonitis and pulmonary edema associated with it. To clarify these aspects of the model, four additional animals were killed and examined. Two were anesthetized and killed immediately, and the lungs were fixed for microscopy (nonlavage control). The remaining two were anesthetized, lavaged, and then killed, and the lungs were fixed (lavage control). The distribution and severity of pneumonitis and pulmonary edema was assessed and compared to the CMV and HFO groups.

Statistical analysis of the arterial blood gas data was done using Student's *t* test.

RESULTS

Arterial Blood Gas Data

Five hour experiments. Arterial blood gas data for the 5-h experiments are summarized in Table 1; Pa_{O₂} data is summarized in Fig. 1.

pH and arterial blood CO₂ partial pressure (Pa_{CO₂}) values were not significantly different between the CMV and HFO groups at any time. Similarly, the prelavage, postlavage, and pre-SI Pa_{O₂} values were not significantly different between groups. However, the post-SI Pa_{O₂} (409 Torr) for the HFO group was significantly greater ($P <$

TABLE 1. Arterial blood gas data for 5-h experiments

| | | Control | | Before SI | After SI | 1 h | 3 h | 5 h |
|---------------------------------------|-----|---------------|--------------|-------------|-------------|-------------|-------------|-------------|
| | | Before lavage | After lavage | | | | | |
| pH | CMV | 7.47 ± 0.06 | 7.28 ± 0.03 | 7.37 ± 0.05 | 7.37 ± 0.02 | 7.34 ± 0.05 | 7.33 ± 0.03 | 7.29 ± 0.07 |
| | HFO | 7.46 ± 0.05 | 7.30 ± 0.04 | 7.34 ± 0.05 | 7.34 ± 0.03 | 7.41 ± 0.04 | 7.36 ± 0.03 | 7.32 ± 0.03 |
| Pa ₀ ₂ , Torr | CMV | 466 ± 16 | 88 ± 11 | 84 ± 17 | 111 ± 33 | 98 ± 16 | 129 ± 53 | 87 ± 29 |
| | HFO | 401 ± 35 | 82 ± 9 | 125 ± 25 | 409 ± 32* | 407 ± 31* | 407 ± 36* | 408 ± 35* |
| Pa _c 0 ₂ , Torr | CMV | 30 ± 2 | 47 ± 4 | 40 ± 4 | 42 ± 2 | 41 ± 3 | 42 ± 4 | 49 ± 7 |
| | HFO | 31 ± 4 | 44 ± 5 | 47 ± 2 | 37 ± 2 | 33 ± 2 | 36 ± 3 | 39 ± 3 |

Values are means ± SE; n = 5. SI, sustained inflation; Pa₀₂ and Pa_c0₂, arterial blood O₂ and CO₂ partial pressures, respectively; CMV, conventional mechanical ventilation; HFO, high-frequency oscillation. *Significantly different from corresponding CMV value (P < 0.001).

