Pediatr Cardiol 7:121–127, 1986

Pediatric Cardiology

Original Articles

The Silent Ductus: Its Precursors and Its Aftermath

Cathy Hammerman, Elene Strates, and Sandra Valaitis

Department of Pediatrics, University of Chicago, Chicago, Illinois, USA

SUMMARY. **Prophylactic closure of the patent ductus arteriosus has been recommended as a means of decreasing the morbidity of the very low birth weight neonate. This study was undertaken in order to determine potential risk factors involved in the development of the silent ductus, its impact upon both the early cardiorespiratory symptomatology and the subsequent morbidity of the premature neonate, and finally the potential benefit to be derived from prophylatic closure in this presymptomatic stage.**

Infants with birth weights of 1000 g or less were studied on days 2–3 of life echocardiographically, clinically, and with determination of plasma dilator prostaglandin levels. On entry to the study, those infants with early evidence of silent left-to-right patent ductus arteriosus (PDA) shunting were randomized to receive either prophylactic indomethacin or placebo therapy. Those infants with no evidence of ductal shunting were not treated at all.

Infants with silent PDAs had elevated levels of the dilator prostaglandin metabolite 6-keto $PGF_{1\alpha}$ on admission, although they had no echocardiographic abnormalities. No other risk factors for PDA development could be identified. Silent PDA infants had an increased incidence of subsequent symptomatic PDAs, and overall morbidity and mortality when compared with those with no evidence of PDA (silent or symptomatic). Prophylactic ductal closure decreased the incidence of subsequent PDA development, but had no effect on overall morbidity and/or mortality.

KEY WORDS: **Patent ductus arteriosus — Dilator prostaglandins — Prostacyclin — 6-Keto $PGF_{1\alpha}$ — PGE_2 — Indomethacin**

In 1976, McGrath et al. [17] coined the term *silent ductus* in reference to those premature infants with echocardiographic evidence of left-to-right ductal shunting, but without a murmur or any classic clinical signs of a patent ductus arteriosus (PDA). It has been proposed that early left-to-right shunting across the ductus arteriosus contributes significantly to diminished lung compliance, and thereby to the severity of respiratory distress syndrome (RDS) in the very low birth weight (VLBW) neonate [13]. This assumption forms the basis for the suggestion that early intervention to close prophylactically the silent PDA might improve the respiratory status of the small premature infant, decrease the extent and duration of required ventilatory support, and thereby diminish the subsequent incidence of chronic lung disease. Some clinical trials of prophylactic ductal closure have therefore been undertaken in these infants [14, 16]. These trials, however, have achieved, at best, variable success in affecting the course of chronic lung disease, raising questions as to the effectiveness of such prophylactic therapy and the long-term clinical significance of this early "silent ductus."

The following study, therefore, was designed to evaluate: (a) various factors involved in the development and identification of this silent ductus during the first week of life in the infant weighing 1000 g or less, (b) the implications of having such a silent ductus on the subsequent clinical course of the infant, and (c) whether prophylactic therapy designed to close the PDA at this presymptomatic stage can alter or prevent the development of any PDA sequelae, should they be documented.

Address reprint requests to: Dr. Cathy Hammerman, Department of Pediatrics, Box 325, University of Chicago, 5825 Maryland Avenue, Chicago, IL 60637, USA.

Materials and Methods

All neonates admitted to the Intensive Care Nursery of the University of Chicago with birth weights of 1000 g or less were potential candidates for study. Infants were excluded if there was evidence of cyanotic congenital heart disease, right-to-left ductal shunting (persistent fetal circulation), or if a high umbilical artery catheter (T 7-11) could not be inserted (and thus contrast echocardiography could not be performed).

On the second to third days of life, a contrast echocardiogram was performed on all study infants in order to determine the presence or absence of left-to-right ductal shunting. Based on the echocardiographic findings, the infants were assigned to either:

Group 1. Those with no evidence of ductal shunting at 48–72 h of life, i.e., with a negative contrast echocardiogram *and* with no PDA murmur. No therapeutic intervention was attempted in this group.

