Surgical Closure of the Ductus Arteriosus in Premature Infants


SUMMARY
During a 62-month period patent ductus arteriosus (PDA) was diagnosed in 88 premature infants with birth weights less than 1750 g. Twenty-one of these infants required operative closure of the PDA. Six infants had uncontrolled heart failure without associated pulmonary disease. Fifteen infants had severe idiopathic respiratory distress syndrome (IRDS) and required operation for deteriorating pulmonary function when heart failure developed. Twelve of these 15 infants weighed less than 1250 g at birth. The ductus arteriosus was ligated in 19 patients and was divided in two patients. The six infants without IRDS survived, and four are completely normal. Of 15 infants with IRDS eight had steady improvement in pulmonary function after operation. Three of these eight patients eventually died. In three infants pulmonary function improved slowly and in two patients pulmonary function did not improve after operation; all of these patients eventually died. Two patients died of peritonitis secondary to bowel ischemia. Of the five infants with IRDS who are alive, one is two months of age, two are moderately retarded in psychomotor development, and two, who developed hydrocephalus, are severely retarded. Although operation successfully controls heart failure in premature infants with PDA and IRDS, progressive pulmonary disease and the complications of extreme prematurity pre-empt good results in most of these infants.

Additional Indexing Words:
Idiopathic respiratory distress syndrome  Respiratory assistance  Heart failure
Cardiac catheterization  Cineangiography

Approximately 15% of premature infants with birth weights less than 1750 g have patent ductus arteriosus (PDA), and approximately 60% of these infants also have the idiopathic respiratory distress syndrome (IRDS). Usually, the ductus arteriosus closes spontaneously in these patients; occasionally, the combination of prematurity and severe heart failure from PDA threatens life. When IRDS is also present, the onset of heart failure often causes deterioration of pulmonary function. We have closed the ductus arteriosus by operation in premature infants when the onset of severe heart failure threatens life or causes a pronounced deterioration in pulmonary function.

In the 62 months between January, 1968, and February, 1973, patent ductus arteriosus was diagnosed in 88 premature infants (birth weight less than 1750 g) during their neonatal hospitalization at the University of California, San Francisco. The ductus arteriosus closed spontaneously in 50 patients (57%), and 17 (19%) infants who were not operated upon died from intracranial hemorrhage (nine patients), infection (four patients), peritonitis (three patients), or renal failure (one patient). Twelve of these 17 infants had IRDS. Twenty-one (24%) infants had surgical closure of the patent ductus. This report describes our experience with the 21 infants who had this operation.*

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* Eight of these infants are included in the previous report.1
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Patient Data

Clinical Findings

Eleven infants were born at the University of California Medical Center and ten were transferred from other hospitals 0 to 33 days after birth. The 21 infants were divided into two groups on the basis of the presence or absence of the idiopathic respiratory distress syndrome.

Six infants did not have IRDS. Initially, these babies had normal chest roentgenograms and did not have clinical signs of respiratory difficulty. One infant who was born at an outside hospital had intubation of the trachea at birth for resuscitation; however, within a few hours the tube was removed. The other infants did not have tracheal intubation at any time before operation. Gestational ages ranged from 28 to 35 weeks (mean 31) (fig. 1). Birth weights ranged from 880–1650 g (mean 1260) (fig. 2). All were single births. Three were females.

Fifteen infants with IRDS developed respiratory difficulty and had abnormal chest roentgenograms soon after birth. Thirteen were intubated at birth, all required some form of respiratory assistance with high concentrations of inspired oxygen (continuous positive airway pressure [CPAP] or mask and bag ventilation), and 13 required mechanical ventilation. Gestational ages ranged from 27 to 35 weeks (mean 29.7) (fig. 1). Birth weights ranged from 850–1600 g (mean 1149) (fig. 2). Five were products of multiple births (three sets of twins and two sets of triplets). Eleven were females.

The diagnosis of patent ductus arteriosus was first suspected by 1) the appearance of a coarse systolic murmur over the left anterior chest; 2) an increase in arterial pulse pressure, or 3) increasing respiratory difficulty associated with a rise in arterial carbon dioxide tension. All of the 21 patients developed a murmur at 3 to 13 (mean 5.7) days of age, and in 14 the murmur eventually extended past the second sound into diastole or became continuous.

The most important clinical signs that indicated the onset of severe heart failure are presented in table 1. All 21 of the infants had at least one of the

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Gestational ages at birth for six infants without IRDS and 15 infants with IRDS are indicated by circles. Horizontal bars represent the mean gestational ages. The difference in mean gestational ages is not significant (P > 0.05).

