Ligation of Patent Ductus Arteriosus in Very Low Birth Weight Infants

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Forty years ago, Gross and Hubbard [*1*] reported the first successful ligation of a patent ductus arteriosus, and until recently there has been little controversy over the indications for the procedure. During the past decade, improved techniques of intensive neonatal care have permitted prolonged survival of low birth weight, premature infants. In these patients, patent ductus arteriosus is being recognized more often [*2–4*] and the various treatment methods including conservative management [*5*], pharmacologic closure [*6–9*] and surgical ligation [*2,3,10–14*], have their proponents. No consensus has emerged and, in particular, the role of surgical ligation of patent ductus arteriosus in the neonatal period has not been clearly defined. In an attempt to develop criteria for surgical ligation of patent ductus arteriosus in neonates with respiratory distress, we reviewed our experience at this center.

Material and Methods

Twenty-five patients had ligation of the patent ductus arteriosus in the neonatal period at Oklahoma Children's Memorial Hospital during the past 4 years. Patient charts were analyzed for birth weight, gestational age, age at procedure, pre- and postoperative ventilator settings, arterial blood gases, chest roentgenograms and echocardiographic findings. The duration of postoperative ventilatory support, complications, associated diseases, mortality and status at follow-up were also recorded. Infants with congenital cardiac anomalies in addition to patent ductus arteriosus were excluded from the study. Data were analyzed by Student's t test for paired and unpaired data and by chi-square analysis. Values are reported as mean ± standard error of the mean.

The average birth weight of 13 female and 12 male neonates was 1,007 g (range 600 to 1,340). The average estimated gestational age was 28.8 weeks (range 26 to 32). Thirteen patients (52 percent) had bronchopulmonary dysplasia, 8 patients (32 percent) had significant intracranial hemorrhage during hospitalization, and 9 patients (36 percent) were diagnosed as having necrotizing enterocolitis. All patients required ventilatory assistance preoperatively. On the day of operation, 23 patients required ventilatory assistance, 1 patient received supplemental oxygen by tent, and 1 patient was breathing room air. Preoperative chest roentgenography demonstrated bronchopulmonary dysplasia in 10 patients, pulmonary infiltrates in 10 patients, and pulmonary edema or increased vascularity in 3 patients. Preoperative echocardiograms were performed on 24 patients, with findings of left ventricular volume overload in 23. All patients referred for ligation of patent ductus arteriosus had congestive heart failure refractory to medical management.

The clinical diagnosis of persistence of patent ductus arteriosus was made in all patients by the presence of bounding pulses, a hyperactive precordium, a harsh systolic murmur usually continuing into diastole, or widening of the pulse pressure. All patients developed congestive heart failure as manifested clinically by tachycardia, gallop rhythm, rales, hepatomegaly, or episodes of apnea and bradycardia. Congestive heart failure was treated with digitalization, diuretic therapy with furosemide, limited fluid intake and appropriate ventilatory support. Infants whose condition improved within 48 to 72 hours were continued on medical management and are not included in this study. The patients not responding to aggressive medical therapy after 48 to 72 hours underwent ligation of the patent ductus arteriosus.

Response to therapy was determined by clinical and echocardiographic assessment. A primary echocardiographic indication of left ventricular volume overload was the ratio of measured left atrial dimension to mean left atrial dimension for premature infants of corresponding weight without patent ductus arteriosus. If this ratio was greater than 1.5, it was interpreted as strongly indicating

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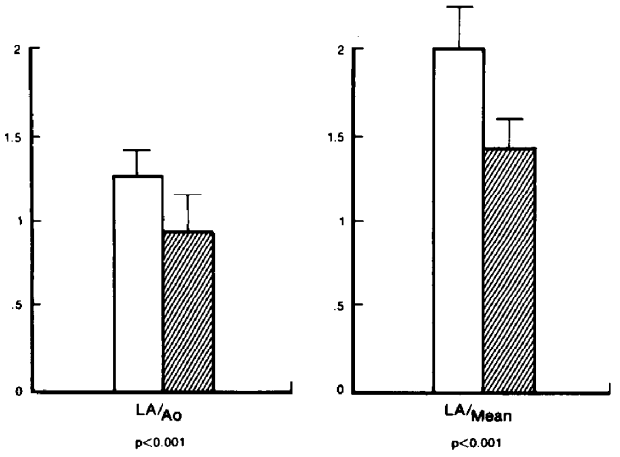

Figure 1. Comparison of preoperative (white bars) and postoperative (shaded bars) left atrial dimension (LA) to aortic root (Ao) ratio and left atrial dimension to literature mean ratio. Horizontal lines represent the standard error of the mean.