Group 2. Those with echocardiographic evidence of a patent ductus arteriosus and shunting at 48–72 h of life. Group-2 infants were then randomized in a double-blind fashion to either:

Subgroup 2A. Infants who were treated with early intravenous indomethacin therapy at 0.2 mg/kg/dose q 12 h × 3 doses.

Subgroup 2B. Infants with evidence of PDA who received placebo (0.45 NS) at an equivalent volume and dosing schedule.

Randomizations were assigned by a statistician and drug or placebo was prepared and dispensed by a clinical pharmacologist without the knowledge of any of the clinicians involved in either the care of the baby or in the study.

On entrance to the study, 1.5-ml blood samples were taken for the measurement of plasma levels of PGE_2 and of 6-keto $PGF_{1\alpha}$, a stable metabolite of the potent vasodilator prostacyclin. Also at this time, an M-mode echocardiogram was performed in order to calculate LA–Ao ratios and left ventricular systolic time intervals.

Those with evidence of ductal left-to-right shunting (group 2) then received their study drug as prescribed. All infants were carefully monitored throughout the neonatal period. The natural course of respiratory distress was assessed in both groups, including severity of disease, duration and extent of ventilatory assistance required, and changing x-ray patterns. Subsequent clinical signs of ductal patency with or without the need for ductal closure were documented. Data was also collected on attendant medical problems, i.e., evidence of bronchopulmonary dysplasia, necrotizing enterocolitis, sepsis, and intraventricular hemorrhage.

Diagnostic Criteria

Patent Ductus Arteriosus (PDA). The diagnosis of a clinically significant PDA (sPDA) was based on the presence of an infraclavicular and precordial systolic murmur consistent with PDA, in the absence of anemia plus any two of the following: active precordium, bounding pulses, diastolic pressure of ≤30 mmHg, pulmonary plethora on chest x-ray, or cardiomegaly on chest x-ray.

Necrotizing Enterocolitis (NEC). The diagnosis of NEC was based on the presence of heme positive stools together with x-ray evidence of pneumatosis intestinalis or free air in the peritoneum.

Bronchopulmonary Dysplasia (BPD). Chest radiographs were obtained regularly during the neonatal course. BPD was diagnosed by one of two pediatric radiologists, in a double-blind fashion. Diagnostic criteria included a pattern of dense streaking filling the interstitium and air spaces with or without hyperexpansion [5].

Intraventricular Hemorrhage (IVH). Head ultrasounds were performed on a weekly basis throughout the neonatal period. They were graded, as described by Papile et al. [18], by radiologists unaware in a double-blind fashion. Only hemorrhages of grade II or above were considered significant for purpose of this study.

Sepsis. Positive blood and/or CSF cultures were considered confirmatory evidence of sepsis.

Laboratory Methods

Echocardiography. Echocardiograms were performed by pediatric cardiology technicians, using a 5-mHz nonfocused transducer with an M-mode echocardiograph (Hoffrel System 201, Norwalk, Connecticut) and strip-chart recorder; and they were analyzed by them in a double-blind fashion. The transducer was placed in the suprasternal notch and angled to image the pulmonary valve, pulmonary artery, the transverse aortic arch, left atrium, and left ventricle. Left ventricular dimensions were measured at the level of the posterior mitral valve leaflet. Systolic time intervals were measured as described by Hirschfeld et al. [12]. An ECG with a well-defined Q wave was simultaneously recorded. Left preejection times were measured from the onset of the QRS complex to the opening of the aortic valve, and left ejection time from opening to closure of the aortic valve. From these measurements, the ratio of LVPEP/LVET was calculated. Tracings were obtained at a paper speed of 75 mm/s to minimize errors in measurements of systolic time intervals. In attempt to further reduce potential errors, three different complexes were measured and averaged to obtain the final value.

