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Association of Antegrade Pulmonary Artery Diastolic Velocity with Spontaneous Closure of the Patent Ductus Arteriosus in Extremely Low Birth Weight Infants

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Abstract

Objective—Determine echocardiographic parameters associated with spontaneous patent ductus arteriosus (PDA) closure in extremely low birth weight (ELBW) infants.

Study Design—Retrospective demographic review and analysis of echocardiograms from 189 ELBW infants with suspected and confirmed hemodynamically PDA identified on an initial echocardiogram was performed. Comparison of echocardiographic parameters was made between infants with spontaneous closure vs those who received treatment.

Results—Mean birth weight (787 ± 142 vs 724 ± 141 g, $P=0.04$) and gestational age (27.4 ± 2.8 vs 26.2 ± 1.6 weeks, $P=0.03$) were higher in the spontaneous closure vs the treatment group.

Antegrade pulmonary artery (PA) diastolic velocity was lower in infants with spontaneous PDA closure vs those who received treatment (0.15 ± 0.06 vs 0.22 ± 0.12 m/sec, $P=0.009$).

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Conflict of interest

The authors declare no conflict of interest.

Conclusion—Heavier and more mature ELBW infants and a lower antegrade PA diastolic velocity were likely to have spontaneous closure of the PDA.

Keywords

extremely low birth weight infant; ductus arteriosus; echocardiography

Introduction

Since the 1980s, survival of extremely low birth weight (ELBW, birth weight <1000 g) infants has dramatically increased due to improvements and innovations in neonatal intensive care.¹ Nearly half of ELBW infants are diagnosed with a PDA, and despite improvements in care and survival, the number of cases receiving treatment for PDA has remained unchanged in recent comparisons.¹ The presence of a symptomatic left-to-right shunt across the PDA in ELBW infants has been associated with chronic lung disease, difficulty weaning from the ventilator,² intraventricular hemorrhage,³ necrotizing enterocolitis,⁴ and periods of decreased myocardial performance when diastolic pressure is low.^{5,6}

Management of PDAs in premature infants has not only varied depending on the era, but has also varied between institutions and amongst individual physicians. These practice variations range from a less aggressive approach of modest fluid restriction and “watchful waiting”, to pharmacologic and/or surgical intervention.⁷ Pharmacotherapy includes the cyclooxygenase inhibitors indomethacin or ibuprofen;⁸ these agents have side effects including renal failure, brain white matter injury, spontaneous intestinal perforation⁹, necrotizing enterocolitis, and increased bleeding secondary to reduced platelet function, all in the face of treatment failure rates as high as 40% in very premature infants.^{10–12} For infants in whom pharmacotherapy is contraindicated or is unsuccessful, surgical ligation can be performed.¹³ However, ligation has been complicated by bleeding, infection, postoperative hypotension, vocal cord paralysis, chylothorax, pneumothorax, and adverse neurodevelopmental outcome.¹⁴ Expediting PDA closure with current treatment options is clearly not without risk.

As high as 97% of infants >1000 g have spontaneous PDA closure.¹⁵ Prospective studies have also revealed spontaneous closure rates in 32% of ELBW infants¹⁶ and as high as 42% in infants <27 weeks gestation.¹⁷ Given the potential for spontaneous closure in many of these infants, and the risks and side of effects of pharmacotherapy and surgical ligation, it remains unclear as to what is the best approach and timing for management of PDA.

Previous studies have evaluated various echocardiographic parameters predictive of developing a hemodynamically significant or symptomatic PDA that results in significant pulmonary overcirculation and systemic hypoperfusion.^{18,19} Some studies have attempted to delineate if these parameters may be useful in predicting the proper duration of pharmacotherapy.^{20,21} Identification of parameters associated with spontaneous PDA closure or ductal responsiveness to pharmacotherapy would be very useful to facilitate appropriate management for ELBW infants with PDA. Therefore, we sought to determine the echocardiographic parameters associated with spontaneous closure of PDA in ELBW infants.