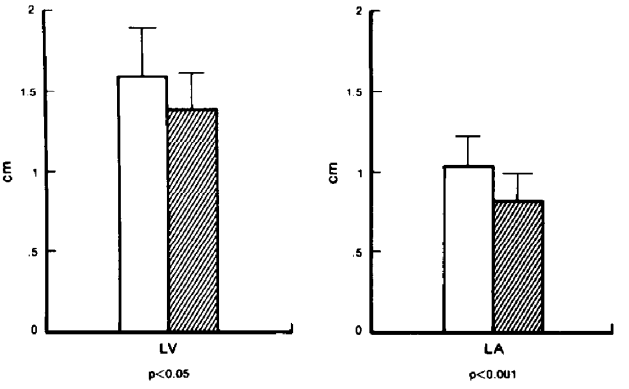

Figure 2. Comparison of preoperative (white bars) and postoperative (shaded bars) left ventricular (LV) dimension and left atrial (LA) dimension. Horizontal lines represent the standard error of the mean.

left ventricular volume overload. A secondary echocardiographic indication of left ventricular volume overload was the presence of a ratio of left atrial dimension to aortic root dimension of greater than 1.15. Serial echocardiograms were obtained in most cases. Trends in the echocardiographic findings were considered more significant than isolated values.

The criteria in this study for ligation of patent ductus arteriosus were (1) clinical signs of patent ductus arteriosus, and (2) respiratory failure complicated by congestive heart failure which did not improve either clinically or echocardiographically after 48 to 72 hours of aggressive medical management. Low birth weight or gestational immaturity were not taken as contraindications to operation. Indomethacin was not used for pharmacologic closure of the ductus.

Candidates for ligation were transported from the neonatal intensive care unit to the operating room in an Ohio® warming unit with temperature and cardiac monitors functioning. Ventilatory assistance was maintained and a physician was in attendance. Under general endotracheal anesthesia, left posterolateral thoracotomy was performed in the fourth intercostal space. The lung was retracted anteriorly and the parietal pleura overlying the ductus was visualized and incised. The vagus and recurrent laryngeal nerves were carefully protected from injury. A suture ligature was placed at each end of the ductus. The wound was irrigated and the parietal pleura was reapproximated. A small chest tube was placed through a separate stab incision and the thoracotomy closed in layers. The skin was closed with an absorbable subcuticular suture. The chest tube was connected to an underwater seal and removed within 24 hours. Patients were returned to the neonatal intensive care unit in the Ohio unit with cardiac and temperature monitors functioning.

Results

Twenty-five patients underwent ligation of patent ductus arteriosus at an average age of 25 days. There were no intraoperative deaths. Two patients (8 percent) died from persistent cardiorespiratory failure at 31 and 143 days postoperatively. Two deaths secondary to intracranial hemorrhage occurred at 7 and 104 days postoperatively. One patient died from pneumonia superimposed on bronchopulmonary dysplasia 72 days postoperatively (4 percent). One patient (4 percent) was found dead in his crib 124 days postoperatively, and his death was attributed to sudden infant death syndrome. Total hospital mortality from all causes was 24 percent.

The length of follow-up averaged 14.5 months. There was one late death at age 8 months secondary to pneumonia. Severe neurologic compromise was noted in three patients and blindness secondary to retrolental fibroplasia in two patients.

Comparison of preoperative with postoperative echocardiographic findings (Figure 1) demonstrated a reduction in the left atrial to aortic root ratio from 1.26 ± 0.03 (mean ± standard error of the mean) to 0.93 ± 0.05 ($p < 0.001$). The ratio of left atrial dimension to a literature mean for left atrial dimension decreased from 1.99 ± 0.06 to 1.42 ± 0.05 ($p < 0.001$). Absolute left ventricular dimension decreased from 1.59 ± 0.06 cm to 1.38 ± 0.05 cm ($p < 0.05$), and left atrial dimension decreased from 1.03 ± 0.04 cm to 0.81 ± 0.04 cm ($p < 0.001$) (Figure 2). Left ventricular dimension decreased dramatically in surviving infants from 1.65 ± 0.08 cm to 1.37 ± 0.03 cm ($p < 0.001$). Infants who ultimately died in the hospital showed no change in left ventricular dimension after ligation: the mean was 1.4 cm both before and after operation.