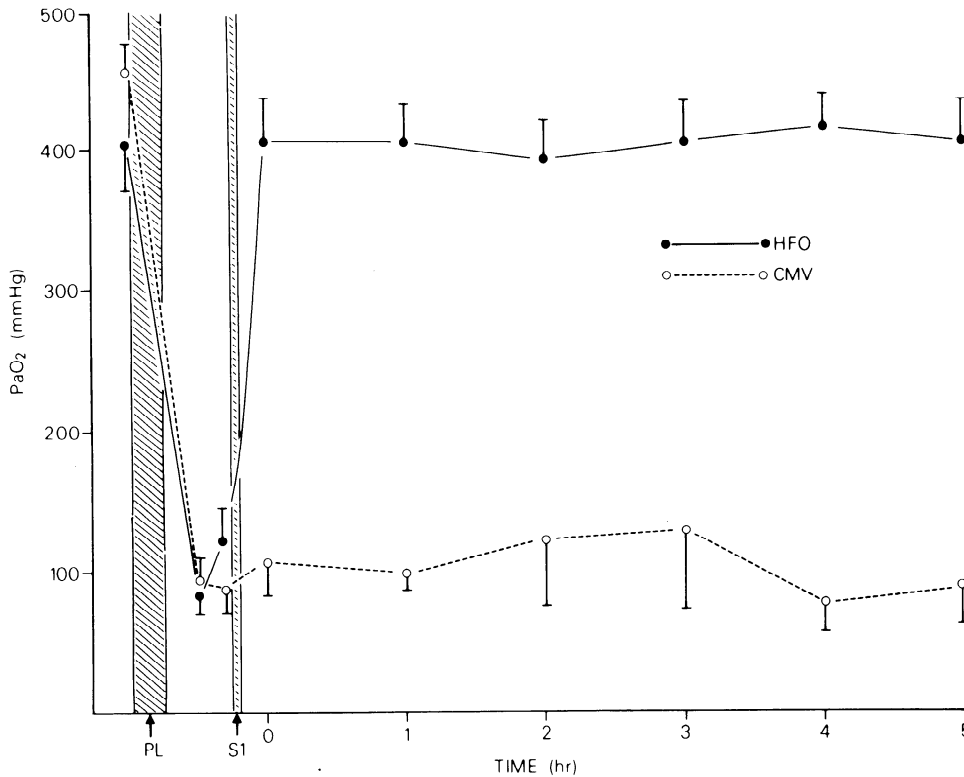


FIG. 1. Plot of arterial PO₂ (Pa₀₂) vs. time for 5-h experiments. Values appearing immediately before and after wide crosshatched area represent control values before and after pulmonary lavage. Values appearing before and after narrow crosshatched area represent pre-SI and post-SI values. Vertical bars denote SE.

0.005) than the post-SI Pa₀₂ for the CMV group (111 Torr). All subsequent Pa₀₂ values for the HFO group were also significantly greater than the corresponding values for the CMV group (P < 0.005). Furthermore, the post-SI Pa₀₂ on HFO (409 Torr) was significantly greater than the pre-SI Pa₀₂ on HFO (125 Torr, P < 0.005). In contrast, the post-SI Pa₀₂ on CMV (111 Torr) was not significantly different from the pre-SI Pa₀₂ on CMV (84 Torr, P > 0.10).

Twenty-hour experiments. Arterial blood gas data for the 20-h experiments are summarized in Table 2; Pa₀₂ data are summarized in Fig. 2. All of the CMV animals died before the 20-h protocol was completed. Two animals died from tension pneumothorax, and three died from hypotension and bradycardia related to progressive respiratory/metabolic acidosis and hypoxemia. In contrast, of the 5 HFO animals survived to complete the 20-h protocol with no significant deterioration in arterial blood gases. In two of these animals the improvement in Pa₀₂ from a single SI lasted for 20 h. The other animals were occasionally disconnected from the HFO circuit for tracheal suctioning, thus the duration of the effect of the

previous SI was limited by this factor. The remaining HFO animal died of pneumothorax at 8 h.

Pathology Findings

General findings in the model. When the sections were examined by light microscopy, all animals in both experimental groups showed evidence of pneumonitis, pulmonary edema, and bronchial and bronchiolar epithelial desquamation and necrosis. The pneumonitis was similar to that described by Lachmann et al. (17) in that the infiltrates were composed mainly of eosinophils with some neutrophils. The pneumonitis was diffuse, involving the interstitium, the peribronchial areas, and, in some cases, the lumina of terminal airways and alveoli. The cellular characteristics and distribution of the pneumonitis were similar in both the HFO and CMV groups. The two nonlavage control animals showed no evidence of pneumonitis, whereas the two lavage control animals showed a pneumonitis that was similar in extent and distribution to the experimental animals.

In the Bouin's-fixed sections diffuse proteinaceous

TABLE 2. Arterial blood gas data for 20-h experiments

| | | Control | | Before SI | After SI | 1 h | 5 h | Final |
|--------------------------|-----|---------------|--------------|-------------|-------------|-------------|-------------|-------------|
| | | Before lavage | After lavage | | | | | |
| pH | CMV | 7.43 ± 0.01 | 7.31 ± 0.03 | 7.31 ± 0.12 | 7.35 ± 0.08 | 7.35 ± 0.04 | 7.26 ± 0.02 | 7.15 ± 0.07 |
| | HFO | 7.45 ± 0.02 | 7.35 ± 0.04 | 7.35 ± 0.05 | 7.36 ± 0.07 | 7.41 ± 0.03 | 7.37 ± 0.03 | 7.29 ± 0.11 |
| Pa _{o2} , Torr | CMV | 418 ± 11 | 90 ± 12 | 97 ± 12 | 110 ± 25 | 101 ± 18 | 129 ± 35 | 56 ± 4 |
| | HFO | 426 ± 18 | 87 ± 4 | 148 ± 35 | 353 ± 10* | 389 ± 12* | 389 ± 13* | 403 ± 26* |
| Pa _{co2} , Torr | CMV | 34 ± 1 | 42 ± 3 | 42 ± 3 | 38 ± 4 | 37 ± 2 | 51 ± 3 | 56 ± 5 |
| | HFO | 33 ± 2 | 39 ± 4 | 40 ± 3 | 41 ± 5 | 36 ± 3 | 34 ± 3† | 37 ± 3† |