Patients and Methods

Patient population

Retrospective review of medical records and echocardiograms of ELBW infants admitted to Arkansas Children's Hospital and the University of Arkansas for Medical Sciences neonatal intensive care units from January 2008 to January 2011 was performed. Subjects were identified from an institutional neonatology database. Only ELBW infants diagnosed with a PDA on the initial echocardiogram were included in the study. Echocardiogram was obtained on infants requiring increasing ventilator support, murmur, and/or hemodynamic signs of PDA such as widening of pulse pressure. Infants with major congenital cardiac lesions, diagnoses incompatible with life, chromosomal abnormalities, or incomplete echocardiographic studies were excluded. PDA closure was verified in all non-ligation cases based on subsequent echocardiograms. Those without echocardiographic verification of closure were also excluded from the study. Infants were defined to have spontaneous closure of the PDA if follow-up echocardiogram revealed closure in the absence of treatment with cyclooxygenase inhibitors or surgical ligation. Treatment was defined as either primary cyclooxygenase inhibitor therapy and/or surgical ligation. The study was approved by the University of Arkansas for Medical Sciences Institutional Review Board.

Echocardiographic Analysis

Off-line analysis of the initial echocardiogram was performed (by DMR) to obtain the following parameters: PDA diameter, PDA: left pulmonary artery (LPA) ratio as measured on two-dimensional (2D) short axis view at the bifurcation of the main pulmonary artery,¹⁹ left atrial: aortic root (LA:Ao) ratio as measured on 2D short axis view, antegrade pulmonary artery (PA) diastolic velocity as measured in the MPA, PDA peak systolic velocity, PDA end-diastolic velocity, and descending aorta velocity. Transmitral passive and active flow (E and A waves, respectively), a measure of diastolic filling of the left ventricle, was measured using mitral inflow pulse-wave Doppler in the apical 4-chamber view.¹⁹ PDA Doppler flow patterns were characterized as pulmonary hypertension, growing (bi-directional flow with predominantly left to right shunt), pulsatile, or closing pattern, as described by Su et al^{21,22} Left ventricular end-diastolic dimension (LVEDD) and shortening fraction (SF) were also recorded. All subsequent echocardiograms were reviewed (by DMR) until PDA closure was verified. Study data were collected and managed using the REDCap (research electronic data capture) tool hosted at the University of Arkansas for Medical Sciences.²³

Data Analysis

Demographic and clinical features were summarized by PDA outcome; continuous measures were reported as means and standard deviations while categorical outcomes were reported as frequency and column percentages. Differences between PDA outcome groups concerning demographic, clinical, and echocardiogram parameters were estimated using Wilcoxon Rank Sum for continuous measures and Chi-square test/Fisher's Exact test for categorical variables. Associations between echocardiogram parameters and PDA outcome were estimated using multiple logistic regression adjusting for the subject's birth weight and postnatal age at the time of the first echocardiogram. Postnatal age was used to account for both gestational age and the day of life when the echocardiogram was performed while

conserving statistical estimation given the small sample size within the outcome groups. Predictive capacity was estimated as well and summarized using receiver-operator characteristic (ROC) curves. All statistical analysis was completed using Stata 12.1 (College Station, TX).

Results

Figure 1 illustrates the study sample cohort (n=189). Of the 415 ELBW infants who had echocardiograms performed during the study period, these infants had PDA noted on the initial echocardiogram and PDA closure confirmed by follow-up echocardiogram or surgical ligation. Thirty-one infants (16%) had spontaneous closure, defined as no pharmacotherapy or surgical ligation; 158 (84%) received treatment. Of those who received treatment, 83 underwent primary surgical ligation, 34 received pharmacotherapy alone, and 41 failed pharmacotherapy and underwent subsequent surgical ligation.

Table 1 shows patient characteristics of the spontaneous closure and treatment groups. The birth weight was higher in infants with spontaneous PDA closure compared to those who received treatment (787 ± 142 vs 724 ± 141 g, $P=0.042$). Similarly, the gestational age was higher in infants with spontaneous PDA closure (26.9 ± 2.9 vs 25.5 ± 1.5 weeks, $P=0.03$). Table 2 shows a comparison between the various echocardiographic parameters in infants who had spontaneous closure vs those who received treatment. Despite having similar PDA diameters, the antegrade PA diastolic velocity was significantly lower in infants who had spontaneous PDA closure, in univariate analysis. No other univariate echocardiographic parameters were significantly different between these two groups. Birth weight and postmenstrual age at the time of echocardiogram were added to the multiple logistic regression model. Comparisons were made for echocardiographic parameters at the 25th and 75th quartiles (Table 2). The odds of spontaneous closure in infants with antegrade PA diastolic velocities at the 25th quartile is 4.6 times greater than the odds of spontaneous closure in infants with antegrade PA diastolic velocities at the 75th quartile ($P=0.004$).