Comparison of representative ventilator settings preoperatively and within the first 24 hours postoperatively demonstrated an increase in the fractional inspired oxygen concentration from 0.32 ± 0.02 to 0.38 ± 0.03 ($p < 0.025$). The rate of intermittent mandatory ventilation increased after operation from 13.7 ± 1.4 to 16.8 ± 1.7 cycles/min, but the difference

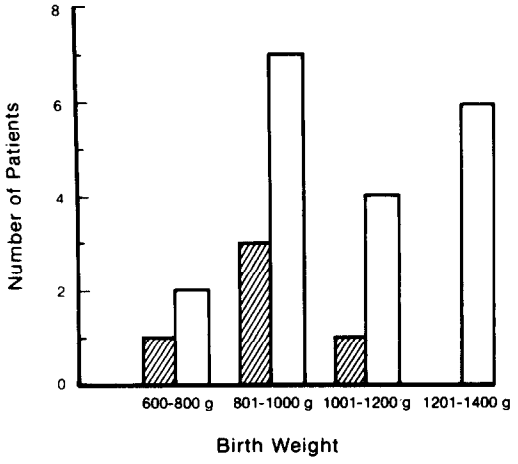

Figure 3. Distribution of hospital deaths (shaded bars) by birth weight. White bars represent patients discharged.

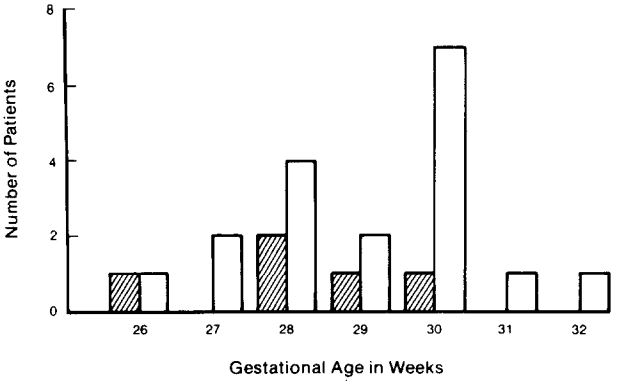

Figure 4. Distribution of hospital deaths (shaded bars) by gestational age. White bars represent patients discharged.

was not statistically significant ($p < 0.20$). Peak ventilatory pressure was unchanged after ligation; the mean remained 22.1 mm Hg. Infants who required fractional inspired oxygen concentration of 0.30 or greater before operation had a 42 percent hospital mortality, while all 10 infants whose oxygen concentration was less than 0.30 when taken to surgery, survived to be discharged ($p = 0.02$, chi-square analysis).

Arterial or capillary blood gases after ligation demonstrated an increase in pH from 7.36 ± 0.01 to 7.39 ± 0.01 ($p < 0.025$) and a decrease in partial arterial carbon dioxide pressure from 49.6 ± 1.7 to 44.9 ± 1.3 mm Hg ($p < 0.025$). No change was found after ligation in the values of base excess, 1.4 ± 0.9 versus 2.1 ± 0.9 mEq/liter or partial arterial oxygen pressure, 51.6 ± 2.3 versus 51.4 ± 2.0 mm Hg. After ligation, patients tended to demonstrate a correction of preexisting respiratory acidosis and to require an elevated oxygen tension in inspired air. Chest roentgenograms obtained 1 to 5 days after ligation demonstrated improvement in 8 patients, worsening in 4 and no change in 12.

Birth weight had a direct bearing on survival (Figure 3). Infants weighing less than 1,000 g at birth had a hospital mortality of 35 percent, whereas infants with a birth weight of 1,000 g or more had a 9.1 percent hospital mortality. Gestational age correlated inversely with mortality (Figure 4). The hospital mortality was 33 percent for infants aged 29 weeks or younger and 10 percent for those older than 29 weeks. These differences were not significant according to chi-square analysis. Sex and race did not correlate with mortality.

Respiratory function improved more rapidly in infants destined to be discharged from the hospital alive. Nineteen hospital survivors were weaned from ventilatory support an average age of 8.5 days postoperatively. Six infants who died in the hospital remained on a ventilator an average of 38 days postoperatively.

There were no intraoperative complications. One patient with pneumomediastinum and two patients with pneumothorax required chest tube drainage beyond 24 hours postoperatively. There were no wound infections.

