Predictors of Respiratory Improvement 1 Week after Ligation of Patent Ductus Arteriosus in Preterm Infants

Kai-Hsiang Hsu, MD[1,2,3], Pierre Wong, MD[4], S. Ram Kumar, MD, PhD[5], Julie Evans, RN, BSHCM[1], and Shahab Noori, MD, MS CBTI[1]

Objective To characterize preterm infants that demonstrates respiratory improvement 7 days after ligation of a patent ductus arteriosus (PDA).

Study design We performed a 2-phase study of preterm infants (birthweight <1500 g between 2010 and 2016). We first did a retrospective analysis using regression modeling of ligation population. We then performed a case-control study comparing a ligation group with infants matched by gestational age, postnatal age, and preligation respiratory condition (ventilator mode, mean airway pressure [MAP], and fraction of inspired oxygen [FiO_2]). Respiratory improvement was defined as either extubation, downgrading of ventilatory mode, reduction in MAP >25%, or decrease in FiO_2 >25%.

Results Forty-five (42%) of 107 preterm infants (gestational age 25.5 ± 1.7 weeks) with ligation showed respiratory improvement at 7 days. Infants on high frequency ventilation (HFV) were more likely to have respiratory improvement (aOR 5.03, 95% CI [1.14-22.18]). In matched-control analysis of 89 pairs, there was no difference in respiratory improvement. Among infants on HFV, the ligation group had an increase in MAP during 3 days prior to ligation. For infants on conventional ventilation, the ligation group had higher MAP and FiO_2 than the control group during the first 2-3 postoperative days.

Conclusions Among infants undergoing PDA ligation, those on HFV were more likely to have respiratory improvement in the first week, possibly because of the prevention of further respiratory deterioration. For infants on conventional ventilation, ligation was associated with higher respiratory support in the immediate postligation period without respiratory benefits at 7 days. As HFV was used as a rescue mode, our findings suggest that those with worse lung disease may achieve greater short term benefit from PDA ligation. *(J Pediatr 2019;205:49-54).*

Patent ductus arteriosus (PDA) is common among very low birth weight (VLBW, <1500 g) preterm infants. Continuous left-to-right ductal shunting increases pulmonary blood flow and lung fluid, thereby reducing lung compliance.[1] A significant PDA is often associated with an escalation in ventilatory support.[2] When closure of PDA is considered, surgical ligation remains the definitive therapy for those who fail or have a contraindication to cyclooxygenase inhibitors treatment. However, because of the invasive nature of the procedure and associated morbidities, there is a growing concern about harmful effects of PDA ligation.[3-7] As a result, there is a move toward delaying the procedure or avoiding ligation altogether except for the extreme cases.[8-12]

Although the treatment of PDA is controversial,[13] the decision to ligate a PDA appears to be heavily influenced by respiratory status and degree of ventilatory support. One study reported that over 90% of neonatologists will consider ligation for moderate-to-severe PDA in infants <900 g and <28 weeks who require mechanical ventilation.[14] The effect of ligation on respiratory function is unclear. Although not conclusive,[3] lung compliance is generally shown to improve after ligation.[15-18] However, lung compliance does not change or even decreases after the procedure in a subset of patients,[16,17] and acute deterioration in oxygenation after ligation has also been reported.[19] In preterm baboons, ligation was associated with worsening oxygenation during the first 24 hours after the procedure, but no difference was noted between ligated and nonligated baboons 1 week later.[20] Long-term benefits of PDA ligation are also unclear; although ligation appears to increase the risk of bronchopulmonary dysplasia,[21] recent studies indicate that prolonged exposure to PDA increases the incidence and severity of

FiO_2	Fraction of inspired oxygen
HFV	High frequency ventilation
MAP	Mean airway pressure
PDA	Patent ductus arteriosus
PMA	Postmenstrual age
RSS	Respiratory severity score
VLBW	Very low birth weight

From the [1]Fetal and Neonatal Institute, Division of Neonatology, Children's Hospital Los Angeles, Department of Pediatrics, Keck School of Medicine, University of Southern California, Los Angeles, CA; [2]Division of Neonatology, Department of Pediatrics, Chang Gung Memorial Hospital Linkou Branch; [3]Graduate Institute of Clinical Medical Science, Chang Gung University, Taoyuan, Taiwan; [4]Division of Cardiology, Children's Hospital Los Angeles, Department of Pediatrics, Keck School of Medicine, University of Southern California; and [5]Heart Institute, Division of Cardiac Surgery, Department of Surgery, Keck School of Medicine of University of Southern California, Los Angeles, CA

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bronchopulmonary dysplasia.[22-25] Given the lack of randomized control trials comparing ligation with no treatment, the causality relationship between either PDA or its ligation and deterioration in respiratory function remain unproven. In this study, we set to identify the predictors of improvement in respiratory status of VLBW infants undergoing PDA ligation 1 week after the procedure. As respiratory status is not only impacted by the ligation surgery but also evolves with time, we sought to compare the respiratory status of these patients to a control group matched by gestational age, postnatal age, and level of ventilatory support.

