Mechanical Ventilation in Newborn Infants With Hyaline Membrane Disease*

INTRODUCTION
The application of modern techniques of artificial ventilation, using a variety of mechanical ventilators, has enabled many newborns with respiratory failure secondary to hyaline membrane disease (HMD) to survive. Most mechanical ventilators are designed to provide intermittent positive-pressure breathing (IPPB) to the lung through a nasal or oral endotracheal tube. The intermittent peaks of pressure may be superimposed on a lower but continuous positive airway pressure (CPAP). This technique has been shown to be an effective means of improving the oxygenation of arterial blood. Thus, therapy with CPAP alone is often tried before the institution of IPPB. If CPAP proves to be inadequate, IPPB is begun. For convenience, these two respiratory techniques are often combined in the same machine (Figure 1).

Although the benefits of present-day methods of mechanical ventilation are clear, they are obtained only with considerable immediate and long-term morbidity. Some of the problems are a result of a combination of mechanical ventilation, prematurity, underlying lung disease, and oxygen. Others are problems to which any critically ill premature infant is subject. They range from acute, life-threatening ventilator-related complications to long-term pulmonary and neurologic handicaps.

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* Respiratory distress syndrome.
Clearly, the decision to ventilate a newborn infant with HMD entails more than a commitment to inhalation therapy; it requires the resources to deal with the many problems common to this group. This article will describe a few of these problems as they occurred in a large referral nursery in 1975.

MATERIALS AND METHODS

The Children's Hospital, Denver, has a 40-bed referral intensive-care nursery with approximately 700 admissions per year. Patients are referred from Denver and the rest of Colorado and from seven neighboring states. During 1975, 129 babies required mechanical ventilation for respiratory failure secondary to severe HMD. This represents 85 per cent of all infants ventilated during that year. The indications for mechanical ventilation were one or more of the following: (1) an arterial P02 of less than 50 mm. Hg in an inspired oxygen concentration of 80 per cent on 6-8 cm. of CPAP, (2) one or more severe episodes of apnea and bradycardia requiring active resuscitation, and (3) severe respiratory acidosis (pCO2 >55).

The criteria for diagnosis of HMD were a typical clinical course and chest x-ray appearance and, in those infants who died, histologic findings. Mechanical ventilation and CPAP were delivered through a nasotracheal tube by a time-cycled, pressure-limited infant ventilator.

RESULTS

Overall survival in this group of infants was 64 per cent. Survival by birth weight and gestational age is shown in Figure 2. Survivors were ventilated for an average of 191 hours (range: 10 to 1,152 hours), with 59 per cent receiving more than 96 hours of

continued
IPPB. Cause of death by gestational age is shown in Table 1. Figure 3 shows the incidence of complications in this group of infants. Complications included intrathoracic air leaks, sepsis, necrotizing enterocolitis, chronic pulmonary disease, intraventricular hemorrhage, hydrocephalus, patent ductus arteriosus, and retrolental fibroplasia. This list does not include problems of jaundice, fluids and electrolytes, temperature support, and feeding and weight gain, which are major in sick premature infants, or, in view of the recent births, problems of residual neurologic impairment.

Infections and necrotizing enterocolitis. Six out of 129 (5 per cent) developed severe infections during their hospital stay. Five had septicemia confirmed by blood culture, and one had pneumonia. Three infants (2 per cent) developed necrotizing enterocolitis, but all had a mild course and responded to medical management.

Air leaks during mechanical ventilation. Forty-seven of 129 infants (36 per cent) developed a major air leak (pneumothorax, pneumomediastinum, pneumopericardium, or pneumoperitoneum) while on mechanical ventilation with CPAP. The mean inspiratory pressure associated with air leak was 26 cm. H₂O, and the mean CPAP was 7 cm. H₂O. In most cases the air leak was preceded by radiologic evidence of interstitial emphysema. In 21 out of the 47 (45 per cent), an air leak occurred at more than one site (e.g., bilateral pneumothoraces) or was recurrent. Table 2 shows the incidence at different gestational ages. Tension pneumothorax was managed by placement of an intercostal tube to sealed underwater drainage. Pneumomediastinum and pneumopericardium were managed by needle aspiration when this was

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**FIGURE 2.** Survival of babies ventilated for hyaline membrane disease, January to December, 1975.