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Weights of both groups of infants at birth and at operation are illustrated. The circle indicates one infant whose birth weight was not recorded. Horizontal bars indicate mean weights. The difference in mean birth weights is not significant (P > 0.05), but the difference in mean weights at operation is significant (P < 0.05).

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Table 1

Clinical Features in 21 Premature Infants with Patent Ductus Arteriosus

<table>
<thead>
<tr>
<th></th>
<th>No IRDS</th>
<th>IRDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic murmur</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Increased arterial pulse pressure</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Episodic apnea</td>
<td>100</td>
<td>73</td>
</tr>
<tr>
<td>Episodic bradycardia</td>
<td>83</td>
<td>93</td>
</tr>
<tr>
<td>Tachypnea &gt; 60/min</td>
<td>83</td>
<td>67</td>
</tr>
<tr>
<td>Hyperactive precordium</td>
<td>83</td>
<td>87</td>
</tr>
<tr>
<td>Gallop rhythm</td>
<td>67</td>
<td>47</td>
</tr>
<tr>
<td>Pulmonary rales</td>
<td>67</td>
<td>73</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>67</td>
<td>80</td>
</tr>
<tr>
<td>CO₂ retention &gt; 60 torr</td>
<td>33</td>
<td>100</td>
</tr>
<tr>
<td>Cardiomegaly</td>
<td>100</td>
<td>33</td>
</tr>
<tr>
<td>Increased pulmonary vascularity</td>
<td>100</td>
<td>80</td>
</tr>
</tbody>
</table>

Physical signs of severe heart failure. All infants with IRDS developed CO₂ retention (> 60 torr), but only two infants without IRDS did. Conversely, all of the infants without IRDS had roentgenographic evidence of cardiomegaly and increased pulmonary vascularity, but only a third of the group of infants with IRDS had enlarged hearts.

The electrocardiogram was normal in three infants without IRDS and showed a pattern of left ventricular hypertrophy in three others. In infants with IRDS the electrocardiogram was usually normal, but occasionally indicated increased (above normal) right ventricular forces. One infant with IRDS had left ventricular hypertrophy.

At the time the ductal murmur appeared, hematocrit averaged 41 (range 36-48) in infants without IRDS, and averaged 39 (range 35-44) in infants with IRDS. At the time of operation, the mean hematocrit was 37 (range 33-45) in both groups of infants.

Ophthalmic examinations for retrolental fibroplasia were made on one or more occasions in all except three patients who died. Retinas were normal in the five infants without IRDS and in ten infants with IRDS. Three infants with gestational ages of 28 weeks at birth developed ophthalmic evidence of retrolental fibroplasia.

Indications for Operation

The indication for operation in the infants without IRDS was heart failure that could not be managed by digoxin, diuretics, and other medical measures. One of these infants had three cardiac arrests prior to operation.

The indication for operation in the 15 patients with associated IRDS was marked deterioration in pulmonary function coincident with the onset of the signs of severe heart failure. Signs of pulmonary functional deterioration included 1) need for more oxygen to maintain arterial oxygen tension within normal limits (12 patients); 2) arterial carbon dioxide tension above 85 torr (ten patients); 3) need for a mechanical ventilator in infants who were receiving continuous positive airway pressure (five patients); 4) severe apnea when off the respirator (seven patients); and 5) more frequent and severe episodes of bradycardia on and off the respirator (14 patients). All except one infant received digoxin and diuretics.

Catheterization and Cineangiograms

A large left-to-right shunt through the patent ductus arteriosus was demonstrated by angiography in 20 infants (fig. 3). The six infants without IRDS had right and left cardiac catheterization to rule out associated heart lesions; except for patent foramen ovale, none were found. Systolic pressure differences between the descending thoracic aorta and pulmonary arteries varied between 3 and 33 mm Hg (mean 18). Mean pressure differences ranged between 4 and 12 mm Hg (mean 6).

Only four of 15 infants with IRDS had full cardiac catheterization; ten had retrograde aortic catheterization through the umbilical or femoral arteries. Aortic and pulmonary arterial pressures were obtained in nine patients. Systolic pressure differences between the descending thoracic aorta and pulmonary artery ranged between 10 and 28 mm Hg (mean 21). Mean pressure difference varied between 0 and 21 mm Hg (mean 9). Because of difficulties in obtaining well mixed samples, calculations of shunts were unreliable.