Methods

We performed a retrospective study of VLBW infants admitted to the neonatal intensive care unit at Children's Hospital Los Angeles from June 2010 to December 2016. The institutional review board approved the study. Exclusion criteria were major anomalies or congenital heart disease other than small atrial or ventricular septal defects, surgery during the study period and 1 week prior to ligation, and not being on ventilator support before ligation. At Children's Hospital Los Angeles, the decision regarding ligation of a PDA is made by the attending neonatologist; however, in selected complex cases the pediatric cardiologist is consulted. A PDA is considered for ligation based upon echocardiographic (ductal size, flow pattern, evidence of volume overloading, and systemic hypoperfusion) and clinical findings (degree of cardiorespiratory support, evidence of end-organ flow compromise [eg, rising creatinine], gestational and chronological age). Ligations are performed by the pediatric cardiothoracic surgeons in the neonatal intensive care unit, and the patient is kept on the same ventilator mode.

The study consisted of 2 phases. In the first phase, the objective was to identify predictors of improvement in respiratory status 7 days after PDA ligation. We chose the 7-day time point because we thought it would be long enough for the patient to overcome any acute deterioration from the surgery and to demonstrate benefit from the removal of excessive pulmonary flow via the PDA. The second phase of the study consisted of an analysis to differentiate the effect of ligation from the natural evolution of lung disease on respiratory function. In this phase, the ligation group was matched to a control group who did not undergo PDA ligation (described below).

Data on demographics and clinical characteristics were collected. The images from the most recent echocardiogram prior to ligation were reviewed by 1 of the authors trained and experienced in echocardiography for ductal diameter at its narrowest point, direction of shunt, ductal flow velocity, and ratio of left atrial to aortic root diameters.

Ventilatory mode was categorized as high frequency (HFV), conventional, or noninvasive ventilation (nasal intermittent mechanical ventilation and continuous positive airway pressure). Ventilatory mode, mean airway pressure (MAP), and fraction of inspired oxygen (FiO_2) were documented at 6, 24, 48, and 72 hours prior to ligation and 6, 12, 24, 48, and 72 hours, and 7 days after ligation. Respiratory severity score (RSS = MAP × FiO_2) was used to assess the severity of respiratory failure.[26,27] The a priori definition of respiratory improvement (the primary outcome) was any one of the following: extubation, a downgrade of ventilatory mode, a wean in MAP >25%, or a decrease in FiO_2 >25% at 7 days after ligation compared with 6 hours prior to ligation.

We matched ligation group with control subjects who did not undergo PDA ligation (1:1) using 5 measures: gestational age (±1 week), postnatal age (±7 days), mode of ventilation, MAP (±2 cmH_2O), and FiO_2 (±0.2) at 6 hours prior to ligation.

Statistical Analyses

The sample size was not predetermined; we included all eligible infants in the study. Statistical analysis was performed using SPSS Statistics 20 (IBM, Armonk, New York). In phase 1, between-group continuous data was tested using independent *t* test, and categorical data were analyzed with χ^2 or Fisher exact tests. A *P* value of <.05 was considered statistically significant. Factors with a $P < .1$ in univariate analysis were considered for further analysis in logistic regression modeling to predict respiratory improvement. Repeated-measures ANOVA was used to compare serial changes of respiratory supports in phase 2.

Results

During the 6.5-year period, 144 infants underwent PDA ligation at our hospital. A total of 107 VLBW infants met the inclusion and exclusion criteria for the ligation group (**Figure 1** and **Table I**; available at www.jpeds.com). Overall, 45 (42%) infants had improvement in respiratory status at 7 days after ligation. Of the 62 infants without improvement, 37 (60%) had no change and 25 (40%) had deterioration in respiratory status. Comparing ligated infants with vs without improvement in respiratory status, there was no significant difference in demographics (**Table I**) and complications of prematurity prior to ligation. Infants with respiratory improvement had higher preligation MAP, FiO_2, and RSS and were more likely to be on HFV at the time of ligation (**Table I**). Considering mode of ventilatory support, 29 of 48 of infants (60%) on HFV, 16 of 54 of infants (30%) on conventional ventilation, and none of 5 infants on noninvasive ventilation had respiratory improvement at 7 days after ligation. Infants on conventional ventilation had higher rates of extubation within 7 days of ligation than those on HFV (13/54 [24%] vs 4/48 [8%], $P = .037$).

Based on univariate analysis, we selected preligation mode of ventilation, MAP, FiO_2, and diameter of PDA as potential predictors of respiratory improvement. In multiple regression analysis, only HFV remained significantly associated with respiratory improvement after ligation (aOR 5.03, 95% CI 1.14, 22.18). Using >25% reduction of RSS instead of >25% reduction in MAP or FiO_2 as definition of respiratory improvement did not change the above finding. As for longer term respiratory outcomes, infants with respiratory improvement had lower FiO_2 and less invasive ventilatory support at 36 weeks postmenstrual age (PMA) (**Table I**).

