The Effect of a Significant Patent Ductus Arteriosus on Doppler Flow Patterns of Preductal Vessels: An Assessment of the Brachiocephalic Artery

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Systemic hypoperfusion secondary to a patent ductus arteriosus (PDA) is thought to only affect post-ductal vessels. In a prospective observational study of 51 preterm infants, we demonstrated that a persistent PDA by day 5-7 is associated with reversed diastolic flow in the brachiocephalic artery when compared with those without a PDA. *(J Pediatr 2017;180:279-81).*

A patent ductus arteriosus (PDA) in preterm infants, particularly if it persists beyond the first 48 hours of age, is associated with distinct hemodynamic changes. Left-to-right shunting across the PDA becomes established once pulmonary vascular resistance falls. This shunting leads to pulmonary overcirculation and systemic hypoperfusion.[1] Echocardiography is used to characterize those changes. Pulmonary overcirculation leads to increased left ventricular preload and usually is identified by a dilating left atrium, a rising left atrial to aortic root ratio (LA:Ao), an increasing left ventricular end-diastolic diameter, and a rising left ventricular output (LVO). Systemic hypoperfusion is identified by demonstrating flow reversal during diastole in the descending aorta and the celiac artery. The severity of those variables recently has been associated with adverse outcomes in preterm infants.[2]

The effect of ductal steal on the cerebral circulation, particularly in the early transitional period, warrants further study. Some studies demonstrate that a large PDA diagnosed beyond the first week of age is associated with reduced cerebral blood flow manifested by a reduction in mean and diastolic flow velocities as measured by pulsed-wave Doppler in cerebral vessels.[3-5] Recent evidence suggests that a long-standing PDA is associated with suboptimal cerebral oxygenation that ultimately may negatively impact brain growth,[6] which may be, in part, explained by chronic cerebral hypoperfusion. Evidence of the early effect of a PDA on cerebral circulation, particularly over the first week of age, however, is lacking. To examine this, we aimed to assess prospectively the impact a PDA has on the first branch of the aortic arch: the brachiocephalic artery (BCA) and the middle cerebral artery (MCA) in a group of preterm infants over the first week of age.

BCA	Brachiocephalic artery
EDV	End-diastolic velocity
LA:Ao	Left atrial to aortic root ratio
LVO	Left ventricular output
MCA	Middle cerebral artery
PDA	Patent ductus arteriosus
VTI	Velocity time index

Methods

This was a prospective, observational study carried out in the Rotunda Hospital, Dublin, Ireland, between July 2015 and March 2016. Infants less than 32 weeks' gestation surviving beyond the first week of age were eligible for inclusion. We excluded infants with known or suspected congenital anomalies and infants with congenital heart disease other than a PDA. This study was approved by the Hospital's Research Ethics Committee, and written informed consent was obtained from all parents before enrollment. Prophylactic treatment with ibuprofen/indomethacin or early PDA treatment during the first week of life is not carried out in our institution.

Basic demographics and clinical characteristics, including gestation, birth weight, 5-minute Apgar score, and sex were collected. Echocardiography (with Vivid S6 [GE Healthcare, Little Chalfont, United Kingdom), and a 12 MHz multifrequency probe) was performed at 3 time points at a median (IQR) of 10 (6-12) hours (day 1), 42 (38-48) hours (day 2), and 143 (132-162) hours (day 5-7). We collected the following measurements in accordance with recent guidelines[7]: PDA diameter measured in 2 dimensions (mm); LA:Ao; LVO (in mL/kg/min); left ventricular end-diastolic diameter (mm); celiac artery end diastolic velocity (m/s); and velocity time index (VTI). In addition, we assessed the pulsed-wave Doppler pattern of the right MCA and the BCA over the 3 time points. The BCA was imaged from the high parasternal view of the aortic arch as the first vessel emerging from the transverse arch. The cursor was aligned with the vessel to keep the angle of insonation less than 20° and the gate (set at <2 mm) placed at the origin. Pulsed-wave Doppler was obtained. The maximum systolic velocity,

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end-diastolic velocity (EDV), and VTI of both vessels were measured by averaging the values from 3 consecutive waves.

The cohort was divided into 2 groups based on the presence or absence of a PDA by day 5-7, regardless of PDA diameter. Continuous variables were presented as medians (IQR) and categorical variables as count (percent). A Mann-Whitney *U* test was used to compare continuous variables between the 2 groups and a χ^2 (or Fisher exact) test was used to compare proportions. Two-way repeated-measures ANOVA was used to compare serial data between the 2 groups. Correlation between variables of interest was assessed with the Spearman correlation coefficient. Linear regression was used to assess the independent effect of the PDA on BCA end-diastolic velocity while we adjusted for gestational age. SPSS (v21; IBM Corp, Armonk, New York) was used to conduct the analysis. We accepted a *P* value less than .05 as significant.