For contrast studies, 1 ml of 0.45% normal saline solution was then injected into an umbilical artery catheter according to the methods described by Allen et al. [1] and Zednikova et al. [20]. A left-to-right shunt via a PDA was considered present if both the transverse arch and the pulmonary artery opacified.

Prostaglandin Radioimmunoassay (RIA). Blood samples (1.5 cc) were collected into heparinized (100 U/ml) syringes and immediately decanted into chilled tubes that contained a final concentration of indomethacin of 2×10^5 *M*. They were centrifuged immediately at 2000 *g* at 4°C for 10 min and the plasma stored at −60°C pending analysis by RIA according to a modification of the methods of Coker et al. [3] and Fitzpatrick et al. [8] as described elsewhere [11].

Plasma samples were assayed in a double-blind fashion for levels of PGE_2 and 6-keto $PGF_{1\alpha}$, a stable metabolite of the vasodilator protacyclin. The accuracy of this method for detection of a known amount of prostaglandin ranges from 92% to 114%. Our intraassay and interassay coefficients of variation are 5%–15% and 11%–15%, respectively. Cross-reactivity of the 6-keto $PGF_{1\alpha}$ antisera with PGE_2 is 0.64% and of the PGE_2 antisera with 6-keto $PGF_{1\alpha}$ is 0.01%. Sensitivity varies somewhat from assay to assay, but generally the smallest amount of 6-keto $PGF_{1\alpha}$ measured is 100 pg/ml and of PGE_2 is 50 pg/ml. Discrete values reported are the means of duplicate determinations performed on each sample.

Table 1. Patient characteristics on admission

Characteristics	Group 1[a] (n = 7)	Group 2[b] (n = 24)	p
Historical risk factors			
Birth weight (g)	837 ± 137[c]	845 ± 210[c]	NS[d]
1-Min Apgar	5 ± 2	3 ± 2	NS
5-Min Apgar	6 ± 1	5 ± 2	NS
PROM[e]	14%	25%	NS
NSVD/total deliveries[f]	57%	75%	NS
Metabolic risk factors			
Fluids (cc/kg/day)	115 ± 19	96 ± 33	NS
Hematocrit	46 ± 3%	46 ± 3%	NS

[a] Group 1, no silent PDA on initial evaluation.
[b] Group 2, silent PDA present on initial evaluation.
[c] Means ± SD.
[d] NS, not significant.
[e] PROM, prolonged rupture of membranes, ≥24 h prior to delivery.
[f] NSVD, normal spontaneous vaginal deliveries.

Table 2. Cardiorespiratory variables on admission

Variables	Group 1[a] (n = 7)	Group 2[b] (n = 24)	p
6-keto $PGF_{1\alpha}$			
Mean ± SD (pg/ml)	196 ± 57[c]	633 ± 481[c]	<0.01
% Elevated	0%	67%	<0.01
PGE_2			
% Elevated	0%	8%	NS[d]
LA/Ao ratio[e]	1.03 ± 0.23	1.09 ± 0.24	NS
LVSTI[f]	0.31 ± 0.06	0.35 ± 0.09	NS
Initial Fio_2	50 ± 12%	50 ± 21%	NS
Initial P_{max}[g]	18 ± 3	21 ± 5	NS

[a] Group 1, no silent PDA on initial evaluation.
[b] Group 2, silent PDA present on initial evaluation.
[c] Means ± SD.
[d] NS, not significant.
[e] LA/Ao ratio, left atrial to aortic root ratio.
[f] LVSTI, left ventricular systolic time interval.
[g] P_{max}, maximal inspiratory pressure.

Analysis of Data. Means and standard deviations were computed for each of the continuous variables, e.g., prostaglandins, and differences were compared using the Student's two-tailed t-test. Categorical variables, e.g., presence versus absence of sPDA, were compared using Chi-square analysis and the Fisher exact test. Significance was accepted at $p < 0.05$.