For phase 2 of the study, a total of 89 patients in the ligation group could be fully matched to a control group. The 18 infants in ligation group who could not be matched had lower BW and higher ventilatory support prior to ligation but no difference in postligation respiratory improvement compared with those that could be matched (data not shown). Among matched controls, 26 infants (29%) had a PDA (88% and 62% were ≥1.5 and 2 mm in diameter, respectively compared with 99% and 83% in the ligation group).

The demographic and clinical characteristics of the matched ligation group and the controls were similar (**Table II**). No infants in either group had intraventricular hemorrhage, bacteremia, necrotizing enterocolitis, or spontaneous intestinal perforation during the week prior to ligation/match.

The rates of respiratory improvement at 7 days after ligation were similar in the ligation group and the matched control groups (48% vs 44%, $P = .548$) (**Table II**). Subgroup analyses according to the ventilator mode prior to ligation/match were performed for 33 matched pairs with HFV and 56 with non-HFV. There was no difference in respiratory improvement at 7 days between the matched ligation and control group for either the HFV or non-HFV subgroup (**Figure 2**; available at www.jpeds.com). The HFV subgroup in both ligation and control groups had a significant reduction in MAP, FiO_2, and RSS post ligation/match by repeated-measures ANOVA; however, there was no difference between the 2 groups. In contrast, when respiratory status was compared between 2-3 days and 6 hours prior to ligation, the ligation group had an increase in MAP and RSS, and a trend for an increase in FiO_2 (**Figure 3**, A). In the non-HFV subgroup, there were no significant within-group changes of MAP, FiO_2, or RSS throughout the study. However, significant between-group differences in MAP, FiO_2, and RSS were noted, with the ligation group having a higher MAP, FiO_2, and RSS compared with the control group during 2-3 days after ligation/match (**Figure 3**, B).

Discussion

In this study, we addressed 1 of the main reasons for considering PDA ligation in preterm infants: respiratory improvement. In our ligation cohort, we found that 42% of infants demonstrated evidence of respiratory improvement 1 week after PDA ligation, which is in line with previous reports.[18,19] Being on HFV at the time of PDA ligation was the only predictor of respiratory improvement. Given that HFV is used as a rescue mode at our institution, our findings suggest that those with worse lung disease are more likely to experience short term respiratory improvement after PDA ligation. The higher MAP, FiO_2, and RSS at the time of ligation further support this notion. Although we did not assess lung mechanics, it is also plausible that compared with conventional ventilation, HFV better maintained lung volume during the ligation procedure and was more effective in lung recruitment after ligation. Interestingly, despite being on higher respiratory support at the time of ligation, infants who had respiratory improvement had lower FiO_2 and were less likely to be receiving invasive ventilation at 36 weeks PMA. Although follow-up data to 36 weeks PMA

Table II. Comparison of characteristics and outcome between ligation and matched control groups

