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Color Doppler Flow Mapping of the Patent Ductus Arteriosus in Very Low Birthweight Neonates: Echocardiographic and Clinical Findings

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SUMMARY. **Forty-eight preterm infants (mean birthweight 1.0 ± 0.3 kg; mean gestational age 28 ± 3 weeks) underwent serial echocardiograms and physical examinations in order to determine the correlation between color Doppler flow mapping (CDFM) results and physical findings of a patent ductus arteriosus (PDA), the predictive value of early CDFM as an indicator of subsequent requirement for treatment of a PDA, and to determine the direction and duration of ductal shunting and the rate of ductal closure and opening. CDFM analysis and cardiac physical examination of left-to-right ductal shunting were usually concordant in infants with a large PDA shunt, the most reliable physical finding being increased precordial activity. CDFM studies on day 2 or 3 of postnatal life had prognostic value with regard to subsequent need for closing the PDA. Additional findings included the absence of right-to-left PDA shunting in infants <1 kg and <28 weeks gestation and the absence of ductal reopening in infants in whom it had closed spontaneously. After complete PDA closure using indomethacin, subsequent ductal reopening is uncommon, except in infants <25 weeks gestation and <700 g bodyweight.**

KEY WORDS: **Color Doppler flow mapping — Patent ductus arteriosus — Premature infants**

Absence of a heart murmur in preterm infants with hemodynamically significant patent ductus arteriosus (PDA) has been reported to occur at an incidence ranging from 20–88% [4, 7, 10, 18]. These studies may be limited in that they either did not include any echocardiographic analysis of ductal patency [7], or they relied on echocardiographic examinations limited to M-mode studies with [4] or without [10] contrast echocardiography or aortic angiography [18]. Furthermore, these studies have concentrated on infants with gestational ages greater than 30 weeks and birthweights greater than 1 kg.

With the development of color Doppler flow mapping (CDFM), and high resolution two-dimensional echocardiography, invasive contrast assessment of ductal shunting or relying upon the M-mode analysis of the LA/Ao ratio as the only parameter to determine shunt presence and size have become obsolete [6, 11, 12]. Color Doppler flow mapping coupled with high resolution two-dimensional imaging have become the conventionally accepted modalities for evaluating ductal patency [9, 11, 12].

To date, no prospective study has compared the CDFM findings with physical examination findings and with the findings from other echocardiographic modalities. Furthermore, no detailed analysis of the direction and duration of ductal shunting and the rate of ductal closure and reopening in infants of very low gestational age and birthweight using the sensitive technique of CDFM has been reported.

Therefore, we prospectively studied a cohort of 48 preterm infants (mean birthweight 1.0 ± 0.3 kg; mean gestational age 28 ± 3 weeks) using serial CDFM and physical examinations in order to determine: (1) whether the physical findings in this population correlated with the CDFM findings of a hemodynamically significant left-to-right shunt through a patent ductus arteriosus (PDA); (2) the predictive value of early CDFM echocardiography as an indicator of subsequent requirement for treat-

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Table 1. Patent ductus arteriosus clinical and echocardiographic treatment criteria

Clinical criteria	Echocardiographic criteria
Heart murmur	Left atrial enlargement or increased LA/Ao ratio
Hyperdynamic precordium	Holodiastolic retrograde flow in DAo
Bounding pulses	PDA width ≥ LPA width by 2D echo
Wide pulse pressure	L to R PDA shunt by CDFM and PWD or CWD
Poor perfusion	
Cardiomegaly on CXR	
Pulmonary edema + increased PVM on CXR	
Increasing ventilatory support	
Failure to wean ventilatory support	
Persistent metabolic acidosis	
Inadequate urine output	
Hepatomegally	
Feeding intolerance	
Necrotizing enterocolitis	

CDFM, color Doppler flow mapping; CWD, continuous wave Doppler; CXR, chest radiograph; DAo, descending aorta; L to R, right to left; LA/Ao, left atrial to aortic ratio; LPA, left pulmonary artery; PDA, patent ductus arteriosus; PVM, pulmonary vascular markings; PWD, pulsed wave Doppler; 2D, two-dimensional.

ment of a PDA; and (3) the direction of PDA shunting and the rate of closure and spontaneous reopening of the ductus arteriosus.