Values are means ± SE; *n* = 5. See Table 1 for abbreviations. All CMV animals died prior to completion of the 20-h protocol (see TEXT and Fig. 2). Four of the five HFO animals survived to 20 h; one died at 8 h (see TEXT and Fig. 2). The final value for each animal is that determined either upon completion of the protocol at 20 h or prior to the death of the animal. * Significantly different from corresponding CMV value (*P* < 0.001). † Significantly different from corresponding CMV value (*P* < 0.01). ‡ Significantly different from corresponding CMV value (*P* < 0.05).

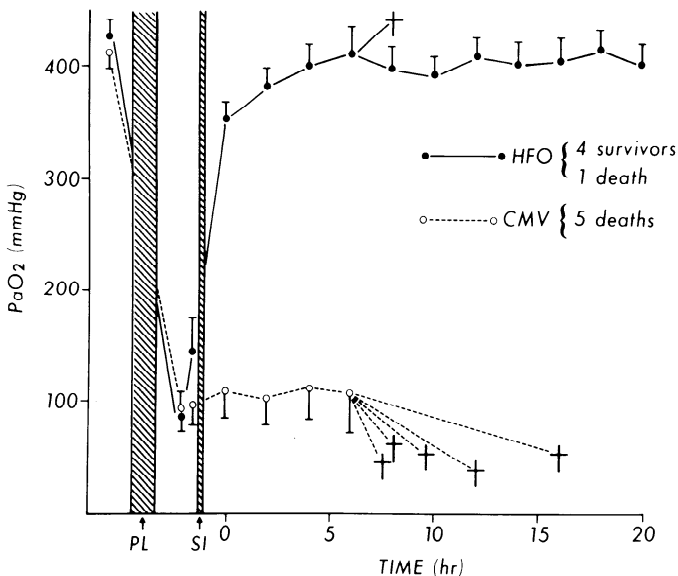


FIG. 2. Plot of arterial PO₂ (Pa_{o2}) vs. time for 20-h experiments. Values appearing immediately before and after wide crosshatched area represent control values before and after pulmonary lavage. Values appearing before and after narrow crosshatched area represent pre-SI and post-SI values. Vertical bars denote SE. For animals that died, time of death and last Pa_{o2} prior to death are denoted by cross.

pulmonary edema was seen in all lavaged animals, but not in the nonlavaged control animals.

A variable degree of sloughing of bronchial and bronchiolar epithelium was present in all lavaged animals. In the lavage control animals, there was multifocal sloughing of bronchial and bronchiolar epithelium, but the cells in the slough were not necrotic. In the CMV group, there was diffuse sloughing and necrosis of the epithelium of these small airways. In the HFO group, these epithelial changes were less prominent; however, there was still sloughing and necrosis of small airway epithelium that varied from focal to multifocal. In contrast, the two nonlavaged control animals showed a completely intact epithelium in all airways.

Hyaline membrane formation: 5-h experiments. The CMV and HFO groups showed striking differences in the extent of hyaline membrane formation (Table 3). Examination of uninflated specimens from the CMV group showed extensive hyaline membrane formation (Fig. 3A). Examination of the inflated specimens showed that this

TABLE 3. Hyaline membrane scores for 5-h experiments

| Group | <i>n</i> | Duration, h | Score |
|-------|----------|-------------|-------|
| CMV | 1 | 5 | 3+ |
| | 2 | 5 | 3+ |
| | 3 | 5 | 2+ |
| | 4 | 5 | 2+ |
| | 5 | 5 | 3+ |
| HFO | 1 | 5 | 0-1+ |
| | 2 | 5 | 0 |
| | 3 | 5 | 1+ |
| | 4 | 5 | 0-1+ |
| | 5 | 5 | 0 |

See Table 1 for abbreviations. See text for explanation of hyaline membrane score.

hyaline membrane formation occurred mainly within the terminal and respiratory bronchioles and at the tips of the alveolar septae. In contrast, lungs of animals in the HFO group showed less hyaline membrane formation (Figure 3B).