Operation

Age at operation ranged between 16 and 44 days (mean 29) for infants without IRDS and between five and 35 days (mean 15) for infants with IRDS. All patients had intravenous catheters, and 15 infants had umbilical, femoral, or radial arterial catheters during operation. Operation was performed with halothane anesthesia in ten infants, with furoxone in nine, and with ketamine in two. The ductus arteriosus was exposed through a posterolateral thoracotomy and was equal to or larger than the diameter of the aortic arch in all patients. The ductus arteriosus was doubly ligated with zero or number 1 gauge silk in 19 patients. In one patient the ductus was divided electively; in another the ductus was divided after the ligature.
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Figure 3

Lateral cineangiogram of an infant without IRDS illustrating the nearly equal size of the patent ductus arteriosus (PDA) and aortic arch (AA).

cut the vessel. Aside from atelectasis and one patient with transient paresis of the left vocal cord no operative complications occurred in the 21 patients.

Results of Operation

Postoperative Course

The six patients without IRDS improved dramatically after operation. In all patients heart failure was controlled, and heart size and pulmonary vascularity decreased in postoperative roentgenograms (fig. 4). All patients were extubated within three days and breathed room air three to 25 days (mean 10) after operation. Atelectasis occurred in four infants but involved lobes of both right and left lungs. In five patients a faint systolic murmur was heard after operation, but all murmurs had disappeared at the time of discharge from the hospital (18 to 51 days after operation).

Postoperative pulmonary function improved steadily in eight of the 15 patients with IRDS. These infants were extubated two to 33 days (mean 13) after operation.

One patient died of intracranial hemorrhage nine days after operation, and one who was extubated and breathing room air died of fluid overload after transfer to another hospital (table 2). The other six patients were discharged home 49 to 109 days after operative closure of the ductus arteriosus.

Respiratory function of three patients improved slowly after operation, but each died during a sudden hypoxic episode 20, 30, and 160 days postoperatively. Two were receiving respiratory assistance at the time of death.

Two patients with IRDS did not improve and died of progressive respiratory insufficiency one and 24 days after operation. Two infants died one and four days after operation from peritonitis secondary to ischemic bowel disease, which was probably present preoperatively.
Of 11 patients with IRDS who had improved pulmonary function postoperatively, seven continued to have brief episodes of bradycardia. Heart size decreased in six of the 11 patients (in two, heart size had appeared normal preoperatively), and pulmonary vascularity decreased in ten. Seven infants had postoperative atelectasis, one developed interstitial emphysema of the right lung, and one required right thoracotomy for recurrent pneumothorax which was present preoperatively. Two infants developed hydrocephalus: one had the Dandy-Walker malformation and one developed hydrocephalus, apparently secondary to intracranial hemorrhage. Both received ventricular-peritoneal shunts.

**Follow-Up**

At present, six operative patients without neonatal IRDS are ten to 60 months of age. Four children are normal and do not have evidence of mental, auditory, or visual losses. Two children are not normal. One of these was born at 28 weeks gestation, weighed 850 g, has mild hemiplegia, grade 1 retrolental fibroplasia, and a developmental quotient of 64 (normal 90 to 110) at 35 months of age. The other child was born at 35 weeks gestation, weighed 1580 g, and has a developmental quotient of 65 at 26 months of age. Environmental influences may be important in the slow development of this child.

One of the six infants who recovered from IRDS and severe heart failure died at home of respiratory infection seven weeks after discharge from the hospital. At autopsy the lungs were found to be fibrotic and grade 1 retrolental fibroplasia was present. The other five patients are two to 23 months of age. The two infants with hydrocephalus are severely retarded, and one of these patients is blind from retrolental fibroplasia. One 23-month-old infant has no speech yet and has psychomotor development appropriate for a 16-month-old infant. One infant nine months of age has development appropriate for the age of five months.

**Table 2**

*Postoperative Change in IRDS in Patients Who Died*

<table>
<thead>
<tr>
<th></th>
<th>Number of Patients</th>
<th>Postoperative Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital Deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improvement in IRDS</td>
<td>2*</td>
<td>9, 18</td>
</tr>
<tr>
<td>Slow improvement in IRDS</td>
<td>3</td>
<td>20, 30, 160</td>
</tr>
<tr>
<td>No improvement in IRDS</td>
<td>2</td>
<td>1, 24</td>
</tr>
<tr>
<td>Peritonitis (Change in IRDS not determined)</td>
<td>2</td>
<td>1, 4</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Late Deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory infection</td>
<td>1</td>
<td>130</td>
</tr>
</tbody>
</table>

* One patient died of fluid overload and the second died of intracranial hemorrhage
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Autopsy Findings

Autopsies were performed in eight of the nine patients who died in hospital. In seven patients, areas of atelectasis, proliferated alveolar septal cells and macrophages, and moderate or severe interstitial fibrosis were present in the lungs. In one of these infants cuboidal cells lined primitive alveoli, and the lungs of two infants had areas that contained hyaline membranes. None of the lungs had congested alveolar capillaries or evidence of squamous metaplasia in the bronchi. The microscopic appearance of the lung of the extubated infant who died of fluid overload did not differ from that observed in infants who had only slow or no improvement in pulmonary function after operation (fig. 5). In contrast, the lung of the infant who died of intracranial hemorrhage nine days after operation was normal.

