ALTHOUGH THE DUCTUS ARTERIOSUS closes spontaneously during the first 24 hr of life in normal full-term infants, delayed closure is not uncommon in premature babies.1-7 The increased incidence of patent ductus arteriosus (PDA) in the respiratory distress syndrome (RDS), which mainly occurs in premature infants, has also been documented by several investigators.8-11 Although no clear relationship between RDS and PDA (which is primarily shunting blood left to right) has been established, several reports have indicated the achievement of a beneficial effect on the course of the respiratory distress syndrome through the ligation of the ductus.2,6,8,10,12

To evaluate the efficacy of PDA ligation in the respiratory distress syndrome, the following study was undertaken.

MATERIALS AND METHODS

During the period February, 1971 through February, 1973, 30 premature infants with respiratory distress syndrome underwent surgical ligation of a patent ductus arteriosus. During this same period, 1880 infants with birth weights less than 2500 g were born at or transferred to the Newborn Center of the Los Angeles County-USC Medical Center. There were 20 males and 10 females; 26 of the 30 patients were Mexican-American, which is consistent with the over-all racial distribution of the neonatal population in our medical center. The gestational ages ranged from 25 to 36 wk, mean 30, and the birth weights varied from 761 to 2010 g, mean 1274 (Table 1). The patients were divided into two groups according to the age and the indications for the institution of assisted ventilation.

Group I consisted of 21 infants with severe hyaline membrane disease, requiring the initiation of assisted ventilation during the first 2 days of life; these babies could not be weaned off the respirator by 10 days of age. Group II was composed of nine patients who required intermittent positive-pressure breathing after a mean age of 8 days due to repeated or continuous apneic spells unresponsive to conservative measures.

The diagnosis of PDA was initially made clinically and corroborated by laboratory tests in all patients. Twenty-five infants had a grade II to III/VI crescendo systolic murmur with an early diastolic component best heard along the upper left sternal border and left infraclavicular area. Five infants had a continuous murmur. It was often necessary to disconnect the infant from the respirator to hear the murmur. Bounding peripheral pulses were present in all patients. In 28 infants, the presence of an indwelling arterial line allowed the documentation of a widened pulse pressure through direct measurement. The degree of left-to-right shunting was evaluated in all patients through dye-dilution studies in 26 babies, cardiac catheterization in seven infants, and cineangiography in nine patients (Fig. 1). Dye-dilution studies were performed by injecting cardiogreen dye into a catheter threaded into the superior vena cava from an antecubital vein; dye concentration was measured by an ear oximeter.

All infants developed heart failure manifested by tachycardia (heart rate greater than 160 beats
per minute), cardiomegaly, hepatomegaly, increased central venous pressure, increased requirements for intermittent positive pressure in order to obtain adequate oxygenation (arterial PO$_2$ of 60-70 mm Hg) and pulmonary ventilation (arterial PCO$_2$ of 40 mm Hg) in Group I, and by repeated periods of apnea of greater than 15-sec duration in Group II. All patients received digitalis and diuretics and small transfusions of packed red cells to maintain the hematocrit above 35%. The above measures often resulted in improvement in cardiopulmonary function and in a decreased incidence of apnea. Surgical ligation of the PDA was considered only after there was no response to the above medical measures and when the following criteria were met: (1) age over 8 days; (2) greater than 50% left-to-right shunt by dye-dilution study; (3) progressive cardiomegaly. The mean age at the time of operation was 23 days and the mean body weight was 1344 g (range 750 to 2010) (Table 2).

### Table 1. Clinical Data on 30 Premature Infants Undergoing PDA Ligation

<table>
<thead>
<tr>
<th>Gestational Age (wk)</th>
<th>Birth Weight (g)</th>
<th>% L → R Shunt</th>
<th>Age at Operation (days)</th>
<th>Weight at Operation (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>30</td>
<td>1274</td>
<td>70</td>
<td>23</td>
</tr>
<tr>
<td>SD</td>
<td>3</td>
<td>378</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

All patients received digitalis and diuretics and small transfusions of packed red cells to maintain the hematocrit above 35%. The above measures often resulted in improvement in cardiopulmonary function and in a decreased incidence of apnea. Surgical ligation of the PDA was considered only after there was no response to the above medical measures and when the following criteria were met: (1) age over 8 days; (2) greater than 50% left-to-right shunt by dye-dilution study; (3) progressive cardiomegaly. The mean age at the time of operation was 23 days and the mean body weight was 1344 g (range 750 to 2010) (Table 2).