Clinical characteristics	Ligation group (n = 89)	Matched controls (n = 89)	*P* value
Gestational age (wk)	25.6 ± 1.7	25.8 ± 1.6	.509
Birth weight (g)	763 ± 177	789 ± 200	.394
Male sex	42 (47%)	47 (53%)	.294
Cesarean delivery	65 (73%)	66 (74%)	.865
Apgar at 1 min	4 (3-6)	4 (2-6)	.198
Apgar at 5 min	7 (5-8)	7 (5-8)	.496
Chorioamnionitis	13 (15%)	14 (16%)	.834
Maternal hypertension	14 (16%)	15 (17%)	.839
Maternal diabetes	11 (12%)	5 (6%)	.116
Antenatal steroid	70 (79%)	69 (78%)	.902
Use of surfactant	86 (97%)	80 (90%)	.117
Use of COX inhibitor	74 (83%)	52 (58%)	<.001
Major complications of prematurity prior to ligation/match*			
SIP	12 (15%)	21 (24%)	.083
NEC any	13 (14%)	19 (21%)	.242
NEC surgical	3 (3%)	10 (11%)	.080
IVH any	26 (30%)	44 (49%)	.006
IVH grade ≥3	13 (15%)	26 (29%)	.018
Bacteremia	12 (14%)	23 (26%)	.038
Age, weight and respiratory support prior to ligation/match			
Age (d)	27.7 ± 16.1	28.3 ± 16.6	.815
PMA (wk)	29.6 ± 2.9	29.8 ± 2.9	.588
Weight (g)	1148 ± 512	1191 ± 526	.600
Ventilator mode			1.000
High frequency	33 (37%)	33 (37%)	
Conventional	52 (58%)	52 (58%)	
Noninvasive	4 (5%)	4 (5%)	
MAP (cmH_20)	10.4 ± 2.7	10.0 ± 2.6	.491
FiO_2	0.38 ± 0.18	0.38 ± 0.19	.886
RSS	4.2 ± 3.2	4.3 ± 3.0	.975
Respiratory outcomes at 7 d postligation/match			
Overall improvement	39 (44%)	43 (48%)	.548
Extubation	17 (19%)	20 (22%)	.579
Downgrade of ventilator	26 (29%)	33 (37%)	.265
Weaning MAP >25%	26 (29%)	29 (33%)	.627
Weaning FiO_2 >25%	24 (27%)	24 (27%)	1.000
Outcomes postligation/match†			
Intubation d total	67.0 ± 57.9	63.5 ± 48.3	.524
Intubation d postligation/match	37.1 ± 57.2	34.5 ± 45.8	.492
FiO_2 >0.21 d total	152 ± 64	123 ± 62	.006
FiO_2 >0.21 d postligation/match	120 ± 64	95 ± 57	.017
FiO_2 at PMA 36 wk	0.34 ± 0.20	0.31 ± 0.16	.109
Ventilator mode at PMA 36 wk			.088
HFV	5/56 (9%)	8/70 (11%)	
Conventional ventilation	16/56 (29%)	11/70 (16%)	
Noninvasive ventilation	19/56 (34%)	16/70 (23%)	
Nasal cannula	15/56 (27%)	30/70 (43%)	
Room air	1/56 (2%)	5/70 (7%)	
Invasive ventilation at PMA 36 wk‡	21/56 (38%)	19/70 (27%)	.215
BPD severe	47/61 (77%)	37/70 (53%)	.004
ROP stage ≥3	17/63 (27%)	26/71 (37%)	.233
Mortality overall	3/65 (5%)	13/80 (16%)	.036
Mortality 30-d	2/71 (3%)	9/86 (10%)	.113

BPD, bronchopulmonary dysplasia; *COX*, cyclooxygenase; *IVH*, intraventricular hemorrhage; *NEC*, necrotizing enterocolitis; *PMA*, post-menstrual age; *ROP*, retinopathy of prematurity; *SIP*, spontaneous intestinal perforation.

Data are mean ± SD or median (IQR) or n (%) or n/available samples (%).

*None of the infants in either group had these complications during the week prior to ligation/match.

†For these longer-term outcomes data on all 89 patients were not available due to back transfer to referring hospital.

‡Invasive ventilation means patients are intubated and on either HFV or conventional ventilation.