ROC analysis (Figure 2) revealed that an antegrade PA diastolic velocity of >0.15 m/sec achieves the best discrimination between infants with spontaneous closure vs those who received treatment groups ($AUC=0.7$). Forward flow >0.1 m/sec in PA during diastole was $>90\%$ sensitive in predicting spontaneous closure of PDA. A velocity >0.27 m/sec had 100% specificity in predicting the infants who received treatment.

Relation of echocardiographic parameters to the success of treatment with cyclooxygenase inhibitors was also analyzed using both univariate and multiple logistic regression analysis (Table 3). Not surprisingly, a smaller PDA diameter was associated with increased odds of successful closure with pharmacotherapy ($P=0.023$). This remained true for PDA size as determined by the PDA:LPA ratio ($P=0.011$). Increase in E and A wave mitral inflow velocities were associated with decreased success with pharmacotherapy ($P=0.014$ and $P=0.021$, respectively). Decrease in passive inflow (E wave) of 0.07 m/s was associated with 45% increased odds of successful pharmacotherapy. Similarly, a decrease in active mitral inflow (A wave) of 0.1 m/s was associated with 59% increased odds of success with pharmacotherapy.

Discussion

This is one of few studies showing an association between specific echocardiographic parameters and spontaneous closure of the PDA in ELBW infants. Specifically, we observed that antegrade PA diastolic velocity, a marker of increased pulmonary blood flow due to the PDA, was associated with spontaneous closure of PDAs in the ELBW population. Additionally, ELBW infants with smaller PDA diameters and lower mitral inflow velocities on the initial echocardiogram, who received treatment, were more likely to respond to cyclooxygenase inhibitor therapy alone. Considering that indomethacin failure rates in the ELBW and very premature population have been reported as high as 41%, these parameters could serve as useful clinical tools for management of ELBW infants with PDA, potentially avoiding unnecessary treatment.^{16,17}

Multiple echocardiographic parameters have previously been used to describe the hemodynamic significance of PDA and/or predict the eventual development of such a PDA. Ductal diameter ≥ 1.5 mm measured in infants <29 weeks on the first day of life has been reported as a sensitive predictor of developing a clinically significant PDA.¹⁸ Koch et al reported that a PDA:LPA ratio >0.5 at <4 days had a 15 times likelihood of receiving treatment compared to those with a ratio <0.5 .²⁴ A prospective study by Thankavel et al supported this finding, predicting spontaneous closure by 10 days when PDA:LPA ratio was <0.5 at 3 days of life in infants born at ≥ 30 weeks gestation. When combined with antegrade LPA diastolic flow ≥ 0.3 m/sec in infants <27 weeks gestation, the predictive accuracy was improved.¹⁷ In our study, while the PDA:LPA ratio and PDA diameter were not associated with spontaneous closure, the PDA diameter on initial echocardiogram was associated with successful response to therapy with cyclooxygenase inhibitors. A study by Carmo et al suggests that using PDA diameter to direct duration of indomethacin treatment leads to similar closure rates when compared to standard length of therapy, but with decreased exposure to medication and possible side effects.²⁰ Additionally, Pees et al found that infants <28 weeks gestation with smaller PDA diameters (from previous measurements) when measured after the first cycle of ibuprofen were more likely to respond to further treatment.²⁵ These data support the use of echocardiography as an important clinical tool for not only diagnosis of PDA, but for its management as well.

Of the echocardiographic parameters measured in this study, the antegrade PA diastolic velocity was significantly higher in those that received treatment, suggesting that increased forward flow during diastole is associated with development of a hemodynamically significant PDA, compared to the purely systolic flow seen when no PDA is present. This concept of hemodynamically significant PDA and increased diastolic flow velocity of the LPA has previously been described.^{26,27} The recent finding by Thankavel et al that LPA forward diastolic flow was predictive of PDA closure after adjusting for PDA:LPA ratio, supports this finding. When stratifying for gestational age (<27 weeks) and targeting infants who typically have a lower incidence of spontaneous closure, they found that their false positive rate for predicting spontaneous closure was significantly decreased when LPA forward diastolic flow was taken into account, improving specificity from 55% to 86%.