### Table 2. Comparison of Two Groups of Premature Infants with RDS and PDA

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>Birth Weight (mean in g)</th>
<th>Gestational Age (mean in wk)</th>
<th>% L → R Shunt (mean)</th>
<th>Age at Operation (mean in days)</th>
<th>Weight at Operation (mean in g)</th>
<th>Hours of FIO$_2$ &gt; 60% Before Operation (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I*</td>
<td>21</td>
<td>1313</td>
<td>30</td>
<td>69</td>
<td>21</td>
<td>1363</td>
</tr>
<tr>
<td>Group II†</td>
<td>9</td>
<td>1182</td>
<td>30</td>
<td>74</td>
<td>28</td>
<td>1303</td>
</tr>
</tbody>
</table>

*Premature infants with RDS requiring assisted ventilation shortly after birth.
†Premature infants with RDS requiring assisted ventilation because of apnea during the later neonatal period.
The infants were anesthetized with nitrous oxide and curare, and the electrocardiogram and rectal temperature were monitored in all patients. The ductus was approached transpleurally through a left lateral thoracotomy in the fourth intercostal space. In all cases, the ductus was as large as the aortic arch and in some cases it was larger. The ductus was ligated with 2.0 silk ligatures in each case. The ductus wall appeared quite friable at the time of operation. Air was evacuated from the left pleural cavity during closure of the chest, and no chest tubes were left in place postoperatively. After operation, the babies were returned to the neonatal intensive care unit and were maintained on a respirator.

RESULTS

Intra-arterial blood pressures were obtained in 28 of the 30 infants. The average systolic, diastolic, and pulse pressures were 53, 29, and 24 mm Hg, respectively. Some degree of cardiomegaly was present in 26 of the 30 infants prior to operation. This was particularly evident when serial chest x-rays revealed a relative increase in heart size. All infants in Group II had evidence of increased pulmonary blood flow on chest x-ray, whereas evaluation of increased pulmonary vascularity was difficult in Group I because of the presence of various degrees of bronchopulmonary dysplasia (Fig. 2). Electrocardiograms were obtained in all infants and revealed right ventricular hypertrophy in nine patients, left ventricular hypertrophy in ten infants, combined ventricular hypertrophy in three babies, and no abnormalities in eight patients. There was no correlation between electrocardiographic findings and the degree of left-to-right shunting or operative survival. The mean left-to-right shunt calculated from the dye-dilution studies was 70% (range 56%–95%) (Fig. 3).

There was one operative complication consisting of a tear in the ductus. This was relatively easily controlled with an extra silk ligature. This baby did not develop any postoperative complications or problems. There were no other operative or postoperative complications. After operation, oxygen requirements were significantly reduced; among the survivors, assisted mechanical ventilation was discontinued an average of 9 days after operation. All infants in Group II survived the operation and left the hospital well; 14 of the 21 patients in Group I survived. The seven deaths in Group I were directly related to severe broncho-

Fig. 2. Severe bronchopulmonary dysplasia in premature infant with RDS and a large PDA. The baby had been on a respirator since birth with the FIO2 increasing to 100% and the inspiratory pressure on the respirator increasing to 80 cm H2O; this resulted in an arterial pO2 of 16 mm Hg.
pulmonary dysplasia; two of these seven patients also had significant necrotizing enterocolitis.

Comparison of Groups I and II and the survivors and the nonsurvivors shows that there were no significant differences in birth weight, gestational age, degree of left-to-right shunting, or weight at the time of operation (Tables 2 and 3). There was a significant difference in the number of hours of mechanical ventilation with a greater than 60% inspired oxygen concentration prior to operation between Groups I and II and between the survivors and nonsurvivors. This period consisted of 103 hr in Group I and 47 in Group II; and 57 hr in the survivors and 184 hr in the nonsurvivors. This is an indication of the severity of the associated lung disease in the infants in Group I, which included all the nonsurvivors.