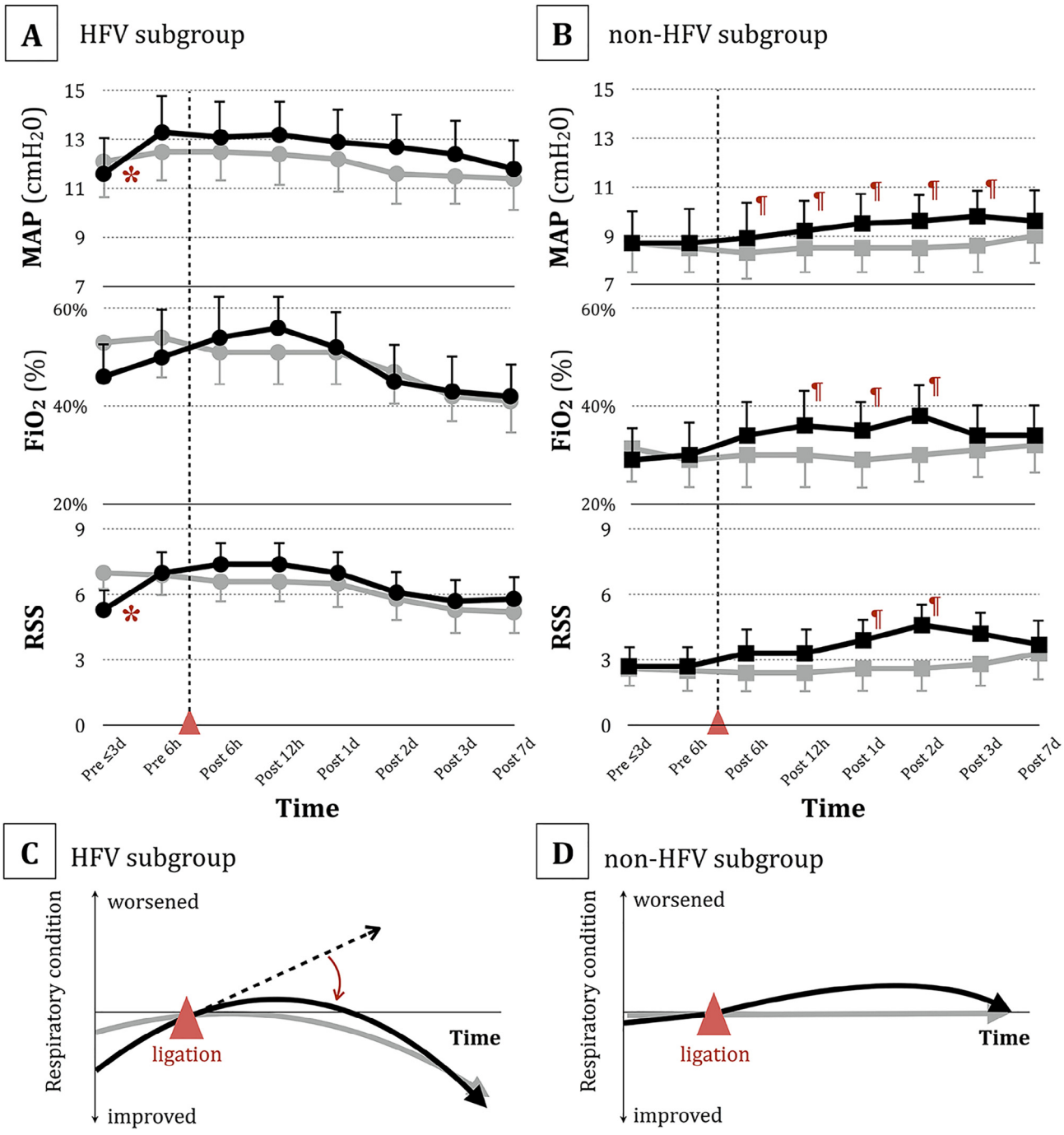

Figure 3. Subgroup analysis of phase 2 study according to mode of ventilation and schematic drawing of interpretation of the findings. **A,** Pattern of changes in MAP, FiO_2, and RSS in HFV ligation group (*black circles*) and HFV matched controls (*gray circles*) throughout the study course. In both ligation and control groups, there was a significant reduction in MAP, FiO_2, and RSS post ligation/match (repeated-measures ANOVA, all $P < .04$). The significant increase (*) in MAP ($P = .02$) and RSS ($P = .044$), and a trend for an increase in FiO_2 ($P = .16$) from 3 days to 6 hours before ligation for HFV ligation group indicates an escalation of ventilatory support before ligation. **B,** Pattern of changes in MAP, FiO_2, and RSS for non-HFV ligation group (*black squares*) and non-HFV matched controls (*gray squares*) throughout the study course. Non-HFV ligation group had significantly higher MAP from 6 hours to 3 days (¶) after ligation, higher FiO_2 from 12 hours to 2 days (¶), and higher RSS 1-2 days after ligation compared to matched controls. **C,** Schematic drawing of our interpretation of the study findings depicting beneficial effect of ligation in HFV group (*black line*) by preventing ongoing respiratory deterioration (*dotted line and single arrow line*). **D,** Schematic drawing of our interpretation of the study findings depicting acute deterioration in respiratory status in non-HFV ligation group (*black line*) shortly after ligation and resolution of this deterioration by the end of our study period (ie, 7 days after the procedure). Triangles indicate the time of surgical ligation.

were not available for all babies, the above findings do suggest that the respiratory benefits extend beyond 7 days and that ligation confers respiratory benefits for a subset of patients. The PDA was smaller in the group with respiratory improvement. Although statistically significant, the difference between the 2 groups was very small and of uncertain clinical significance.

The finding of similar respiratory outcome at 7 days in ligation and matched control groups challenges the assumption that removal of PDA shunt improves short term respiratory outcome in patients undergoing ligation. However, subgroup analysis revealed that a subset of patients may experience respiratory benefits following ligation. Although HFV use at the time of ligation predicted respiratory improvement in the original cohort study, subgroup analysis in the matched case-control population revealed no difference in respiratory outcome at 7 days after ligation/match in either HFV or non-HFV subgroups. However, depending on the ventilatory mode, the ligation group exhibited different respiratory patterns than the control group. Among infants on HFV, the ligation group had an increase in MAP and RSS during the 3 days prior to ligation. Therefore, although the respiratory status as assessed by the degree of ventilatory support were matched at 6 hours prior to ligation, there was a worsening of respiratory status in ligation group in the preceding 2-3 days (**Figure 3**, A). Based on these findings, we speculate that babies on HFV undergoing ligation would most likely have continued to deteriorate if not ligated and that ligation was beneficial for this subset of patients (**Figure 3**, C). The fact that the 2 groups had similar improvement at 7 days despite the ligation group being exposed to a surgical procedure with known adverse respiratory effects[20] further supports that removal of PDA shunt was beneficial in the subset receiving HFV. On the other hand, for those not on HFV, the ligation group had a significantly higher MAP, FiO_2, and RSS during 2-3 postoperative days (**Figure 3**, B and D).