The peak systolic and end diastolic flow across the PDA itself were not different between the spontaneous closure vs treatment groups. There was also no difference in ductal flow velocities amongst infants who responded to cyclooxygenase therapy vs those that received secondary surgical ligation. One would expect that smaller, more restrictive PDAs with higher velocities would be more likely to close spontaneously or have increased responsiveness to pharmacotherapy. Unlike our study, previous studies have reported that a high ductal flow velocity at the time of treatment is associated with improved responsiveness to pharmacotherapy.^{25,28} Previous studies, however, have described velocities measured, on average, as early as day of life 2. The initial echocardiograms on which we based our analysis were, on average, obtained later. Delay in echocardiogram and treatment initiation in these groups could affect responsiveness to pharmacotherapy, thus the discrepancy between ductal flow velocity and success of pharmacological closure seen here.

Likewise, increased pulmonary venous return, indicated by increased left atrial volume, as one might expect in a hemodynamically significant PDA, was not increased in the group that received treatment when compared to the spontaneous closure group. Interestingly, increasing LA volume, and ostensibly larger PDA shunt, made no difference in responsiveness to pharmacotherapy. This remained true for LA:Ao ratio, a commonly used parameter for evaluating hemodynamic significance of PDA.^{29,30} This study found no association between this LA:Ao ratio and spontaneous closure of the PDA, which is consistent with an earlier study done by Ramos et al to evaluate predictors of a hemodynamically significant PDA.²⁴

Left ventricular shortening fraction, a load-dependent index used to assess contractility, was not significantly different between the spontaneous closure and treatment groups, despite increases in left-sided flow. One could presume that presence of a patent foramen ovale likely served to decompress any left-sided volume overload seen secondary to PDA.³¹

Another commonly used tool for monitoring the hemodynamic significance of a PDA is the Doppler flow pattern, as described by Su et al.²² While the majority of the ELBW infants with spontaneous closure were found to have a closing pattern on initial echocardiogram, there was no single flow pattern that predicted spontaneous closure or response to pharmacotherapy. A previous prospective study by Su et al²¹ demonstrated reduction in duration of indomethacin treatment as guided by Doppler flow pattern on echocardiogram, suggesting that classifying flow pattern within the PDA at the time of treatment is beneficial. In our retrospective study, however, flow pattern at the time of dosing could not be assessed.

Sehgal et al reported that the ratio of the passive and active mitral inflow velocities is higher in infants with pulmonary overcirculation/systemic hypoperfusion related to PDA shunting, as passive flow is increased with rising LA pressures.¹⁹ Previous studies have shown no relationship between E/A ratio and prediction of spontaneous closure,¹⁷ which remains true for our study. The E/A ratio itself did not change but the E and A wave velocities were found to be significantly lower in those likely to have successful response to pharmacotherapy.

The incidence of PDA in premature infants is inversely related to birth weight and gestational age,³² and has been reported to occur in nearly half of ELBW infants.¹ A similar

trend is seen with PDA closure, where lighter and less mature infants are more likely to maintain patency of their PDA while their larger, more mature counterparts are more likely to achieve spontaneous closure.^{15,16} Koch et al reported spontaneous closure rates as high as 34% in ELBW infants studied; Nemerofsky et al reported similar findings, with a 31% spontaneous closure rate in ELBW infants by 7 days of life compared to 97% of infants 1001–1500 g.^{15,16} ELBW infants in the present study had a significantly lower rate of spontaneous closure, which could potentially be due to trends at this institution as well as exclusion from this study in the absence of available follow-up echocardiogram to verify closure.

Our aim was to investigate echocardiographic parameters, on initial echocardiogram, which were associated with either spontaneous closure or response to therapy. This could be better assessed in a prospective study, designed to control for day of life, treatment timing, and specific indications for treatment choices. Due to the retrospective nature of this study, there is no randomization for management strategies, which is a significant limitation. Additionally, frequent strategies in the clinical management of ELBW infants may contribute to PDA closure. These include, but are not limited to, fluid management, administration of diuretics, surfactant administration, and ventilator support. Although these variables were not compared between the two groups, the medical management prior to treatment for PDA was practiced similarly between neonatologists at our center.

Moreover, spontaneous closure rates may be skewed secondary to set inclusion criteria. Multiple ELBW infants in whom the PDA appeared to have closed clinically were excluded from the study as they lacked the follow-up echocardiogram required for verification of closure. This may have significantly reduced the spontaneous closure rate for our institution. It is also possible that some infants in the treatment group could have eventually achieved spontaneous closure, had they been managed more conservatively, and not treated. The somewhat aggressive nature of treatment at this center likely underestimates the number of patients that would have closed their PDA spontaneously, without complications.