Hyaline membrane formation: 20-h experiments. All of the CMV animals showed multifocal to diffuse hyaline membrane formation, whereas the HFO animals showed significantly less (Table 4). The extent of hyaline membrane formation in the 20-h groups was not greater than in the 5-h groups for either CMV or HFO.

DISCUSSION

This study demonstrates that both physiologically and pathologically the development of the disease process following serial pulmonary lavage is modified markedly when gas exchange is supported by HFO rather than CMV. We recently reported (32) that during oleic acid-induced hemorrhagic pulmonary edema in dogs, the same Pa_{o2} was achieved on HFO and CMV for the same applied mean airway pressure. Subsequently, however, we demonstrated (16), in both oleic acid pulmonary edema and in the present lung lavage model, that a SI was capable of recruiting lung volume and substantially increasing the arterial Pa_{o2} during HFO but not during CMV. The arterial blood gas data in the present study confirm these latter observations. Kolton et al. (16) did not, however, investigate the duration of this improvement in oxygenation nor the impact of HFO on the pathological evolution of the underlying pulmonary le-

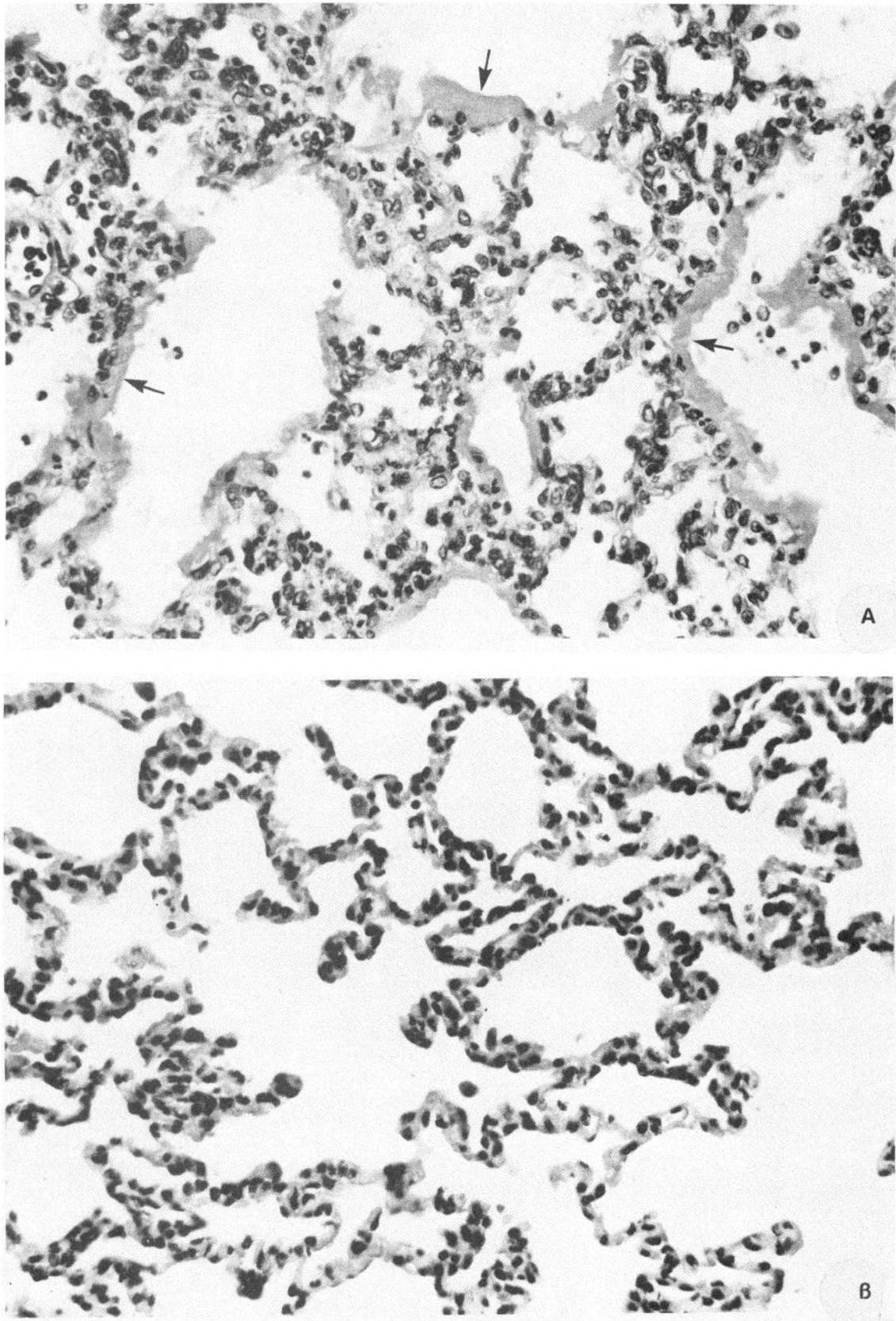


FIG. 3. Sections of uninflated lung fixed by immersion in Bouin's fixative. A: diffuse hyaline membrane formation (*arrows*) in the uninflated lung of an animal treated with conventional mechanical ventilation (CMV). (Hematoxylin and eosin stain, magnification $\times 250$.)

Arrows indicate hyaline membranes. B: appearance of uninflated lung of an animal treated with high frequency oscillatory ventilation (HFO). There are no hyaline membranes visible. (Hematoxylin and eosin stain, magnification $\times 250$.)

TABLE 4. Hyaline membrane scores for 20-h experiments

| Group | n | Duration, h | Score |
|-------|---|-------------|-------|
| CMV | 1 | 8 | 3+ |
| | 2 | 7.5 | 3+ |
| | 3 | 16 | 3+ |
| | 4 | 12 | 2-3+ |
| | 5 | 9.5 | 3+ |
| HFO | 1 | 20 | 0-1+ |
| | 2 | 20 | 1+ |
| | 3 | 20 | 0 |
| | 4 | 20 | 1+ |
| | 5 | 8.5 | 0 |

See Table 1 for abbreviations. See text for explanation of hyaline membrane score.