Results

A total of 37 neonates entered the study. Two infants (one each from group 1 and group 2B) were eliminated from the analysis because they expired on the day of entry, and thus no follow-up data could be obtained. One infant from group 2A did not complete the study protocol, and thus was removed from analysis. Three additional infants had clinical PDA murmurs on initial evaluation, but had negative contrast echocardiograms, and thus did not fit into any of our group assignments. Of the remaining 31 infants, seven were in group 1 and 24 in group 2. Of these, ten were in group 2A (indomethacin treated) and 14 in group 2B (placebo treated).

PDA Risk Factors

There were no differences between the groups with respect to various obstetric parameters including birth weight, gestational age, the incidence of prolonged rupture of membranes, and the proportion of vaginal deliveries versus caeserian sections (Table 1). No differences were found in the amount of fluid administered to the two groups on the day that the initial echocardiogram was performed, in the severity or in the incidence of early neonatal hypocalcemia, or in the hemoglobins or hematocrits of the two groups at the time of admission to the study.

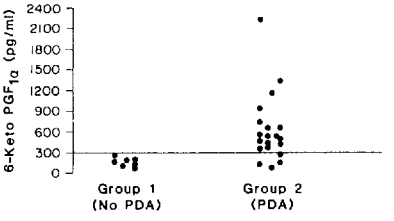

Fig. 1. Plasma 6-keto $PGF_{1\alpha}$ levels (pg/ml) of individual members of group 1—those who had no clinical or echocardiographic evidence of ductal shunting when initially evaluated on days 2–3 of life: and group 2—those with echocardiographic evidence of silent ductal shunting on initial evaluation. Note that all group-1 infants have levels below 300 pg/ml, while 67% of the silent ductus infants have levels above 300 pg/ml.

Silent PDA Clinical Correlates

Prostaglandins. Levels of the dilator prostaglandin metabolite, 6-keto $PGF_{1\alpha}$ (Table 2) were elevated in the PDA group as compared with the non-PDA infants (633 ± 481 vs 196 ± 57 pg/ml; $p < 0.01$). In addition, 67% of the PDA infants had 6-keto $PGE_{1\alpha}$ levels above 300 pg/ml (Fig. 1), while none of the non-PDA infants had levels in this range ($p < 0.01$). Two infants in the PDA group also had elevated PGE_2 levels as compared with none of the non-PDA group.

Table 3. Subsequent clinical course

Clinical course	Group 1[a] (n = 7)	Group 2[b] (n = 24)	p
sPDA incidence[e]	14%	58%	<0.01
Day diagnosed	9	8 ± 4[c]	NS[d]
Treated PDAs	14%	29%	NS
BPD incidence[f]	57%	88%	<0.01
Day BPD diagnosed	12 ± 4[c]	17 ± 9	NS
Days on ventilator	37 ± 22	36 ± 32	NS
Days on supplemental Fio_2	46 ± 24	47 ± 32	NS
IVH[g]	14%	29%	NS
NEC[h]	0%	14%	NS
Sepsis	14%	42%	NS
Deaths	0%	42%	<0.05

[a] Group 1; no silent PDA on initial evaluation.
[b] Group 2; silent PDA present on initial evaluation.
[c] Means ± SD.
[d] NS, not significant.
[e] sPDA, symptomatic PDA.
[f] BPD, bronchopulmonary dysplasia.
[g] IVH, intraventricular hemorrhage.
[h] NEC, necrotizing enterocolitis.

Echocardiographic Variables. No differences in LA/Ao ratios or LVSTIs were noted between the groups on admission to the study.

Respiratory Symptoms. On admission to the study, all infants had respiratory distress syndrome and were receiving assisted ventilation. The initial FiO_2s were 0.50 ± 0.12 (group 1) and 0.50 ± 0.21 (group 2); peak inspiratory pressures on entrance to the study were 22 ± 5 vs 21 ± 5 mmHg, respectively. Thus both the PDA and non-PDA infants had similar degrees of respiratory distress as manifested by the levels of ventilatory support required.