After adjusting for BW and GA, in ELBW infants, a low antegrade PA diastolic velocity on initial echocardiogram is associated with spontaneous PDA closure. Additionally, these infants are more likely to have successful response to pharmacotherapy if they have smaller PDA diameters and lower mitral inflow velocities on initial echocardiogram. Prospective studies in ELBW infants at different institutions with less aggressive early treatment of PDAs are needed to determine if antegrade PA diastolic velocity is truly predictive of spontaneous closure, and not merely an association. Additionally, this data suggests that there is a need for future prospective studies aimed at evaluating the predictive value of mitral inflow velocity in successful cyclooxygenase inhibitor therapy in extremely low birth weight infants.

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Abbreviations

PDA	patent ductus arteriosus
ELBW	extremely low birth weight
PA	pulmonary artery
LPA	left pulmonary artery
2D	two-dimensional
LA:Ao	left atrial:aortic root
LVEED	left ventricular end-diastolic dimension
SF	shortening fraction
ROC	receiver-operator characteristic

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Figure 1.
Population and treatment summary, COX = cyclooxygenase

Figure 2.
Antegrade PA diastolic velocity 0.15 m/sec achieves best discrimination between spontaneous closure and treatment group.

Table 1

Demographic and Clinical Features of Subjects by PDA Closure Group

	All Subjects		Received Pharmacotherapy Only		
	Treated	Spontaneous Closure	P	COX Inhibitor + Ligation	COX Inhibitor Alone
N	158	31		41	34
Gestational Age (weeks)	25.46 (1.47)	26.90 (2.93)	0.028	25.74 (1.64)	25.66 (1.21)
Age at Echo (days)	5.73 (5.28)	3.55 (2.80)	0.021	7.73 (7.38)	5.53 (4.65)
Postnatal Age at Echo (weeks)	26.28 (1.58)	27.40 (2.83)	0.117	26.86 (1.82)	26.45 (1.30)
Birth Weight (grams)	724.49 (141.45)	787.76 (142.77)	0.042	761.75 (151.66)	738.21 (141.99)
Apgar Score @ 1 minute	3.37 (2.08)	3.38 (2.08)	0.933	4.16 (2.06)	3.45 (2.21)
Apgar Score @ 5 minute	5.72 (1.78)	6.35 (1.70)	0.053	6.18 (1.39)	6.30 (1.63)
Race			0.234 [*]		
<i>African-American</i>	68 (43%)	9 (29%)		22 (54%)	12 (35%)
<i>Caucasian</i>	79 (50%)	19 (61%)		19 (46%)	20 (59%)
<i>Hispanic</i>	10 (6%)	2 (7%)		0	2 (6%)
<i>Other</i>	1 (1%)	1 (3%)		0	0
Male Gender	83 (53%)	14 (48%)	0.649 [†]	20 (50%)	19 (56%)
					0.613 [‡]

^{*} N (Column %) and Fisher's Exact test reported. Otherwise, Mean (SD) and Wilcoxon Rank Sum reported.

[†] N (Column %) and Chi-square test reported.

COX = Cyclooxygenase

Table 2
Summary Between-Group Differences and Associations with Spontaneous Closure by Echocardiographic Parameter