sion. In the current study we have shown that the SI during HFO not only increases Pa_{O_2} acutely but also results in an increase in Pa_{O_2} lasting several hours with no evidence of a decrease toward values observed prior to the SI. The 20-h experiments demonstrated that the increase in Pa_{O_2} achieved with a single SI does not deteriorate even over a period of 20 h. It was clear that as long as the distending pressure (mean airway pressure) was maintained, volume recruitment persisted. Disconnection from the oscillator circuit (e.g., for tracheal suctioning) allowed the lung to collapse passively to functional residual capacity (FRC); however, we observed that a repeat SI after reconnection to the circuit consistently resulted in an immediate and sustained improvement in Pa_{O_2} back to the previous level.

As well as these differences in oxygenation, distinct differences in the extent of hyaline membrane formation were evident in the two study groups. It was obvious, however, that our pulmonary lavage model involved more than surfactant deficiency with hyaline membrane formation. We invariably observed pneumonitis, pulmonary edema, and bronchial and bronchiolar epithelial changes in our animals.

Although bacterial colonization of the respiratory tract is common in laboratory colonies, frank pneumonitis is less common and its distribution and cellular characteristics are quite different from what we observed. Furthermore, the absence of pneumonitis in the nonlavage control animals suggested that our rabbit colony did not have endemic pneumonitis. The presence of pneumonitis in all lavaged animals, including the lavage control animals, plus the marked eosinophilia in all of these animals suggested that a chemical pneumonitis had been induced by the lavage process.

The pulmonary edema that we observed was similar in severity and distribution to that originally described by Lachmann et al. (17).

The airway epithelium in the nonlavage control animals was normal, whereas the lavage control animals showed extensive desquamation. These observations are consistent with those of Lachmann et al. (17) and suggest that the lavage process induces considerable airway damage. We speculate that the epithelial desquamation seen in the HFO group was due to damage induced by the lavage, since its severity in this group was comparable to the lavage control group. In contrast, the epithelial le-

sions seen in the CMV group were more severe than in either the HFO or the lavage control animals. This finding, plus the presence of hyaline membranes in the CMV group, suggests that considerable airway trauma from CMV was superimposed on the initial lesion.