Methods

Study Population

All preterm infants admitted to the intensive care nursery on the first day of life were eligible for entry into the study. Those with congenital anomalies, chromosomal defects, dysmorphic syndromes, hematologic disorders, infants of diabetic mothers, and congenital infections were excluded. All infants had at least mild respiratory distress syndrome. On day 3 of life 92% were mechanically ventilated and 38% were receiving supplemental oxygen. Of 63 families interviewed, 48 consented to enroll their child in the study. The birthweight data ranged from 0.54–1.74 kg (median = 1.0 kg, mean = 1.0 ± 0.3 kg). Gestational age ranged from 24–33 weeks (median = 28 weeks, mean 28 ± 3 weeks). Twenty-five patients were female and 23 were male. All were maintained in negative fluid balance as is the standard policy in our nursery. Surfactant treatment was used in only four infants, all of whom required treatment for a patent ductus arteriosus.

Study Design

The initial cardiac physical examinations and echocardiogram were performed on either day 1 or 2 of life. Serial examinations and echocardiograms were performed at a maximum interval of 48 h. After the ductus arteriosus closed, studies were performed every 3 days for two examinations, and weekly thereafter until 1 month of age or transfer to another institution. Physical examinations were performed immediately prior to the echocardiographic examination by a cardiology or neonatology fellow or attending who was blinded from the echocardiographic findings. All infants receiving mechanical ventilation were briefly disconnected from the ventilator during cardiac auscultation. A significant PDA murmur was arbitrarily considered to be present if it was located over the left precordium or left subclavicular area and had an intensity of ≥2/6 and was continuous or systolic ejection in timing. We considered the precordial activity to be hyperdynamic if a left precordial and substernal lift was palpable and visible. Hyperdynamic pulses were defined as visible axillary pulses and palpable palmar pulses. Pulse pressure was considered to be increased if ≥25 torr. Equivocal physical examination findings were considered negative.

Treatment for a Patent Ductus Arteriosus

The usual methods of consultation and evaluation were carried out if the clinical neonatologist suspected a PDA. The decision whether or not to treat the infant for a PDA was made by the clinical neonatal attending with consultation from a clinical cardiologist. Research echocardiogram and physical examination results were not made available to the clinicians. The color Doppler flow mapping parameters measured for the research echocardiograms were not measured at clinical echocardiograms and were therefore not used in the determination by the clinician as to whether or not a PDA required treatment.

Clinical criteria employed by the neonatologist in determining whether treatment was required are presented in Table 1. All infants treated for a PDA had more than four clinical criteria. Echocardiographic criteria used to confirm the clinical diagnosis of a significant PDA are also presented in Table 1. All treated infants met three or more echocardiographic criteria. All treated infants had all of the echocardiographic treatment criteria except holodiastolic retrograde flow in the descending aorta, which was present in 30 of 35 (85.7%) of the treated infants.

The treatment group was comprised of the 35 infants (72.9%) who were treated with either indomethacin, surgical ligation, or both, and the no-treatment group consisted of 13 infants (27.1%) who had spontaneous closure of the PDA. Treatment and no-treatment infants did not differ with respect to birthweight (1.0 ± 0.3 vs. 1.1 ± 0.3 kg, $p = 0.34$) or gestational age (28 ± 3 vs. 29 ± 3 weeks, $p = 0.15$). The mean age at the initial echocardiogram was identical for the two groups (2 ± 1 day).