Our study has several limitations. We could not match the control group by PDA status as those infants with a significant PDA were treated. Instead, by design we focused on respiratory status. We matched the degree of lung disease and state of maturity. The comparable respiratory status at the time of ligation/match enabled us to investigate the impact of removal of shunt on respiratory status. Another limitation was that not all markers of PDA were consistently obtained by echocardiography. Furthermore, although commonly used, fractional shortening is a weak index of left ventricular function. However, by reviewing all echocardiographic images and rating them by one of the investigators, we tried to minimize the variability in reading the echocardiograms. Because we used HFV as rescue mode, our findings may not apply to populations in which HFV is used as primary mode of ventilation. Finally, as a significant number of patients were transferred back to the referring hospital, the outcome at 36 weeks PMA and discharge was not available for all patients.

In conclusion, we found that 42% of preterm infants undergoing PDA ligation had respiratory improvement 7 days after the procedure. The odds of respiratory improvement at 7 days was 5-fold higher in infants on HFV compared with other modes of ventilation at the time of ligation. Although the ligation group and matched controls demonstrated similar proportion of respiratory improvement 7 days after ligation/match, for those on HFV, ligation appears to confer respiratory benefits by preventing further deterioration. However, for infants on other modes of ventilatory support, ligation was associated with higher respiratory support in the immediate postligation period without any respiratory benefit at 7 days. If PDA ligation is being considered to improve respiratory status, our findings suggest that babies with severe respiratory failure may be most likely to benefit from the procedure. ■

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Reprint requests: Shahab Noori, MD, MS CBTI, Fetal and Neonatal Institute, Division of Neonatology, Children's Hospital Los Angeles, Department of Pediatrics, Keck School of Medicine, University of Southern California, 4650 Sunset Blvd, Los Angeles, CA 90027. E-mail: snoori@chla.usc.edu

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50 Years Ago in *The Journal of Pediatrics*

Amyloidosis in Childhood

Strauss RG, Schubert WK, McAdams AJ. J Pediatr 1969;74:272-82

In this article, the authors presented the case of a 16-year-old female with systemic juvenile rheumatoid (idiopathic) arthritis (JRA/JIA) who developed amyloidosis after 10 years of disease and reviewed an additional 76 childhood cases from the literature.

Amyloidosis encompasses a group of rare and often fatal diseases caused by the extracellular accumulation of amyloid, an insoluble fibrillar protein. The type of amyloidosis is classified according to the fibril protein present; more than 30 have been identified, most exclusively in adults. Amyloid deposits can be detected in biopsied material (renal/liver/rectal or even in subcutaneous fat) with Congo red staining showing apple-green birefringence using cross-polarized light.

In this series, all cases were of the AA type, which is a result of chronic inadequately treated inflammation; 43% of the patients had JRA/JIA, 18% had familial Mediterranean fever (FMF), and 39% had a chronic infection, mainly tuberculosis or a pyogenic infection, most commonly osteomyelitis. The mean duration of disease until the development of amyloidosis ranged from 2.3 years for chronic infection to 8.1 years for FMF. In all cases, proteinuria was the presenting sign, often accompanied by hepatosplenomegaly in JRA/JIA.

AA amyloidosis is primarily the result of the overproduction of the precursor protein serum amyloid A (SAA), an acute-phase reactant produced by the liver. Thus, the "treatment" of AA amyloidosis is principally to prevent the production of SAA by decreasing inflammation. The authors stated that only 2 of the cases related to chronic infection occurred after 1940, presumably due to the use of antibiotics. Indeed, today AA amyloidosis has almost disappeared among children in the developed world, owing to the use of effective anti-inflammatory medications. In JIA, these treatments include methotrexate and biological modifiers, especially tumor necrosis factor, interleukin (IL)-1 and IL-6 inhibitors, and colchicine in FMF. IL-1 inhibitors are effective for patients with FMF not responsive to colchicine and for patients with other rare autoinflammatory diseases also associated with AA amyloidosis. Indeed, some case reports and series indicate that IL-1 inhibitors can even reverse, or at least stabilize, existing renal amyloidosis.

Laboratories that measure SAA levels to monitor for inflammation are not widely available, and C-reactive protein can usually serve as a reliable surrogate. In patients at risk for amyloidosis, periodic urinalysis is crucial to detect the first signs of proteinuria.