Pulmonary hyaline membranes were first described by Hocheim (15) in premature infants dying with respiratory failure. Since then the presence of hyaline membranes has become the pathognomical histological feature of the infant respiratory distress syndrome (2, 5, 9, 18). Furthermore it has become clear that hyaline membranes are also frequently found in the lungs of adults dying from respiratory failure due to a variety of causes (4, 8, 26). Although the early studies (1, 8) suggested that the distribution of hyaline membranes in the infant and adult diseases differed, more recent evidence (3, 4, 13, 26) has shown that these lesions are confined mainly to respiratory bronchioles and alveolar duct in both age groups, suggesting the possibility of a common etiologic mechanism. Factors such as transudation of plasma protein (2, 14, 31), ineffective pulmonary fibrinolytic activity (19, 20), and oxygen toxicity (4, 22, 26) were some of those cited as being responsible for hyaline membrane formation. Although CMV had been employed in these studies, its contribution was largely ignored. In the early 1970s evidence that implicated CMV in the formation of hyaline membranes began to accumulate. McAdams et al. (21), studying premature rhesus monkeys, demonstrated that all animals treated with mechanical ventilation for 5 min or more developed either bronchiolar epithelial necrosis or hyaline membranes or both. However, they attributed these findings to the effects of gastric aspiration rather than to CMV itself. The subsequent study of Schweiler and Robertson (29) using liquid ventilation in premature rabbits provided strong evidence that CMV, when applied to the abnormal lung, results in bronchiolar epithelial damage and hyaline membrane formation. They argued that in atelectatic lung, the air-liquid interface exists in the terminal conducting airways rather than in the alveoli. They suggested that when a distending force is applied to this interface (as during the inspiratory phase of a CMV cycle), the tissue elastic forces of the bronchiole may not be able to withstand the pressure which must be generated to push the interface toward the alveolus. This could result in expansion of the bronchiolar wall with subsequent epithelial disruption and, eventually, hyaline membrane formation. Nilsson et al. (23) later provided more evidence, in the same model, that CMV is a critical factor in producing damage to the noncompliant lung.

In the present study, we have demonstrated that hyaline membranes can develop within only 5 h of starting CMV and that the severity of hyaline membrane formation is such that it cannot be distinguished from that seen several hours later. Furthermore, the paucity of hyaline membranes following ventilation by HFO is in direct contrast to this finding. The absence of a difference in hyaline membrane formation between the 5- and 20-h experiments in both groups suggests that O_2 toxicity did not play a role in the genesis of hyaline membranes in this study. The mechanism by which HFO appears to protect the lung from hyaline membranes is entirely

speculative. It has been shown that mechanical ventilation depletes surfactant and increases lung retractive force (11, 12). These changes can be prevented by using positive end-expiratory pressure or slowly reversed by static lung inflation. In some respects HFO is analogous to ventilation with positive end-expiratory pressure or a sustained inflation. Lung lavage depletes the surfactant pool, and it is possible that HFO facilitates the repletion. In contrast, CMV may impair surfactant repletion. The surfactant depletion may account for the atelectasis and shunting on CMV. However, atelectasis, per se, does not lead to hyaline membrane formation, and these lesions appear to be related to the pressure-time profiles of the two methods of ventilation. During HFO the gas exchange is excellent, indicating a substantial open alveolar volume, and the small volume excursion would produce little stretching of epithelial surfaces. In contrast, on CMV, at end expiration there is extensive atelectasis (Ref. 16, Fig. 7), and the large volume, and hence pressure swings, could cause disruption and desquamation of the epithelium. What is unanswered in this study is the effect of HFO on a lung with extensive atelectasis. Even small volume excursions, if distributed predominantly to airways, may create large pressure excursions that might cause epithelial damage.

All CMV animals died of either acute barotrauma or progressive hypoxemia and acidosis prior to completion of the 20-h protocol, whereas all but one of the HFO animals survived to 20 h without such problems. Thus, not only does HFO improve gas exchange and lessen airway trauma compared with CMV, but in doing so the pathophysiological progression of the underlying disease process is markedly altered. The superimposition by CMV of airway epithelial trauma and hyaline membrane formation on the initial lesion almost certainly contributed to the eventual demise of the CMV animals. In contrast, HFO appeared to prevent this evolution of the disease process by maintaining adequate gas exchange (and presumably lung volume) without adding further parenchymal lung damage to the initial lesion. We postulate that this ability of HFO to moderate the evolution of the disease process has considerable application to the

acutely injured human lung.