**TABLE 1**

<table>
<thead>
<tr>
<th>Gestational age (weeks)</th>
<th>Total No. of deaths</th>
<th>HMD</th>
<th>IVH</th>
<th>CLD</th>
<th>CHD</th>
<th>MPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-27</td>
<td>11</td>
<td>4</td>
<td>6</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28-31</td>
<td>16</td>
<td>4</td>
<td>9</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>32-35</td>
<td>15</td>
<td>4</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>36-40</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>46</strong></td>
<td><strong>15 (33)</strong></td>
<td><strong>22 (48)</strong></td>
<td><strong>6 (13)</strong></td>
<td><strong>1</strong></td>
<td><strong>2 (4)</strong></td>
</tr>
</tbody>
</table>

HMD = Hyaline membrane disease.
IVH = Intraventricular hemorrhage.
CLD = Chronic lung disease.
CHD = Congenital heart disease.
MPH = Massive pulmonary hemorrhage.
indicated for severe symptoms.

**Intracranial hemorrhage.** Twenty-two of 129 infants (16 per cent) had postmortem evidence of intraventricular hemorrhage. Eight additional infants developed obstructive hydrocephalus requiring ventriculoperitoneal shunting following a clear-cut episode of deterioration that was presumed to have been due to an intracranial hemorrhage. Table 3 shows the occurrence of this complication in relationship to gestational age.

*continued*
Patent ductus arteriosus. Evidence of a patent ductus arteriosus (PDA) with radiologic cardiopulmonary changes was found in 56 of 129 infants (43 per cent) during their admission, largely within the first two weeks of life. Diagnosis of a PDA was based on clinical features and the chest roentgenogram, supplemented by echocardiographic measurement of the ratio of the left atrial to aortic root diameter. Patients were intensively managed medically for cardiac failure with digoxin, diuretics, fluid restriction, and CPAP, sometimes with mechanical ventilation. Only after four or five days of progressive worsening despite medical management was the ductus ligated surgically. Of the 56 patients, 21 (38 per cent) required eventual surgical ligation. Table 4 shows the incidence of PDA in relation to gestational age, the complication being most common in infants of 32 weeks gestational age or less. Ten of the infants with PDA and cardiac failure died, eight without ligation and two after ligation. However, death was from causes other than cardiac failure or complications of surgery; in infants in whom surgery was indicated by the above-mentioned criteria, most improved postoperatively with reduction in heart size and pulmonary congestion.

Chronic lung disease. Twenty-eight of 129 infants (22 per cent) had radiologic and clinical evidence of chronic lung disease (CLD). Table 5 shows that this condition occurred with equivalent frequency in each gestational age group until 36 weeks.

Six of these infants eventually died from progressive respiratory failure. At autopsy, all six showed severe changes of bronchopulmonary dysplasia with very little normal lung tissue present.

When the infants who developed CLD were compared with those who did not, the following results emerged: 1. In infants who developed CLD, the mean time of initial exposure to inspired oxygen concentrations of at least 80 per cent was nine days and that to concentrations of 40 to 79 per cent was 42 days, compared with two and 10 days, respectively, in those who did not. 2. In infants who developed CLD, the mean time of IPPB was 25 days, compared with six days in those who did not. 3. Among infants who developed CLD, the mean time of intubation was 30 days, compared with seven days in those who did not.

Retrolental fibroplasia. One of the most serious complications in terms of long-term handicap (blindness...
and myopia) is retrolental fibroplasia (RLF). Twenty-one of 129 infants (16 per cent) were found to have changes indistinguishable from RLF by a pediatric ophthalmologist at indirect ophthalmoscopy before discharge. These cases were found despite very careful attention to oxygenation in this nursery. Changes were graded as mild (tortuosity of vessels), moderate (hemorrhage or vascular proliferation), or severe (end-stage disease with retinal detachment and blindness). Table 6 shows the incidence in relation to gestational age groups and the number of survivors examined. All six severe cases were in infants of 26 to 28 weeks gestational age; the three infants with moderate changes were of 28, 30, and 35 weeks gestational age. One infant estimated to be of 36 weeks gestational age developed mild changes after treatment of very severe HMD, but it was the very immature infant (less than 28 weeks gestational age) who was particularly prone to develop RLF.