Echocardiograms

Echocardiograms were performed by one of the investigators who was blinded from the physical findings and not responsible for clinical management. Studies were performed without sedation using warmed contact gel. Infants remained in their usual isolette or radiant warmer open crib. Measurements were made during intervals of cardiac and respiratory basal conditions for heart rate, blood pressure, and pulse oximeter oxygen saturation. Therefore, interruptions of actual imaging time were necessary in some of the more premature and unstable infants.

Echocardiographic transducer positions included the para-

sternal short axis, parasternal sagittal, suprasternal notch, and subcostal sagittal. The sequence with which the various echocardiographic modalities and views were employed was randomly alternated at each examination.

Two-dimensional and color Doppler flow mapping echocardiography was performed with a 5 MHz short focus transducer interfaced with a Hewlett-Packard Sonos 500 echocardiographic system (Hewlett-Packard, Andover, MA). In all patients the same transducer was used and gain settings were set at the lowest possible levels commensurate with accurate two-dimensional and color Doppler flow mapping [18].

The PDA width was defined as the width (mm) of the color Doppler flow jet within the narrowest portion of the ductal lumen. We defined the jet width as the maximum width (mm) of the ductal color Doppler jet within the main pulmonary artery and the length of the ductal color Doppler jet (mm) as the maximum distance traversed by the ductal jet from the pulmonary arterial orifice of the ductus toward the pulmonary valve within the pulmonary trunk. The ductal jet area was planimetered from the pulmonary orifice of the ductus as it extended toward the pulmonary valve. The largest values for the above parameters obtained from the respective echocardiographic views were used in the statistical analyses.

Additional echocardiographic measurements in all cases included two-dimensional guided M-mode measurement of the LA/Ao ratio [16] and the presence vs. absence of holodiastolic retrograde flow within the descending aorta at the level of the diaphragm [14, 15]. A dedicated continuous-wave Doppler probe and pulsed wave Doppler were used to confirm the presence, direction, and timing of ductal flow. By the middle of the study period, all of the above echocardiographic measurements could be performed from multiple echocardiographic views typically in ≤10 min imaging time.

Statistics

Results are presented in mean ± standard deviation form. Intergroup differences for continuous data were compared using an unpaired *t*-test, and categorical data were compared using Fisher's exact test. The level of statistical significance was set at $p \leq 0.05$.

Consent

This study was conducted using informed consent with the approval of the Committee for Human Research at our institution.

Results

Physical Examination vs. Echocardiographic Parameters

Precordial Activity. Significantly greater values were obtained in the group with increased precordial activity vs. the group with normal precordial activity (Table 2) for PDA width (2.63 ± 0.60 vs. 1.95 ± 0.69 mm, $p = 0.008$), CDFM ductal jet width (3.49 ± 1.05 vs. 2.65 ± 0.88 mm, $p = 0.018$), CDFM ductal jet length (10.99 ± 01.8 vs. 9.1 ± 2.6 mm, $p = 0.032$), CDFM ductal jet area (39.6 ± 15.26 vs. 25.5 ± 12.3 mm^2, $p = 0.008$), and the incidence of holodiastolic retrograde flow in the descending aorta (73.3% vs. 15.4%, $p = 0.004$). The intergroup difference in the LA/Ao ratio was of borderline statistical significance (1.5 ± 0.29 vs. 1.24 ± 0.22, $p = 0.055$).

Murmur. The CDFM ductal jet length was significantly greater in those with a murmur (10.8 ± 1.9 mm) vs. those without a murmur (9.1 ± 2.5 mm)