Conceptually, HFO can be compared to apneic oxygenation with the important exception that HFO incorporates a mechanism for CO₂ removal. In a recent study using apneic oxygenation and extracorporeal CO₂ removal, Pesenti et al. (24) reported findings analogous to those of our study. They demonstrated that premature fetal lambs treated with apneic oxygenation and extracorporeal CO₂ removal for up to 66 h did well, clinically. Subsequent histological examination of the lungs showed good alveolar expansion and no cellular damage. In contrast, a group of control animals treated with CMV developed progressive respiratory and metabolic acidosis; most of these died within 24 h. The lungs of all CMV animals showed extensive atelectasis and hyaline membrane formation. They attributed their findings in the apneic oxygenation animals to the absence of large phasic pressure-volume changes within the airways. We have arrived at similar conclusions using a different animal model and HFO.

Since current concepts of hyaline membrane formation relate directly to airway pressure (23, 27, 29), it was crucial to match the mean airway pressure in each treatment group. The choice of a mean airway pressure of 15 cmH₂O was based first on the observation that the CMV animals became unacceptably hypoxemic (Pa_o₂ < 50 Torr) at lower mean airway pressures, and second on the knowledge that a mean airway pressure of 15 cmH₂O is within the range used in patients with pulmonary disease who are being mechanically ventilated. However, in separate studies in the same model, we have observed that during HFO a mean airway pressure of 10–12 cmH₂O will maintain oxygenation equivalent to that seen at 15 cmH₂O. Therefore a relative degree of lung overdistension may exist during HFO at 15 cmH₂O, and one might predict the occurrence of pneumothoraces under these circumstances. The occurrence of only one pneumothorax in the HFO animals is, based on this argument, encouraging.

Received 20 April 1982; accepted in final form 3 February 1983.

REFERENCES

1. ANONYMOUS. Hyaline membrane formation in the adult lung. (leading article). *Lancet* 1: 362–363, 1962.
2. AVERY, M. E., AND J. MEAD. Surface properties in relation to atelectasis and hyaline membrane disease. *Am. J. Dis. Child.* 97: 517–523, 1959.
3. BARTER, R. A. The neonatal pulmonary hyaline membrane. *Lancet* 2: 160–161, 1959.
4. BARTER, R. A., L. FINLAY-JONES, AND M. WALTERS. Pulmonary hyaline membranes: sites of formation in adult lungs after assisted respiration and inhalation of oxygen. *J. Pathol. Bacteriol.* 95: 481–488, 1968.
5. BARTER, R. A., AND T. G. MADDISON. The nature of the neonatal pulmonary hyaline membrane. *Arch. Dis. Child.* 35: 460–464, 1960.
6. BOHN, D. J., K. MIYASAKA, B. E. MARCHAK, W. K. THOMPSON, A. B. FROESE, AND A. C. BRYAN. Ventilation by high frequency oscillation. *J. Appl. Physiol.: Respirat. Environ. Exercise Physiol.* 48: 710–716, 1980.
7. BUTLER, W. J., D. J. BOHN, A. C. BRYAN, AND A. B. FROESE. Ventilation by high frequency oscillation in humans. *Anesth. Analg.* *Cleveland* 59: 577–584, 1980.
8. CAPERS, T. H. Pulmonary hyaline membrane formation in the adult. *Am. J. Med.* 31: 701–710, 1963.
9. CLAIREAUX, A. E. Hyaline membranes in the neonatal lung. *Lancet* 265: 749–753, 1953.
10. ENHORNING, G., AND B. ROBERTSON. Lung expansion in the premature rabbit fetus after tracheal deposition of surfactant. *Pediatrics* 50: 58–66, 1972.
11. FARIDY, E. E. Effect of distention on release of surfactant in excised dogs' lungs. *Respir. Physiol.* 27: 99–114, 1976.
12. FARIDY, E. E., S. PERMUTT, AND R. L. RILEY. Effect of ventilation on surface forces in excised dogs lungs. *J. Appl. Physiol.* 21: 1453–1462, 1966.
13. FINLAY-JONES, J.-M., J. M. PAPADIMITRIOU, AND R. A. BARTER. Pulmonary hyaline membrane: light and electron microscopic study of the early stage. *J. Pathol.* 112: 117–124, 1974.
14. GAIRDNER, D., J. MARKS, J. D. ROSCOE, AND R. O. BRETTELL. The fluid shift from the vascular compartment immediately after birth. *Arch. Dis. Child.* 33: 489–498, 1958.
15. HOICHEIM, K. Ueber Einige Befunde in den Lungen von Neugeborenen und die Beziehung Dersel ben sur Aspiration von Fruchtwasser. *Centralblatt Path.* 14: 537–546, 1903.
16. KOLTON, M., C. B. CATTRAN, G. KENT, G. VOLGYESI, A. B.