Discussion

After the twentieth week of gestation the human ductus arteriosus constricts in response to oxygen, acetylcholine, alpha receptor catecholamines, histamine, 5-hydroxytryptamine, and bradykinin.6-12 In vitro the response to high oxygen concentrations can be blocked by atropine and acetylcholinesterase,11,12 but is not blocked by dibenamine.8 In fetal lambs, the degree of ductal constriction by oxygen is proportional to blood oxygen tension and to gestational age.7,13 This relationship may be related to the growth of cholinergic nerves in the ductus between the twentieth week and term.9 Although the exact mechanisms that cause closure of the ductus arteriosus of term infants at birth are not clearly understood, the reduced cholinergic innervation and reduced response to oxygen partially explain the high incidence of patent ductus.
arteriosus in premature infants. This hypothesis is supported by the finding that in many cases the ductus arteriosus does not close spontaneously until the premature infant reaches its full gestational age.\(^2\)\(^,\)\(^3\)\(^,\)\(^5\)

Injections of acetylcholine at the origin of the ductus arteriosus from the aorta have shown that the patent ductus in premature infants is capable of constriction.\(^14\) Although the ductus has remained closed in some infants, the effectiveness of this method of therapy has not been completely investigated. Our experience, and that of others,\(^15\)\(^\text{--}^\text{17}\) indicates that ligation of the ductus can be performed in premature infants without neonatal IRDS with low operative mortality and morbidity. Since most patent ducti eventually close spontaneously, operation is usually not necessary in premature infants.\(^1\)\(^\text{--}^\text{3}\)\(^,\)\(^5\)

Operation is clearly indicated for infants without IRDS who have heart failure that cannot be controlled by medical means. Cardiac catheterization confirms the presence of a large ductus arteriosus and rules out other cardiac lesions. Because the ductus is often friable, ligation is more rapid and safer than division. In this selected group of patients, both early and late results are satisfactory. The certain retardation in one infant probably resulted from an exceptionally short gestation. The slow development of a second infant is not explained by past medical events and still may prove to be temporary.

In each of our 15 patients with prematurity, IRDS, and PDA, definite deterioration in pulmonary function occurred when signs of severe heart failure developed. As pulmonary vascular resistance decreased after birth,\(^14\) the left-to-right ducal shunt presumably caused pulmonary congestion interstitial edema, and elevated pulmonary venous pressure. Although we do not know that heart failure increases pulmonary damage in patients with IRDS, we do know that the advent of heart failure increases pulmonary dysfunction in some infants. When medically uncontrollable heart failure occurs and respiratory status worsens, operation is the only potentially effective therapeutic course available.

Our results in premature infants with severe IRDS and heart failure from PDA are disappointing. Although operation controls heart failure, most of the infants die from progressive and irreversible lung disease or from complications of extreme prematurity. With the exception of one infant who is only two months of age, all of the surviving patients have brain damage or are retarded in psychomotor development. Premature infants with birth weights less than 1250 g have an increased incidence of brain damage and retrolental fibroplasia,\(^19\) and in these extremely premature infants, IRDS increases the likelihood of intellectual impairment.\(^20\) Of our 15 infants with IRDS and PDA, 12 had birth weights less than 1250 g. Operation successfully controlled heart failure in these patients; however, progressive and irreversible lung disease in some, and complications of prematurity in others, precluded satisfactory results.

Brain damage, retrolental fibroplasia, bowel ischemia, and progressive, irreversible lung disease are not inevitable consequences of prematurity and severe IRDS without heart failure. As far as we can determine, operation does not induce these complications. Early control of heart failure, by operation if necessary, removes the immediate threat to life, prevents additional pulmonary dysfunction due to pulmonary congestion and edema and should produce some healthy survivors. Unfortunately, our experience shows that progressive lung disease and the complications of extreme prematurity still preempt a successful outcome in the majority of these tiny patients.

**Acknowledgment**

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