	Two-Group Comparison		Multiple Logistic Regression		
	Treated	Spontaneous Closure	P	Comparison [*]	Odds Ratio (95% CI) P
PDA Diameter (cm)	0.21 (0.07)	0.20 (0.07)	0.893	0.16 to 0.25	1.66 (0.87, 3.15) 0.124
Antegrade PA Diastolic Velocity (m/s)	0.22 (0.12)	0.15 (0.06)	0.009	0.12 to 0.27	4.62 (1.62, 13.20) 0.004
PDA peak systolic velocity (m/s)	1.58 (0.63)	1.66 (0.58)	0.664	1.14 to 1.99	1.03 (0.55, 1.94) 0.929
PDA end diastolic velocity (m/s)	0.81 (0.58)	0.82 (0.74)	0.973	0.41 to 1.15	1.21 (0.65, 2.23) 0.553
Passive Mitral Inflow Doppler (m/s)	0.44 (0.14)	0.41 (0.16)	0.115	0.33 to 0.53	1.66 (0.90, 3.04) 0.103
Active Mitral Inflow Doppler (m/s)	0.53 (0.14)	0.50 (0.15)	0.276	0.43 to 0.63	1.24 (0.68, 2.27) 0.485
Descending Aorta Doppler (m/s)	1.02 (0.32)	1.08 (0.31)	0.365	0.82 to 1.19	1.02 (0.63, 1.63) 0.945
Left Ventricular Shortening Fraction (%)	38.19 (8.55)	36.17 (8.44)	0.338	33.00 to 44.00	1.53 (0.85, 2.73) 0.156
PDA : Left Pulmonary Artery Ratio	0.92 (0.27)	0.95 (0.34)	0.921	0.72 to 1.07	1.09 (0.62, 1.92) 0.773
Left Atrial: Aortic Ratio	1.34 (0.40)	1.40 (0.45)	0.644	1.66 to 1.04	1.57 (0.82, 3.00) 0.175
Doppler Flow Pattern	0.417 [‡]				
<i>Pulmonary Hypertension</i>	12 (9%)	2 (9%)			
<i>Growing</i>	4 (3%)	2 (9%)			
<i>Pulsatile</i>	78 (60%)	11 (48%)			
<i>Closing</i>	36 (28%)	8 (35%)			

* Odds Ratios represent 25th and 75th quartile change in parameter estimated from logistic regression adjusting for birth weight and postnatal age of ECHO.

[‡] N (Column %) and Fisher's Exact reported. Otherwise, Mean (SD) and Wilcoxon Rank Sum reported.

Table 3
Summary Between-Group Differences and Associations with Successful COX Inhibitor Response by Echocardiographic Parameter

	Two-Group Comparison		Multiple Logistic Regression		
	COX Inhibitor + Ligation	COX Inhibitor Alone	P	Comparison*	Odds Ratio (95% CI) P
PDA Diameter (cm)	0.22 (0.07)	0.18 (0.05)	0.023	0.15 to 0.24	2.53 (1.06, 5.99) 0.036
Antegrade PA Diastolic Velocity (m/s)	0.23 (0.13)	0.20 (0.11)	0.336	0.13 to 0.30	1.22 (0.57, 2.59) 0.613
PDA peak systolic velocity (m/s)	1.73 (0.65)	1.68 (0.65)	0.852	2.12 to 1.16	1.06 (0.48, 2.37) 0.881
PDA end diastolic velocity (m/s)	0.85 (0.60)	0.77 (0.59)	0.453	0.42 to 1.12	1.00 (0.53, 1.89) 0.990
Passive Mitral Inflow Doppler (m/s)	0.48 (0.15)	0.40 (0.11)	0.014	0.36 to 0.53	2.37 (1.17, 4.78) 0.016
Active Mitral Inflow Doppler (m/s)	0.57 (0.17)	0.49 (0.11)	0.021	0.44 to 0.63	2.33 (1.08, 5.05) 0.031
Descending Aorta Doppler (m/s)	1.06 (0.28)	1.00 (0.36)	0.182	0.81 to 1.22	1.14 (0.58, 2.24) 0.697
Left Ventricular Shortening Fraction (%)	39.71 (6.31)	39.15 (8.90)	0.450	35.00 to 45.00	1.14 (0.61, 2.12) 0.690
PDA: Left Pulmonary Artery Ratio	1.01 (0.29)	0.82 (0.21)	0.011	0.71 to 1.06	2.67 (1.20, 5.98) 0.017
Left Atrial: Aortic Ratio	1.42 (0.37)	1.48 (0.40)	0.517	1.70 to 1.11	1.28 (0.62, 2.66) 0.504
Doppler Flow Pattern	0.257 [‡]				
<i>Pulmonary Hypertension</i>	4 (4%)	5 (9%)			
<i>Growing</i>	0	1 (2%)			
<i>Pulsatile</i>	58 (56%)	29 (54%)			
<i>Closing</i>	41 (40%)	19 (35%)			

* Odds Ratios represent 25th and 75th quartile change in parameter estimated from logistic regression adjusting for birth weight and postnatal age of ECHO.

[‡]N (Column %) and Fisher's Exact reported. Otherwise, Mean (SD) and Wilcoxon Rank Sum reported.

COX = Cyclooxygenase