Comments

Spontaneous closure of the ductus arteriosus occurs without sequellae in most infants. However, when patency of the ductus arteriosus complicates respiratory distress syndrome in the preterm infant, mortality and serious morbidity rates are high. Siassi et al [*15*], in a prospective study of 150 low birth weight infants found that infants with patent ductus arteriosus had a 76 percent incidence of respiratory distress syndrome and a 26 percent mortality. One hundred eight infants without patent ductus arteriosus had a 25 percent incidence of respiratory distress syndrome and a 2 percent mortality. Kitterman et al [*3*] reported a survival of 100 percent in 21 preterm infants without pulmonary disease at the time of identification of patent ductus arteriosus versus a survival of 16 percent in six infants with respiratory distress syndrome at the time of identification of patent ductus arteriosus. Development of criteria for ligation of patent ductus arteriosus in preterm infants depends on differentiation of those patients in whom the ductus will spontaneously close from those in whom the patent ductus arteriosus contributes to death.

A review of the available reports on ligation of patent ductus arteriosus in the neonatal period reveals great variation in the populations reported (Table I). The mean birth weight varies from 1,000 to 1,681 g and the mean gestational age from 27 to 32 weeks. The mean age at operation varies from 8 to 42 days. Mortality varies from zero to 50 percent. Comparison of earlier series to those after 1976 shows

TABLE I Ligation of Patent Ductus Arteriosus in Neonates

Series and Authors	Year	Patients (n)	Mean Gestational Age (wk)	Mean Birth Weight (g)	Mean Age at Operation (days)	Echocardiography Used	Hospital Mortality n	Hospital Mortality %
Gupta et al [*10*]	1972	4	30	...	31	No	1	25
Gay et al [*11*]	1973	45	...	1,400	15	No	15	33
Horseley et al [*16*]	1973	9	29	1,200	29	No	4	44
Edmunds et al [*17*]	1973	21	30	1,181	25	No	10	48
Murphy et al [*18*]	1974	11	30	1,442	21	No	5	45
Zuchman et al [*2*]	1974	27	30	1,400	15	No	9	33
Lewis et al [*19*]	1974	10	31	1,611	11	No	2	20
Kilman et al [*20*]	1974	12	20–34	1,246	2–8	No	2	17
Coran et al [*21*]	1975	30	30	1,274	23	No	7	23
Levitsky et al [*22*]	1976	31	31	1,383	...	No	13	42
Clarke et al [*23*]	1976	22	...	1,054*	27	Yes	5	23
Hall et al [*24*]	1976	28	24–34	700–1,500+	3–127	Yes	13	46
Williams et al [*25*]	1976	20	31	1,280	19	Yes	9	45
Nelson et al [*4*]	1976	32	28.6	1,022	13	No	13	41
Rittenhouse et al [*12*]	1976	11	31	1,325	42	No	2	18
Lippman et al [*26*]	1976	24	29	1,000	13	No	9	37
Naulty et al [*27*]	1978	11	29.5	1,384	15	Yes	5	45
Edmunds [*14*]	1978	9	28	1,039	40	...	1	11
Cooke et al [*28*]	1978	8	27	1,037	28	No	4	50
Hirschklau et al [*29*]	1978	4	30	1,273	...	Yes	0	0
Cotton et al [*13*]	1978	10	29	1,088	8.6	Yes	1	10
Merritt et al [*8*]	1978	28	30	1,358	10	Yes	5	18
Saloman et al [*30*]	1979	25	31	1,000	8	Yes	8	32
Gerber et al [*31*]	1979	17	29	1,138	13	Yes	2	12
Gomez et al [*32*]	1980	14	32	1,681	11.5	Yes	4	29
Gerhardt et al [*33*]	1980	10	31	1,260	15	No	2	20
Total	...	449	...	...	...	...	142	31.7
Current series	1981	25	29	1,007	25	Yes	6	24

* Four weights are not available.

a trend toward lower mean birth weight. Operation tends to be performed at a younger age in more recent series, and echocardiographic measurements were more commonly used. Hospital mortality tended to be lower in the later groups.

Cotton et al [*13*] carried out the only randomized prospective trial of ligation of patent ductus arteriosus in the neonate reported to date. Twenty-five preterm infants with symptomatic patent ductus arteriosus requiring ventilatory assistance at 1 week of age were randomly assigned to continued medical management or surgical ligation. Mortality in the surgical group (10 percent) did not differ significantly from that in the medical group (20 percent). However, the duration of ventilator dependence, morbidity and costs were significantly greater in the medical group. The study was terminated for ethical reasons when decreased morbidity was demonstrated in the surgical group.

The present study represents the experience with a group of infants identified by both clinical and echocardiographic criteria as having not responded to aggressive medical management. The marked improvement in echocardiographic parameters after ligation supports the contention that these measured quantities reflect the volume of left to right shunting. Others have presented data that agree with these findings [*29,34–37*]. Moreover, the improvement in echocardiographic parameters after ligation shows that the infants selected for ligation did indeed have hemodynamically significant shunting before ligation of the ductus. The survival rate in these severely compromised infants was 76 percent, which compares favorably with that in reported series, especially when the size and immaturity of our patients are considered.