Table 2. Comparison of echocardiographic and physical examination findings

	Increased PA	PA WNL	*p*
PDA w (mm)	2.6 ± 0.6	2.0 ± 0.7	0.008
CDFM w (mm)	3.5 ± 1.1	2.7 ± 0.9	0.019
CDFM l (mm)	11 ± 2	9 ± 3	0.032
CDFM area (mm^2)	39.6 ± 15.3	25.5 ± 12.3	0.008
LA/Ao	1.5 ± 0.3	1.2 ± 0.2	0.055
RQDAO +	73.3%	15.4%	0.004
	Murmur	**No murmur**	
PDA w	2.5 ± 0.6	2.2 ± 0.9	0.146
CDFM w	3.3 ± 1.1	3.0 ± 1.2	0.262
CDFM l	11 ± 2	9 ± 3	0.032
CDFM area	37.3 ± 15.4	28.8 ± 14.9	0.074
LA/Ao	1.5 ± 0.3	1.2 ± 0.2	0.089
RQDAO +	60.0%	30.7%	0.167
	Pulses full	**Pulses WNL**	
PDA w	2.4 ± 0.7	2.5 ± 0.8	0.340
CDFM w	3.1 ± 0.8	3.3 ± 1.2	0.348
CDFM l	10 ± 2	10 ± 2	0.413
CDFM area	33.1 ± 12.2	34.9 ± 16.9	0.389
LA/Ao	1.5 ± 0.3	1.4 ± 0.3	0.271
RQDAO +	50.0%	42.9%	≥0.50
	Increased PBP	**PBP WNL**	
PDA w	2.6 ± 0.7	2.4 ± 0.8	0.261
CDFM w	3.3 ± 0.9	3.1 ± 1.0	0.310
CDFM l	11 ± 2	10 ± 2	0.136
CDFM area	36.8 ± 13.1	31.7 ± 15.9	0.291
LA/Ao	1.3 ± 0.3	1.5 ± 0.3	0.145
RQDAO +	36.4%	50.0%	≥0.50

CDFM area, color Doppler flow map area of ductal jet; CDFM l, color Doppler flow map length of ductal jet; CDFM w, color Doppler flow map width of ductal jet; LA/Ao, left atrial to aortic root diameter ratio; PA, precordial activity; PBP, systemic arterial pulse blood pressure; PDA w, patent ductus arteriosus width by CDFM; RQDAo +, presence of holodiastolic retrograde flow in the descending aorta; WNL, within normal limits.

Table 3. Comparison of the clinical and echocardiographic features in those treated to close a PDA vs. those not treated to close the PDA

	Treatment group (n = 35)	No treatment group (n = 13)	p
Clinical feature			
Murmur (%)	80	15	0.001
Hyperdynamic pulses (%)	46	8	0.015
Hyperdynamic precordium (%)	80	8	0.001
Pulse pressure (torr)	22 ± 5	22 ± 5	0.41
Birthweight (kg)	1.0 ± 0.3	1.1 ± 0.3	0.34
Gestational age (weeks)	28 ± 3	29 ± 3	0.15
Duration ductal patency (days)	7 ± 5	5 ± 4	0.11
Incidence PDA at first echo (%)	100	62	0.001
Echocardiographic feature			
PDA width (mm)	2.6 ± 0.7	1.8 ± 0.8	0.01
Jet width (mm)	3.4 ± 1.0	2.5 ± 1.2	0.01
Jet length (mm)	10.4 ± 1.9	7.1 ± 5.0	0.01
Jet area (mm^2)	36.3 ± 15.1	24.9 ± 15.7	0.086
LA/Ao ratio	1.5 ± 0.3	1.2 ± 0.3	0.01
RQDAo + (%)	68	0	0.001

no treatment, not treated to close PDA: Treatment, treated to close a PDA with indomethacin, ligation, or both. Other abbreviations as per previous tables.

(p = 0.032). No difference was found in the PDA width, CDFM ductal jet width, CDFM ductal jet area, LA/Ao ratio, or the incidence of holodiastolic retrograde flow in the descending aorta between those with vs. those without a murmur (Table 2). The murmur was a systolic ejection type in 73% and continuous in 27%. There was no correlation between the timing of the murmur and any of the CDFM flow parameters.