**DISCUSSION**

A review of the incidence of ductal patency in our neonatal center has indicated that 36% of premature infants with birth weights less than 2000 g have a PDA defined as patency beyond 3 days of age. The estimated incidence in all infants weighing less than 2500 g at birth is 21.5% at our institution. This is a higher incidence than that reported by Kitterman et al. The prevalence of PDA in premature infants appears to be directly related to the degree of pre-

| Table 3. Comparison of Survivors and Nonsurvivors After PDA Ligation |
|-----------------------------------|----------------|----------------|----------------|----------------|
|                                    | Gestational Age | Age at Operation | Weight at Operation | Hours FIO₂ > 60% |
|                                    | (wk)            | (days)           | (g)               | Before Operation |
| Survivors                          |                 |                 |                  |                |
| Number of patients                 | 23              | 23              | 23               | 23             |
| Mean                               | 29              | 26              | 1325             | 57             |
| SD                                 | 3               | 11              | 380              | 63             |
| Nonsurvivors                       |                 |                 |                  |                |
| Number of patients                 | 7               | 7               | 7                | 7              |
| Mean                               | 31              | 13              | 1411             | 184            |
| SD                                 | 2               | 3               | 365              | 123            |
maturity. The reason for delayed ductal closure is not known but may be related to decreased media in the ductus in premature infants, unresponsiveness of ductal enzyme systems to oxygen, and prolonged hypoxia in infants with RDS.

The detection of the presence of a PDA may be difficult since the murmur may be hard to hear during assisted ventilation and may not be a typical continuous murmur. The palpation of bounding peripheral pulses or the observation of a widened pulse pressure on direct arterial measurement may be the first clue to the presence of a PDA. The electrocardiogram is of no diagnostic value and the chest x-ray is usually not helpful. Cardiac catheterization was performed in seven of the infants early in the series, but the morbidity associated with this procedure did not justify its continuation, especially since the clinical accuracy of our cardiologists proved to be 100%. The dye-dilution studies were associated with no morbidity and gave a rough estimate of the degree of left-to-right shunting. No infant with a shunt of less than 50% underwent operation, since we felt that a PDA with a less than 50% left-to-right shunt probably did not significantly contribute to the clinical course of the patient.

The relationship between PDA and RDS is not clear since both increase with decreasing gestational age. In the mechanically ventilated infant with RDS, a large shunting PDA increases pulmonary blood volume and, thereby, decreases lung compliance, necessitating higher pressures to deliver an adequate tidal volume and higher FIO2's to oxygenate the blood. Continuation of mechanical ventilation with high pressures and high inspired oxygen content leads to severe lung damage (bronchopulmonary dysplasia) fairly rapidly. Ductal ligation probably improves lung compliance, making it easier to wean the infant from the respirator.

Our series differs from the others reported in that all our patients were on mechanical ventilators prior to operation. This fact is an indication of the critical status of all these babies prior to operation. In addition, the increasing pressure and FIO2 required to maintain an adequate arterial pO2 predicted poor success in weaning these patients from the ventilator. Ductal ligation appears to have reversed the vicious cycle of prolonged mechanical ventilation and irreversible lung damage in the majority of cases. The seven patients who died demonstrated severe bronchopulmonary dysplasia at autopsy; in two infants, no alveoli were seen on histologic section, the lungs consisting of bronchioles and fibrous tissue. These infants underwent PDA ligation too late in that the irreversible lung damage was present prior to operation. This fact supports the contention that ductal ligation should be carried out early rather than late in the course of the respiratory distress syndrome.

The separation of our patients into Groups I and II was a valuable aid in predicting the eventual outcome of these cases. Group II infants demonstrated severe congestive heart failure unresponsive to medical management and unassociated with significant pulmonary pathology. Heart failure was manifested by frequent or continuous apnea spells eventually requiring mechanical ventilation. PDA ligation in these babies was uniformly successful, with 100% survival. Group I infants all had severe hyaline membrane disease at birth requiring mechanical ventilation and developed significant bronchopulmonary
dysplasia prior to operation. The seven deaths were all due to end-stage lung disease. The over-all survival rate of 77% compares quite favorably with the 67% survival rate reported from the only other large series in the literature.

**SUMMARY**

During the period from February, 1971 to February, 1973, 30 premature infants underwent surgical ligation of patent ductus arteriosus. The gestational ages ranged from 25 to 36 wk (mean 30), and the birth weights ranged from 760 to 2010 g (mean 1274). The patients were divided into two groups on the basis of the indications for assisted ventilation. Group I consisted of 21 patients with severe hyaline membrane disease who required assisted ventilation during the first 2 days of life and could not be weaned off the respirator by 10 days of age. Group II was composed of nine infants who required intermittent positive-pressure breathing after a mean age of 8 days because of repeated apneic spells secondary to uncontrollable heart failure. All infants in Group II survived the operation and left the hospital well. Fourteen of the 21 patients in Group I survived; the seven deaths were all due to underlying severe pulmonary disease (bronchopulmonary dysplasia). The value of PDA ligation in premature infants with uncontrollable heart failure is demonstrated in this study; this procedure also appears to be beneficial in neonates with severe respiratory distress syndrome.

**REFERENCES**

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