Table. Basic demographics and echocardiography measurements on days 5-7 in the 2 groups

	PDA (n = 25)	No PDA (n = 26)	P
Gestation, wk	26.0 (25.0-26.7)	30.4 (27.8-31.2)	<.001
Birth weight, g	930 (660-1060)	1263 (1033-1583)	.002
5-min Apgar score	8 (7-9)	9 (8-9)	.16
Male sex	10 (40)	11(42)	1.0
Diastolic BP, mm Hg	28 (23-36)	39 (33-36)	.002
PDA diameter, mm	2.7 (2.2-3.2)	0	NA
LA:Ao	1.8 (1.6-2.0)	1.4 (1.2-1.6)	<.001
LVO, mL/kg/min	266 (216-325)	173 (161-204)	<.001
LVEDD, mm	12.7 (12.0-15.4)	11.9 (10.5-13.0)	<.001
Celiac artery VTI	6.4 (4.8-8.4)	10.4 (8.0-15.2)	.003
Celiac artery EDV, m/s	0.07 (-0.02–0.1)	0.15 (0.12-0.23)	<.001
MCA VTI	4.3 (2.8-6.2)	8.7 (6.6-9.2)	<.001
MCA EDV, m/s	0.06 (0.00-0.09)	0.10 (0.09-0.12)	<.001
BCA VTI	4.2 (3.4-5.4)	5.7 (4.3-6.1)	.03
BCA EDV, m/s	–0.08 (-0.10–0.00)	0.04 (0.0-0.06)	<.001

BP, blood pressure; *LVEDD*, left ventricular end-diastolic diameter; *NA*, not applicable.
Values are presented as medians (IQR) and count (%).

Results

Fifty-one infants with a median (IQR) gestation and birth weight of 27.0 (25.1-30.7) weeks and 1060 (750-1360) g, respectively, were enrolled between July 2015 and March 2016 (**Figure 1**; available at www.jpeds.com). The cohort had a 5-minute Apgar score of 9 (8-9) and a median first pH of 7.31 (7.29-7.37). On day 1, 50 (98%) infants had a PDA; this reduced to 35 (67%) on day 2 and by day 5-7, the PDA remained open in 25 (49%) infants with a median diameter of 2.7 (2.2-3.2) mm (range 1.2-4.1 mm). Infants with a PDA on day 5-7 had a lower gestation and birth weight (all $P < .01$; **Table**). In addition, infants with a PDA on day 5-7 had a greater LVO, LA:Ao, left ventricular end-diastolic diameter, and a lower celiac artery diastolic velocity and VTI (all $P < .01$; **Table**).

Figure 2 illustrates the progression of LVO, BCA, and MCA EDV in the 2 groups over the study period. Infants with a PDA on day 5-7 developed reversed diastolic flow in the BCA by day 2. A difference in MCA EDV was only apparent on day 5-7 (**Table** and **Figure 2**). This difference occurred in association with a rising LVO in the infants with a PDA by day 5-7. There was a significant negative correlation between BCA EDV and PDA diameter (r = –0.72) and between BCA EDV and LVO (r = –0.46). BCA EDV positively correlated with both celiac EDV (r = 0.67) and MCA EDV (r = 0.54) (all correlation $P < .01$). On linear regression, the association between the presence of a PDA on day 5-7 and BCA remained significant when we adjusted for gestation (model R square 0.42, PDA standardized β –0.72, $P < .001$).

Discussion

In this prospective observational study, we demonstrated that the BCA, a preductal vessel, can be exposed to the effects of left-to-right shunting as early as the second day of life, with the MCA only becoming affected on day 5-7. Infants with a PDA by day 5-7 demonstrated diastolic flow reversal in the BCA compared with infants without a PDA who had forward diastolic flow (**Figure 3**). There was a negative relationship between an increasing PDA diameter and LVO and BCA diastolic flow and a positive relationship between diastolic flow in the studied vessels (BCA, MCA, and celiac artery). The relationship between a PDA and reversed diastolic flow in the BCA remained significant when we adjusted for gestation, which supports the

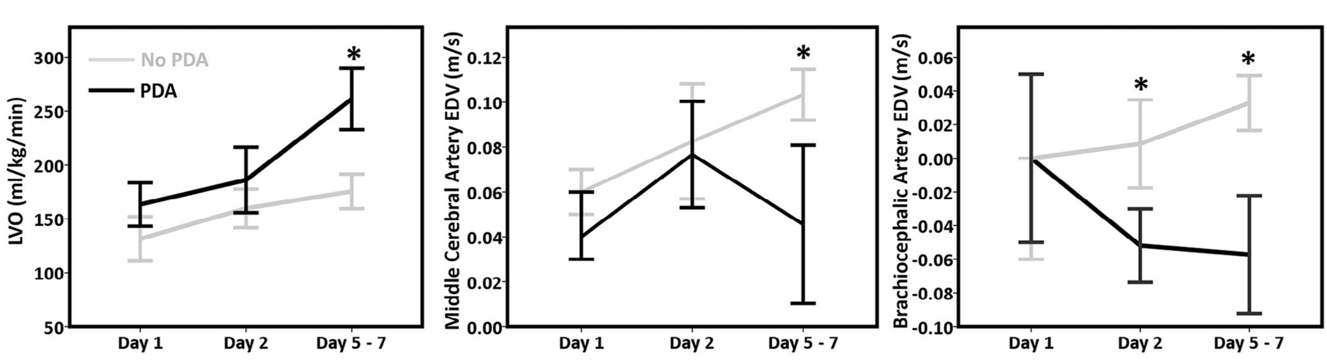

Figure 2. LVO, MCA, and BCA EDV over the study period in the 2 groups. Values are presented as medians with the error bars representing 95% CIs. * $P < .05$.