Philip J. Hashkes, MD, MSc
Pediatric Rheumatology Unit
Shaare Zedek Medical Center
Jerusalem, Israel

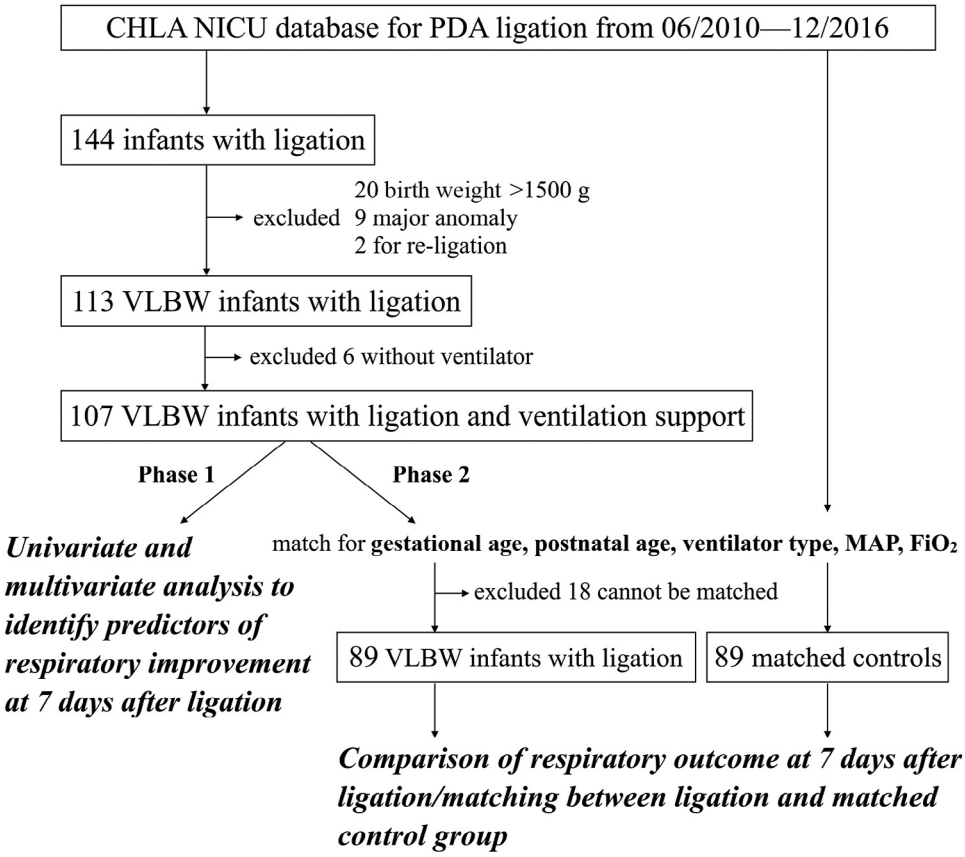

Figure 1. Flow diagram of infant enrollment and study phases. *CHLA*, Children's Hospital Los Angeles; *NICU*, neonatal intensive care unit.

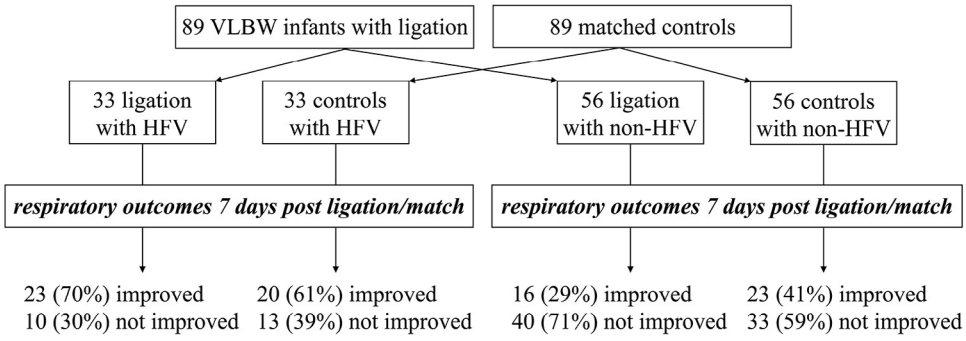

Figure 2. Flow diagram of phase 2 study. Subgroup analysis according to ventilator mode of HFV or non-HFV. There was no difference regarding respiratory outcomes for each subgroup.

Table I. Characteristics and outcome of 107 VLBW infants who underwent PDA ligation