Subsequent Clinical Course

Subsequent Symptomatic PDAs (sPDA). The incidence of subsequent sPDA development (Table 3) was significantly different between the groups (14% for those who never had any evidence of PDA versus 58% for the silent PDA group; $p < 0.05$). The time of appearance of clinical PDA symptoms and the severity of the shunting, however, as determined by the proportion of sPDAs requiring further therapeutic intervention, were similar.

BPD. 57% of the group-1 infants developed BPD as compared with 88% of group-2 infants (Table 3).

IVH. 14% of group-1 infants versus 29% of group-2 infants developed a significant intraventricular hemorrhage of grade 2 or greater.

NEC. None of the group-1 infants had evidence of necrotizing enterocolitis, while 14% (three infants) of the silent ductus infants had evidence of NEC, two of which were associated with perforation and death.

Sepsis. There was one case (14%) of culture proven sepsis in group 1 and, in contrast, ten infants (42%) in group 2 had positive blood and/or CSF cultures. There were no differences in the number or duration of indwelling umbilical artery catheters.

Overall Morbidity. Considering the five specific disease entities studied, within group 1, which has seven babies, there is a total potential morbidity of 35 patient/disease entities, and an actual incidence in this group of seven such entities, yielding a morbidity rate of 20%. Similar calculations for group 2 provide a potential of 120 with an actual morbidity incidence of 51, yielding a rate of 42% ($p < 0.05$).

Mortality. While there were no deaths in the non-PDA group, ten of the 24 silent ductus infants died ($p < 0.05$). Of these, five were in group 2A and five were in group 2B.

Effect of Treatment on Clinical Course

There were no differences on admission between the infants within the two PDA subgroups, i.e., the PDA infants treated with prophylactic indomethacin (subgroup 2A) and those treated with placebo (subgroup 2B), with respect to any of the historical or metabolic risk factors monitored. They were also similar in the severity of their initial PDA symptomatology as assessed by pretreatment prostaglandin levels, echocardiographic variables, and levels of respiratory support.

Prophylactic treatment did affect the subsequent incidence of sPDAs (30% in subgroup 2A versus 79% in subgroup 2B; $p < 0.05$). Again the time of diagnosis and PDA severity were similar. The incidence of BPD, IVH, NEC, and sepsis was similar when comparing the two subgroups, although not necessarily similar to the non-PDA group, as described earlier (Fig. 2).

Perspective

Overall Morbidity and Mortality. Although few particular disease entities were specifically related to the existence of early ductal shunting, the general morbidity of the PDA group was higher than that of the never-shunted group. The mortality of group 2 was also higher than that of group-1 infants (42% vs 0% $p < 0.05$), while the mortalities within the PDA