DISCUSSION
Survival. The overall survival of infants receiving mechanical ventilation for HMD has increased over the past 10 years.\textsuperscript{1,8} Some of this improvement is undoubtedly due to advances in ventilatory techniques, but the importance of improved physiologic support and nursing care must not be underestimated. Certainly, mechanical ventilation can be consistently effective only in an environment where other aspects of care are at the highest level and where complications can be recognized and treated immediately.

It is difficult to make more specific use of survival statistics. For example, it is difficult to decide, from a comparison of survival figures from various neonatal intensive-care units, which of the many techniques proposed for mechanical ventilation is the "best." The status of infants on admission, their size and gestational age, and the criteria for mechanical ventilation heavily influence survival, and all may vary in different centers.\textsuperscript{1} A technique that is efficacious in one nursery may not be in another with a different approach to a different patient population.\textsuperscript{6}

Sepsis and necrotizing enterocolitis. The incidence of these complications was low during 1975. Both are periodically much more of a problem,\textsuperscript{10} for reasons that are not clear. The unpredictability of such complications emphasizes the complexity of their causes.

Intrathoracic air leaks. In recent reports, the incidence of pneumothoraces with or without pneumomediastinum in infants ventilated for HMD varies from 14 to 40 per cent.\textsuperscript{1,8,11-13} The differences in incidence may relate to differing indications for ventilation in various centers. Hall and Rhodes noted an increase from an 11 to a 20 per cent incidence of pneumothorax in their nursery in infants treated with mask CPAP.\textsuperscript{14} They suggested that the rise may have been due to a change in protocol that resulted in the application of CPAP to infants with relatively mild pulmonary disease. If the

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**TABLE 6**

RETROLENTAL FIBROPLASIA IN SURVIVORS

<table>
<thead>
<tr>
<th>Gestational age (weeks)</th>
<th>Incidence in patients examined (%)</th>
</tr>
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<tbody>
<tr>
<td>24-27</td>
<td>6/6 (100)</td>
</tr>
<tr>
<td>28-31</td>
<td>9/17 (53)</td>
</tr>
<tr>
<td>33-35</td>
<td>5/34 (15)</td>
</tr>
<tr>
<td>36-40</td>
<td>1/13 (8)</td>
</tr>
</tbody>
</table>
same is true of ventilated patients, indications for ventilation might influence the incidence of pneumothorax.

The clinical presentation of a pneumothorax may be insidious, with gradually increasing hypoxemia and hypercarbia, or sudden, with severe cyanosis and respiratory arrest. The diagnosis can be confirmed by physical examination (especially if a shift in the cardiac impulse is present), by radiologic examination, or by transillumination. Emergency management consists of cardiopulmonary support and, if necessary, aspiration of the chest with a scalp vein needle attached to a large syringe by a three-way stopcock. Definitive treatment is by chest tube with water-seal drainage.

The alarming frequency of symptomatic pneumothoraces in ventilated infants requires the constant presence of personnel trained to recognize and manage them, at least on an emergency interim basis.

**Intracranial hemorrhage.** Intracranial hemorrhage was found in 48 per cent of infants who died in this series. This is similar to the experience of others and emphasizes the association of intracranial hemorrhage with prematurity and HMD.

Any acute deterioration in the clinical status of a critically ill premature infant within the first days of life may be due to an intraventricular hemorrhage. The management of such an episode is complicated by the difficulty in ruling out other possibilities, such as overwhelming sepsis, septicemia or metabolic diseases.

Even when a hemorrhage is diagnosed before death, management is complicated by the fact that, in the past, intracranial hemorrhage has been diagnosed almost entirely at autopsy. As a result, the lesion has been assumed to be fatal. This is no longer true. Some premature infants survive an episode of shock and acute anemia and go on to develop hydrocephalus, while others develop hydrocephalus in the absence of signs of intracranial hemorrhage. It is probable that many of these infants have suffered and survived an intracranial hemorrhage. Some may have satisfactory outcomes.

The major block to the rational management of intracranial hemorrhage is ignorance of the course of infants who do not die, by virtue of an inability to make an unequivocal diagnosis of intraventricular hemorrhage before death.