Hyperdynamic Pulses and Increased Pulse Pressure. No difference in any of the echocardiographic parameters was found between babies with vs. those without hyperdynamic pulses or increased pulse pressure.

The Predictive Value of CDFM

Examinations performed on day 2 or 3 of life were predictive of the presence or development of clinically significant ductal shunting in all cases. No patient in whom the ductus was closed at the initial evaluation subsequently developed a ductus arteriosus. All cases who were treated for a ductus arteriosus had one present at the initial evaluation.

CDFM Data. All infants in the treatment group had a PDA at the initial echocardiogram but only 62% of the no-treatment group had a PDA at the initial study (p = 0.001). Significant differences between the two groups were found for three of the four CDFM parameters at the initial echocardiographic examination on day 2 ± 1 of age. (Table 3). The PDA width (2.6 ± 0.7 vs. 1.8 ± 0.8 mm, $p \leq 0.01$), jet width (3.4 ± 1.0 vs 2.5 ± 1.2 mm, $p \leq 0.01$), and jet length (10.4 ± 1.9 vs. 7.1 ± 5.0 mm, $p \leq 0.01$) were all significantly greater in the treatment group. These differences were present despite excluding the four cases in the no-treatment group who had a closed ductus arteriosus at the initial echocardiogram from the above mean ± standard deviation calculations. The area of the CDFM jet did not differ between the groups with high probability (treatment = 36.3 ± 15.1 mm^2, no-treatment = 24.9 ± 15.7 mm^2, p = 0.074).

Direction and Duration of Ductal Shunting

The direction of ductal shunting was exclusively in a left-to-right direction in 90.9% (40 of 44) of those with a PDA at the initial echocardiogram on day of life 2 ± 1. All four infants with bidirectional shunting had a birthweight ≥ 1.0 kg (range 1.0–1.6, mean = 1.4 kg) and a gestational age ≥ 28 weeks (range 28–33, mean = 30.5 weeks). Three of the four infants with bidirectional shunting required mechanical ventilation, supplemental oxygen, and treatment to close the PDA. No infant had a purely right-to-left shunt.

The duration of shunting in treatment vs. no-treatment groups (7 ± 5 vs. 5 ± 4 days, respectively) was not significantly different (Table 3). Excluding the three cases who underwent ductal ligation without prior indomethacin treatment, the treatment group was divided into those who responded to indomethacin with complete and permanent ductal closure (n = 22, 68.8%) vs. those who failed to have such a response (n = 10, 31.2%). Significant differences in ductal shunt duration were found between those who failed to respond to indomethacin (10.7 ± 5.9 days) vs. those who responded to indomethacin (5.5 ± 2.4 days, p = 0.001) and also those who were not treated to close the PDA (4.8 ± 3.8 days, p = 0.005). There was no difference in the duration of ductal shunting between those who were treated with indomethacin and responded and those who were not treated for a patent ductus arteriosus.

Ductal Closure and Reopening

No infant with spontaneous closure of the PDA had subsequent reopening of the ductus. Of the infants who were treated with indomethacin, only 6.3% (2 of 32) had complete closure and subsequent reopening of the ductus. Both were of 24 weeks gestation, birthweights were 540 and 680 g, respectively. Both were treated with three doses or more of indomethacin and ultimately required surgical ligation.

Discussion

The Not So Silent Ductus

Previous studies have deemphasized the importance of physical examination for detecting PDA in this population [7, 19]. We found careful physical examination including auscultation during brief interruption of mechanical ventilation to be important and complementary to CDFM in the management of the very preterm infant. Valdes-Cruz and Dudell [20] reported a similar 72% rate of clinically apparent and contrast echocardiographically proven PDA. The large discrepancy between the 20% incidence of silent ductus in our series and the 88% incidence in the series of Thibeault et al. [19] and the 100% incidence in the series from Drayton and Skidmore [2] may be related to their failure to disconnect the infants from the ventilator during auscultation. Although the necessity of this maneuver has been previously reported [5], it deserves to be reemphasized.