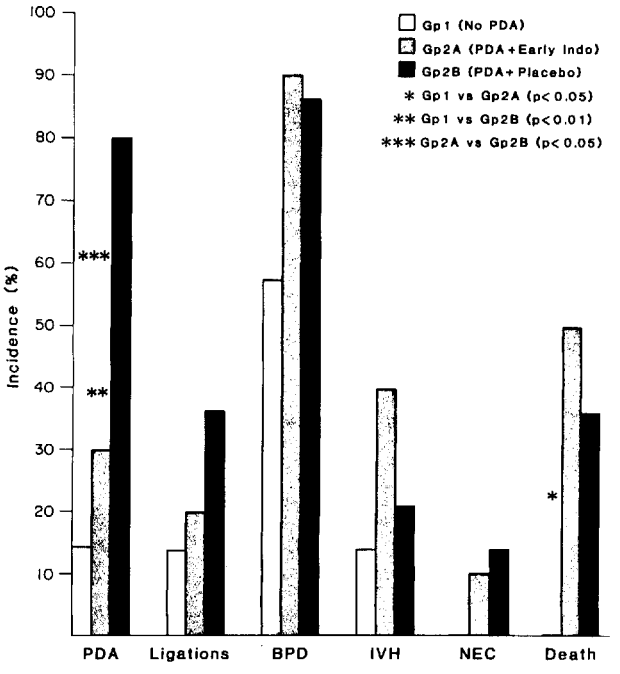

Fig. 2. Incidence of various disease entities, plotted as % of total for group 1—never shunted infants; subgroup 2A—PDA infants treated prophylactically with intravenous indomethacin; and subgroup 2B—PDA infants treated with placebo. Significant differences are found for the incidence of subsequent symptomatic PDA (group 1 vs 2B and group 2A vs 2B) and of death (group 1 vs 2A).

subgroups were similar. Interestingly, the presence or absence of early treatment aimed at ductal closure had little effect on either morbidity or mortality, as manifested by the differences between groups versus the lack of differences between the subgroups.

Discussion

For infants with birth weights of 1000 g or less, the incidence of PDA is estimated to be anywhere from 40% to 80% [6, 7]. The absence of a murmur, especially in infants with severe respiratory distress syndrome (RDS), does not necessarily mean that the ductus is closed. In fact, it has been postulated [13] that, in very low birth weight babies, the initial manifestations of RDS, even without any classic signs of PDA, are largely due to left-to-right shunting through a PDA with a relatively smaller contribution of surfactant deficiency. Of the infants in the National Collaborative PDA Study, 11% had no murmur on the day of diagnosis [10]. Dudell and Gersony have recently demonstrated [4], using contrast echocardiography, that 60% of infants <1000 g have evidence of ductal shunting on day 3 of life. In our study, a similar 61% showed echocardiographic evidence of early ductal shunting. These early, presymptomatic PDAs can also be detected by pulsed Doppler or continuous-wave Doppler echocardiography when these techniques are available.

Although the prevalence of this silent ductus in the VLBW population is well documented, its longer-range clinical significance is not. Several studies of prophylactic therapy to close such a ductus in the VLBW infant have been undertaken with the assumption that prophylactic ductal closure will improve overall morbidity and mortality in these infants [14, 16]. In fact, however, this assumption of clinical significance has never been verified. Furthermore, the success of these investigations has been limited.

The goal of this study was therefore to evaluate some of the factors involved in the development of this silent ductus in an at risk population, as well as the clinical impact of early, untreated, left-to-right ductal shunting upon the subsequent development of various disease entities.

At the time of initial evaluation, the PDA infants were asymptomatic from the standpoint of absence of murmur, congestive heart failure, and other classic symptoms of ductal symptomatology and increased respiratory distress. It is known that both increased LA/Ao [19] ratios and decreased LVSTIs [11] are associated with symptomatic PDAs. We therefore measured these echocardiographic variables to determine whether they were at all correlated with ductal shunting in the presymptomatic stage. They were not, which is consistent with the assumption that the ductus at this early stage is cardiologically insignificant, and thus has no effect on either cardiac dimensions or function as measured by echocardiography.

The only significant difference between the PDA and the non-PDA groups at this presymptomatic stage was in the incidence and extent of elevation of 6-keto $PGF_{1\alpha}$ levels. Increased dilator prostaglandin levels have also been previously documented in conjunction with symptomatic PDA [9, 15]. It is not known, as yet, whether this elevation of dilator prostaglandins is the cause or effect of ductal patency, and therefore it was difficult to anticipate whether they would be increased in the presymptomatic stages of PDA development. In this study, a significant elevation of 6-keto $PGF_{1\alpha}$ levels (a stable metabolite of the dilator prostaglandin, prostacyclin) was observed even in the silent ductus stage. Our data thus would support the possibility of a pathogenetic role for this dilator prostaglandin.