- FROESE, AND A. C. BRYAN. Oxygenation during high frequency ventilation compared to conventional mechanical ventilation in two models of lung injury. *Anesth. Analg. Cleveland* 61: 323-332, 1982.
17. LACHMANN, B., B. ROBERTSON, AND J. VOGEL. In vivo lung lavage as an experimental model of the respiratory distress syndrome. *Acta Anaesthesiol. Scand.* 24: 231-236, 1980.
 18. LAUWERYS, J. M. Hyaline membrane disease in newborn infants. *Hum. Pathol.* 1: 175-204, 1970.
 19. LIEBERMAN, J. Clinical syndromes associated with deficient fibrinolytic activity. 1. New concept of hyaline membrane disease. *N. Engl. J. Med.* 260: 619-626, 1959.
 20. LIEBERMAN, J., AND F. KELLOGG. A deficiency of pulmonary fibrinolysis in hyaline membrane disease. *N. Engl. J. Med.* 262: 999-1004, 1960.
 21. MCADAMS, A. J., R. COEN, L. I. KLEINMAN, R. TSANG, AND J. SUTHERLAND. The experimental production of hyaline membranes in premature rhesus monkeys. *Am. J. Pathol.* 70: 277-284, 1973.
 22. NASH, G., J. B. BLENNERHASSETT, AND H. PONTOPPIDAN. Pulmonary lesions associated with oxygen therapy and artificial ventilation. *N. Engl. J. Med.* 276: 368-374, 1967.
 23. NILSSON, R., G. GROSSMAN, AND B. ROBERTSON. Lung surfactant and the pathogenesis of neonatal bronchiolar lesions induced by artificial ventilation. *Pediatr. Res.* 12: 249-255, 1978.
 24. PESENTI, A., T. KOLOBOW, D. K. BUCKHOLD, J. E. PIERCE, H. HUANG, AND V. CHEN. Prevention of hyaline membrane disease in premature lambs by apneic oxygenation and extracorporeal carbon dioxide removal. *Intensive Care Med.* 8: 11-17, 1982.
 25. PETTY, T. L., G. W. SILVER, G. W. PAUL, AND R. E. STANFORD. Abnormalities in lung elastic properties and surfactant function in adult respiratory distress syndrome. *Chest* 75: 571-574, 1979.
 26. PRATT, P. C. Pathology of adult respiratory distress syndrome. In: *The Lung: Structure, Function and Disease*, edited by W. M. Thurlbeck. Baltimore, MD: Williams & Wilkins, 1978, vol. 19, p. 44-57.
 27. ROBERTSON, B. Current and counter-current theories on lung surfactant. *Scand. J. Respir. Dis.* 57: 199-207, 1976.
 28. ROSSING, T. H., A. S. SLUTSKY, J. L. LEHR, P. A. DRINKER, R. KAMM, AND J. M. DRAZEN. Tidal volume and frequency dependence of carbon dioxide elimination by high frequency ventilation. *N. Engl. J. Med.* 305: 1375-1379, 1981.
 29. SCHWIELER, G. H., AND B. ROBERTSON. Liquid ventilation in immature newborn rabbits. *Biol. Neonate.* 29: 343-353, 1976.
 30. SLUTSKY, A. S., R. BROWN, J. LEHR, T. ROSSING, AND J. M. DRAZEN. High frequency ventilation: a promising new approach to mechanical ventilation. *Med. Instrum.* 15: 229-233, 1981.
 31. TANNENBERG, J. Fetal and postnatal atelectasis: factors essential in initiating spontaneous respiration and the significance of the hyaline membrane in the lung of the newborn. *Am. J. Clin. Pathol.* 32: 305-319, 1959.
 32. THOMPSON, W. K., B. E. MARCHAK, A. B. FROESE, AND A. C. BRYAN. High-frequency oscillation compared with standard ventilation in pulmonary injury model. *J. Appl. Physiol.: Respirat. Environ. Exercise Physiol.* 52: 543-548, 1982.