Value of CDFM

CDFM is the most rapid and sensitive method for diagnosing a PDA in preterm infants. The results correlate well with other previously reported parameters indicative of significant ductal shunting [14–16], as well as physical examination findings. Although Pesonen et al. have described the limitations of CDFM for quantitative analysis [9], our results support their contention that it provides a reliable and reproducible semiquantitative assessment of ductal shunting in this population.

Importance of Early Evaluation

Our results using CDFM confirm previous reports based on other echocardiographic modalities that an echocardiographic examination at 3 days of age has prognostic value and may identify which infants will required treatment for PDA [3, 8]. In infants who require vigorous respiratory support, the extremely premature infant, or those with intraventricular hemorrhage or necrotizing enterocolitis, we recommend that CDFM analysis be performed no later than day 3 of life, even if physical examination findings suggestive of a PDA are few or absent. By this age, most of the ducts which will close spontaneously will have done so [12]. Certain physical examination findings, especially a hyperdynamic precordium, also should prompt early evaluation. Although physical findings of a ductus arteriosus are usually present, a large ductal shunt may be present in their absence [2–4, 7, 10, 14, 15, 19, 20]. Conversely, physical findings may be nonspecific in this population. Therefore, CDFM is an essential component used in conjunction with physical findings in diagnosing a PDA, estimating the shunt size, and excluding ductal-dependent cardiac anomalies prior to treatment.

Direction of Ductal Shunting

The direction of ductal shunting appears to be determined primarily by gestational age rather than severity of lung disease. Infants less than 28 weeks gestation and 1.0 kg bodyweight, even when studied on day 1 of life, did not demonstrate bidirectional or right-to-left ductal shunting, despite the presence of severe respiratory distress with hypoxemia in some cases. Therefore, these very preterm infants have a lower pressure in the pulmonary artery relative to the aorta throughout the cardiac cycle, as did 52% of the patients in the report by Spach et al. [17]. This observation suggests that pulmonary vascular resistance relative to systemic vascular resistance is low in these subjects even during hypoxemia. This is contrary to the traditional concept of the ductus initially shunting right to left, followed by a reversal of the shunt direction when the lung disease improves and the pulmonary vascular resistance falls [9]. In the early study by Rudolph et al. [13] in which bidirectional shunting was demonstrated by cardiac catheterization, the infants were of older gestational age and were not treated with mechanical ventilation, positive end-expiratory pressure, and surfactant (in some cases) as in our study population.

Ductal Closure and Reopening

This feature was rarely encountered in this series. Only two infants had complete closure of the ductus with subsequent echocardiographic detection of a

PDA. Both were hemodynamically significant and occurred in very preterm infants (24 weeks gestation, birthweight ≤ 0.68 kg) who had the ductus initially closed with indomethacin. These results are concordant with the concept of persistent dilator prostaglandin responsiveness in the very preterm animal reported by Clyman et al. [1]. These results do not support the concept that the ductus arteriosus commonly "opens and closes" during the course of respiratory distress syndrome. Although we have encountered rare cases prior to and following this study in which the ductus spontaneously closed and subsequently became patent, our data and experience indicate that this is an uncommon phenomenon.

Conclusion

Cardiac physical examination and CDFM analysis of left-to-right ductal shunting are usually condordant in infants with a large ductal shunt, with the most reliable physical finding being increased precordial activity. Routine CDFM studies on day 2 or 3 of life have prognostic value with regard to subsequent need for closing the ductus arteriosus. Pulmonary hypertension manifested by right-to-left ductal shunting is rare in infants <1 kg and <28 weeks gestation. Spontaneous ductal closure and subsequent reopening is uncommon. After complete ductal closure using indomethacin, subsequent ductal reopening is also uncommon, except in infants <25 weeks gestation and <700 g bodyweight.

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