It was found that early asymptomatic ductal patency is most highly correlated with later development of symptomatic PDA, which confirms the observations reported by Dudell and Gersony [4] that the existence of ductal shunting on day 3 of life

is highly predictive of subsequent significant PDA. Having an early asymptomatic patent ductus did not, however, imply that subsequent symptomatic PDAs would appear sooner or that they would be more severe when they did appear. This is supported by the study described by Mahoney et al. [16], who found that, by prophylactically treating VLBW infants on the first day of life, they were able to decrease the subsequent incidence of PDAs, but not the need for surgical ligations.

The incidence of bronchopulmonary dysplasia tended to be higher in both PDA groups as compared with the non-PDA infants, although this increased incidence did not reach the level of statistical significance. The pulmonary edema that generally occurs secondary to left-to-right shunting is known to increase the likelihood of development of such chronic lung changes [2]. However, it is interesting that ductal closure did not affect the incidence of BPD development. The initial three days of ductal shunting prior to therapy may be more significant in predisposing the infant to chronic lung changes than are the subsequent days. This is an interesting finding in that it speaks most directly to the controversy concerning prophylactic ductal closure. It has been hypothesized [13] and documented in at least one study [14] that this early treatment would decrease the incidence and severity of subsequent respiratory distress and the duration of ventilatory assistance requirements. These observations were made on larger infants, however, and were not supported by the study of Mahoney et al. [16], who found no difference in the duration of supplemental oxygen or ventilatory support after prophylactic therapy. If, as shown here and as implied by the data of Mahoney et al., early silent ductal shunting does not increase the subsequent risk of chronic lung disease, then this rationale for prophylactic ductal closure disappears.

Several other potential neonatal complications, including NEC, IVH, and sepsis were studied and do not appear to be directly influenced by the existence of an early asymptomatic PDA. Again, if it is true that early ductal patency does not increase the risk of any of these disease entities, then prophylactic ductal closure would not be expected to improve morbidity in this group of infants.

Those infants treated with indomethacin did have significantly fewer subsequent sPDAs than those treated with placebo. In fact, their incidence was indistinguishable from those who never had evidence of ductal shunting. Thus one might expect their subsequent course to most closely resemble this group. On the contrary, the incidence of morbidity in the treated group was more similar to that of the placebo-treated group, and different from that of the non-PDA group.

Deaths were also increased in those with evidence of a silent ductus on days 2–3. Whether or not the PDA was prophylactically closed at this point, again, had less impact on the subsequent clinical course than whether or not it ever existed. In summary:

1) The only identifiable risk factor possibly associated with PDA development was an elevation of plasma levels of the dilator prostaglandin metabolite, 6-keto $PGF_{1\alpha}$.

2) The implications for the small premature neonate of having a silent ductus within the first 2–3 days of life may include an increased incidence of developing a later symptomatic PDA if not closed "prophylactically," a trend toward an increased chance of developing chronic lung disease, and a general increase in morbidity and mortality. These complications may or may not be at all associated with the existence of early ductal patency.

3) Early closure of the silent ductus decreased the subsequent incidence of symptomatic PDAs, but was not successful, in our study, in decreasing overall morbidity and/or mortality. Furthermore, morbidity and mortality were lower in the group of infants who never displayed any evidence of ductal shunting than in those who had silent PDAs that were successfully closed. It is possible that all of these conditions, including the PDA, are manifestations of illness in a group of infants at high risk. Our initial evaluation, however, did not show any increased risk factors in the non-PDA group as compared with the silent ductus group. It is also possible that all of these reflect some as yet unidentified risk factor, or that ductal shunting itself conveys an increased risk for the development of other sequelae. No particular disease entity was associated with the existence of a silent PDA, however, and it seems less likely that ductal shunting would cause a nonspecific increase in overall morbidity. Finally, it is possible that all of the complications noted are related to elevated levels of one specific mediator, e.g., prostaglandins. Further study is required to distinguish between these options.

Acknowledgments. This work was funded in part by Block Fund Grant 6 3340 126094, Children's Research Fund of Chicago Grant 693530, and Clinical Research Center of Chicago Grant 193. The authors would like to thank the nursing and pediatric housestaff and the neonatal fellows for their cooperation and assistance in carrying out study procedures.