Clinical characteristics	Total (n = 107)	Respiratory improvement		*P* value*
		Yes (n = 45)	No (n = 62)	
Gestational age (wk)	25.5 ± 1.7	25.4 ± 1.8	25.6 ± 1.6	.710
Birth weight (g)	749 ± 171	723 ± 174	768 ± 167	.179
Male sex	55 (51%)	23 (51%)	32 (52%)	.959
Cesarean delivery	79 (74%)	36 (80%)	43 (69%)	.374
Apgar at 1 min	4 (3-6)	4 (3-5)	5 (3-6)	.230
Apgar at 5 min	7 (6-8)	7 (5-8)	7 (6-8)	.203
Chorioamnionitis	14 (13%)	3 (7%)	11 (18%)	.146
Maternal hypertension	18 (17%)	9 (20%)	9 (16%)	.454
Maternal diabetes	13 (12%)	5 (11%)	8 (13%)	.779
Antenatal steroid	84 (79%)	39 (87%)	48 (77%)	.226
Use of surfactant	104 (97%)	44 (98%)	60 (97%)	1.000
Use of COX inhibitor	91 (85%)	37 (82%)	54 (87%)	.485
Major complications of prematurity prior to ligation				
SIP	14 (13%)	7 (16%)	7 (11%)	.518
NEC any	15 (14%)	6 (13%)	9 (15%)	.862
NEC surgical	4 (4%)	2 (3%)	2 (3%)	1.000
IVH any	33 (31%)	12 (27%)	21 (34%)	.426
IVH grade ≥3	16 (15%)	6 (13%)	10 (16%)	.689
Bacteremia	19 (18%)	7 (13%)	12 (19%)	.612
Echocardiographic results prior to ligation				
Timing (d)	–2.2 ± 2.4	–2.5 ± 2.6	–2.0 ± 2.3	.362
PDA diameter (mm)	2.37 ± 0.56	2.28 ± 0.38	2.47 ± 0.61	.068
PDA maximum systolic velocity (m/s)	2.10 ± 0.71	2.07 ± 0.63	2.12 ± 0.76	.756
PDA end-diastolic velocity (m/s)	0.73 ± 0.52	0.73 ± 0.49	0.72 ± 0.56	.928
LA/Ao ratio	1.71 ± 0.32	1.73 ± 0.32	1.70 ± 0.32	.637
Fractional shortening (%)	40.8 ± 6.2	40.0 ± 6.4	41.3 ± 6.1	.286
Age, weight, respiratory support, and medication prior to ligation				
Age (d)	28.7 ± 16.9	28.5 ± 18.1	28.9 ± 16.2	.904
PMA (wk)	29.6 ± 2.9	29.5 ± 2.9	29.7 ± 2.9	.749
Weight (g)	1141 ± 509	1105 ± 489	1168 ± 525	.532
Ventilator mode				.001
HFV	48 (45%)	29 (64%)	19 (31%)	
Conventional ventilation	54 (50%)	16 (36%)	38 (61%)	
Noninvasive ventilation	5 (5%)	0 (0%)	5 (8%)	
MAP (cmH_20)	10.4 ± 2.7	11.6 ± 2.8	10.4 ± 2.9	.046
FiO_2	0.40 ± 0.19	0.45 ± 0.20	0.35 ± 0.16	.007
RSS	4.7 ± 3.3	5.6 ± 3.5	4.0 ± 3.0	.021
Use of steroid in 3 d	23 (21%)	11 (24%)	12 (19%)	.267
Use of diuretic in 3 d	65 (44%)	21 (47%)	26 (42%)	.626
Outcomes after ligation†				
Use of steroid in 1 wk	40 (37%)	18 (40%)	22 (35%)	.156
Use of diuretic in 1 wk	65 (61%)	25 (56%)	40 (65%)	.349
Intubation d total	68.4 ± 55.2	63.2 ± 50.3	72.5 ± 59.0	.475
Intubation d postligation	37.1 ± 53.6	29.9 ± 47.1	43.1 ± 58.3	.305
FiO_2 >0.21 d total	154 ± 62	149 ± 39	157 ± 75	.651
FiO_2 >0.21 d postligation	118 ± 61	115 ± 37	120 ± 75	.776
FiO_2 at PMA 36 wk	0.35 ± 0.19	0.30 ± 0.09	0.37 ± 0.23	.035
Ventilator at PMA 36 wk				.263
High frequency ventilation	6/68 (9%)	1/29 (3%)	5/39 (13%)	
Conventional ventilation	19/68 (28%)	5/29 (17%)	14/39 (36%)	
Noninvasive ventilation	26/68 (38%)	13/29 (45%)	13/39 (33%)	
Nasal cannula	16/68 (24%)	10/29 (34%)	6/39 (15%)	
Room air	1/68 (1%)	0/29 (0%)	1/39 (3%)	
Invasive ventilation at PMA 36 wk‡	25/68 (37%)	6/29 (21%)	19/39 (49%)	.018
BPD severe	58/73 (81%)	21/29 (72%)	37/44 (84%)	.227
ROP stage ≥3	23/75 (31%)	13/32 (41%)	10/43 (23%)	.107
Mortality overall	4/78 (5%)	1/31 (3%)	3/47 (6%)	1.000
Mortality 30-d	3/86 (3%)	1/31 (3%)	2/47 (4%)	1.000

BPD, bronchopulmonary dysplasia; *COX*, cyclooxygenase; *IVH*, intraventricular hemorrhage; *LA/Ao*, left atrium to aortic root ratio; *NEC*, necrotizing enterocolitis; *ROP*, retinopathy of prematurity; *SIP*, spontaneous intestinal perforation.

Data are mean ± SD, median (IQR), or n (%) or n/available samples (%).

*Comparisons were between groups with and without respiratory improvement after ligation.

†For these longer-term outcomes data on all 89 patients were not available due to back transfer to referring hospital.

‡Invasive ventilation means patients are intubated and on either HFV or conventional ventilation.