Fortunately, recent studies have shown that the CAT scanner is capable of identifying intraventricular hemorrhage, making accurate pre-mortem diagnosis possible for the first time. Studies can now be designed to answer questions about the prognosis of nonfatal intraventricular hemorrhage, with important implications for management.

We believe that until such studies are available, infants with signs and symptoms of intracranial hemorrhage should **initially** receive continued supportive care, for two reasons: (1) we may be dealing with infection rather than intracranial hemorrhage, and (2) there are insufficient data to state that infants with transient signs of intracranial hemorrhage have poor outcomes if managed optimally. On the other hand, if intracranial hemorrhage is associated with **continued** signs of severe central nervous system dysfunction, the physician must assure himself that vigorous support is not delaying the inevitable death of the infant.

**Patent ductus arteriosus.** The association of prematurity, hyaline membrane disease, and PDA is well recognized. In a prospective
study of premature infants, Siassi et al. found that the incidence of PDA, as judged by the presence of a murmur, rose continuously from 27 per cent at 37 to 40 weeks of gestation to 77 per cent at 28 to 30 weeks. The incidence of PDA in our series of infants was also related to gestational age, although the correlation was not seen at gestational ages of less than 36 weeks. A correlation between gestational age and PDA may well not be so striking in infants who are selected for artificial ventilation.

The appearance of an enlarged heart and pulmonary infiltrate on the chest film and the need for continued ventilatory support may be the only indications of a PDA, but most infants will have a heart murmur and bounding pulses to complete the clinical picture. Controversy exists as to the management of this complication, but preliminary data support a trial of digitalis, diuretics, and vigorous fluid restriction before consideration of surgical ligation. When surgery is necessary, it is associated with a low mortality.

The use of indomethacin has recently been suggested for closure of the PDA, but further studies are necessary before a drug with unknown effects on a variety of vascular beds is used routinely on the clinical service.

**Chronic lung disease.** The incidence of CLD in mechanically ventilated survivors has varied from 17 to 68 per cent in recent reports. The development of this complication results in prolongation of oxygen therapy and ventilatory support, as our data show. It also results in a number of pulmonary handicaps (recurrent lower respiratory tract infections, dyspnea, reduced exercise tolerance, and abnormal function) in the first few years of life. Fortunately, in those children who survive, ultimate prognosis is considered good.

Exposure to oxygen and mechanical trauma from IPPB are thought to play a part in the production of this lesion, but there is no consensus as to which is the more important. Until additional data are available, it seems reasonable to minimize both peak inspiratory pressure and oxygen by the use of CPAP and the techniques described by Reynolds and Taglizadek.

The management of this disease depends on prevention. Treatment relies essentially on nutrition, oxygen, and time.

**Retroental fibroplasia.** Kinsey’s classic study showed that oxygen administration, decreasing birth weight, and multiple birth were associated with an increase in the incidence of RLF, but the relative importance of these factors in differing combinations is not at all clear. There are a number of reports that document the occurrence of retroental fibroplasia in term infants and in premature infants who have received very little oxygen. A recent report documented the occurrence of RLF in a 940-gm. infant with cyanotic congenital heart disease.

A distinction among the factors contributing to RLF is made much more difficult by the currently available methods for monitoring the arterial $P_{O_2}$ ($PaO_2$). Information obtained from continuous oxygen monitoring has shown that intermittent measurements of the $PaO_2$ may be a poor reflection of the prevailing situation, and both low and high $PaO_2$ values can be missed.

The six severely affected infants in this study were very immature; two were twins. The $PaO_2$ was monitored closely using umbilical, temporal, or radial artery blood to prevent high values. Were the monitoring techniques insufficient, or were the $PaO_2$
values, although within the “safe” range, too high for an immature infant? The answers to such questions await further studies using constant oxygen monitoring, but it is possible that oxygen has little to do with RLF in some infants. Vasoproliferative retinopathy is a response to a variety of causes of retinal hypoxia, of which oxygen is only one.39 In any case, it is difficult to underestimate the magnitude of this problem. In this series, six of the 13 survivors under 1,000 gm. birth weight are blind.

The research for this article was supported in part by a grant from the American Lung Association of Colorado.

BIBLIOGRAPHY

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