References

1. Allen H, Sahn D, Goldberg S (1978) New serial contrast techniques for assessment of left-to-right shunting patent ductus arteriosus in the neonate. *Am J Cardiol 41*:288–294

2. Brown E (1979) Increased risk of bronchopulmonary dysplasia in infants with patent ductus arteriosus. *J Pediatr 95*:865–866
3. Coker S, Clarke B, Zeitlin I (1982) Radioimmunoassay techniques for the determination of the local release of prostaglandins and thromboxanes. *J Pharmacol Methods 7*:207–217
4. Dudell G, Gersony W (1984) Patent ductus arteriosus in neonates with severe respiratory disease. *J Pediatr 104*:915–920
5. Edwards D, Jacob J, Gluck L (1980) The immature lung: radiographic appearance, course and complications. *Am J Radiol 135*:659–666
6. Ellison R, Peckham G, Lang P, Talner N, Lerer T, Lin L, Dooley K, Nadas A (1983) Evaluation of the preterm infant for patent ductus arteriosus. *Pediatrics 71*:364–372
7. Emmanouilides G (1977) Persistent patency of the ductus arteriosus in premature infants: incidence, perinatal factors and natural history. In: *The 75th Ross conference on pediatric research*. Ross Laboratories, Columbus OH
8. Fitzpatrick F, Gorman R, McGuire J, Kelly R, Wynalda M, Sun F (1977) A radioimmunoassay for thromboxane B_2. *Anal Biochem 82*:1–7
9. Freidman Z Demers L (1978) Essential fatty acid, prostaglandins and respiratory distress syndrome of the newborn. *Pediatrics 61*:341–347
10. Gersony W, Peckham G, Ellison R, Miettinen O, Nadas A (1983) Effects of indomethacin in premature infants with patent ductus arteriosus: results of a national collaborative study. *J Pediatr 102*:895–906
11. Hammerman C, Strates E, Zaia W, Berger S, Aldousany A (1986) Prostaglandins and echocardiography in the assessment of the patent ductus arteriosus. *Crit Care Med 14*:462–465
12. Hirschfeld S, Meyer R, Schwartz D, Korfhagen J, Kaplan S (1975) Measurement of right and left ventricular systolic time intervals by echocardiography. *Circulation 51*:304–309
13. Jacob J, Gluck L, Di Sessa T, Edwards D, Kulovich M, Kurlinski J, Merritt T, Friedman W (1980) The contribution of PDA in the neonate with severe RDS. *J Pediatr 96*:79–87
14. Kaapa P, Lanning P, Kolvisto M (1983) Early closure of patent ductus arteriosus with indomethacin in preterm infants with idiopathic respiratory distress syndrome. *Acta Paediatr Scand 72*:179–184
15. Lucas M, Mitchell M (1978) Plasma prostaglandins in preterm neonates before and after treatment for patent ductus arteriosus. Lancet *2*:130–132
16. Mahoney L, Caldwell R, Girod D, Hurwitz R, Jansen R, Lemons J, Schreiner R (1985) Indomethacin therapy on the first day of life in infants with very low birth weight. *J Pediatr 106*:801–805
17. McGrath R, McGuiness G, Way G, Wolfe R, Nora J, Simmons M (1978) The silent ductus arteriosus. *J Pediatr 93*:110–113
18. Papile L, Burstein J, Burstein R, Koffler H (1978) Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 grams. *J Pediatr 92*:529–534
19. Silverman N, Lewis A, Heymann M, Rudolph A (1974) Echocardiographic assessment of ductus arteriosus shunt in premature infants. *Circulation 50*:821–825
20. Zednikova M, Baylen B, Yoshida Y, Emmanouilides G (1982) Precordial contrast echocardiographic detection of patent ductus arteriosus in small preterm infants. *Pediatr Cardiol 2*:271–275