Other methods of treatment are not addressed in this study but have been dealt with elsewhere. Nadas [*38*] questions the safety of indomethacin administration in view of the documented renal toxicity and unknown long-term effects. Edmunds [*14*] reviews recent experimental studies of potential neurologic effects of indomethacin administration and concludes that its use should be limited to controlled clinical trials. The effectiveness of indomethacin in low birth weight infants was questioned in two recent reports. Ivey et al [*39*] found no lasting response to indomethacin administration in any of six infants weighing less than 1,100 g at birth. Cooke and Pickering [*40*] found closure of patent ductus arteriosus in only two of seven low birth weight infants receiving indomethacin. The one report championing conservative management alone [*5*] with no recourse to operation is difficult to compare to this or other

surgical series. The patients were larger (mean birth weight 1,665 g) and less premature (mean gestational age 31 weeks) than in most surgical series reported to date.

Surgical ligation of patent ductus arteriosus remains the accepted mode of therapy for patients unresponsive to aggressive medical management. This study shows that infants identified by the criteria used, that is, respiratory failure with clinical signs of uncomplicated patent ductus arteriosus, echocardiographic evidence of left ventricular volume overload and failure to improve with aggressive medical management, may undergo ligation with rapid, objective evidence of improved cardiac functional status and an encouragingly high rate of survival. The study further shows that this may be done in very low birth weight infants with an acceptable mortality. Surgical ligation of patent ductus arteriosus is therefore recommended in the neonate with respiratory failure and echocardiographic evidence of left ventricular volume overload who has failed to respond to 48 to 72 hours of aggressive medical management, irrespective of the patient's birth weight and gestational age.

Summary

Twenty-five low birth weight, premature neonates who were refractory to aggressive medical management underwent ligation of symptomatic patent ductus arteriosus. The mean birth weight was 1,007 g and the mean gestational age 29 weeks. Six patients (24 percent) died before discharge, two from continued cardiorespiratory failure. Echocardiography showed significant improvement in left atrial and left ventricular dimensions after ligation. In the premature neonate with respiratory distress and congestive heart failure refractory to aggressive medical management, surgical ligation may be accomplished with an acceptable hospital mortality in very low birth weight infants.

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Discussion

Carl C. Gill (Cleveland, OH): None of the patients in this series died as a result of surgery or complications directly related to the surgical procedure. The efficacy of interrupting the left-to-right shunt in these very sick infants with respiratory distress syndrome has been clearly demonstrated. The efficacy of M-mode echocardiography in delineating left ventricular volume overload has also been shown. The mortality in this group of patients occurred predominantly in the small, very immature infants, those weighing less than 1,000 g with a gestational age of less than 29 weeks.

The patients that I would like to call attention to, however, are those with complications resulting from the ongoing disease process. Fifty percent of the patients had bronchopulmonary dysplasia, and 30 percent had significant neurologic damage that persisted at the time of discharge. A large group had intracranial hemorrhage and necrotizing enterocolitis. If these patients are to be helped, the only hope is to interrupt the pathophysiologic process earlier in its development. All of the patients in the series had frank congestive heart failure when admitted to the study and therefore were well into the pathophysiologic cycle. Furthermore, all of the patients were relatively older when the ductus was ligated. Twenty-five days is not a long time, but if that time is spent on the ventilator, the ravages are apparent.

We recently used nuclear imaging to determine left ventricular ejection fraction and the ratio of pulmonary to systemic flow. This can be accomplished at the bedside through a peripheral intravenous catheter with the administration of technetium-tagged albumin, and it has been very reliable. If these children are to be helped, it will be procedures similar to this that allow us to demonstrate the shunt before it becomes clinically obvious and interrupts the pathophysiologic process before further complications develop.

Michael G. Nagle (closing): In reference to the age at operation, the neonatologists stated that they usually did not see clinical signs of patent ductus arteriosus in their children before 1 to 2 weeks of age. In reviewing the data from the charts of these patients, I found no statistically significant difference between survivors and nonsurvivors in terms of age at operation.

Echocardiographic assessment is a beneficial tool in these patients and allows quantitation of the left-to-right shunt. We have not used the nuclear imaging techniques that Dr. Gill mentioned. We have used the echocardiographic parameters to predict which patients were going to respond to medical management and which patients were going to require ligation.