

# Patent ductus arteriosus (PDA) staging and splanchnic circulation in high risk preterm infants

## Abstract

**Objective:** To evaluate the influence of PDA on superior mesenteric artery (SMA) and celiac artery (CA) in the immediate postnatal period in preterm infants.

**Methods:** 50 preterm less than 32 week with birth weight less than 1kg was included in the prospective observation study. PDA (PSV: peak systolic velocity, EDV: end diastolic velocity, TAV: time average velocity). Blood flow indices (resistive index; RI, pulsatility index; PI) was calculated. PDA was categorized as small, moderate and large. Values taken at 48hr were considered for statistical calculation.

**Result:** Significant PDA was associated with high SMA PSV and low EDV in both SMA and CA. Large (n=12) and moderate PDA (n=3) was associated with high PSV and low EDV in SMA, hence was associated with significantly high RI (large;  $0.85 \pm 0.04$ , moderate;  $0.80 \pm 0.03$ ) in mesenteric circulation. In celiac circulation, large PDA was associated with low EDV ( $11.66 \pm 6.09$ ) and moderate PDA was associated with significant high PSV ( $64.33 \pm 13.05$ ). This velocity pattern in CA was associated with significant high RI ( $0.77 \pm 0.08$ ) and high PI ( $1.73 \pm 0.52$ ) in large PDA group. Velocities in small PDA and no PDA groups were comparable in both arteries.

**Conclusion:** Significant PDA was associated with attenuated blood velocities in SMA compromising the intestinal perfusion. Celiac artery blood flow velocities were adversely affected by large PDA. Low EDV is the predicting factor for compromised perfusion in both the arteries. PDA diameter and flow in descending aorta was the determining factor.

**Keywords:** preterm infants, patent ductus arteriosus, superior mesenteric artery, celiac artery

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## Introduction

Patent ductus arteriosus (PDA) is a common complication in preterm infants, especially in extremely low birth weight (ELBW) infants with an incidence of 80-90%.<sup>1</sup> The current body of evidence showed a significant association between PDA and neonatal mortality and morbidities, mainly due the presence of left to right shunt -ductal steal phenomena- and consequent hypoperfusion to vital organs.<sup>2,3</sup> However, there is a growing controversy about the role of aggressive therapeutic interventions in the management of PDA, previous reports indicated that 73% of preterm infants with PDA will show spontaneous closure of the duct by the end of first week and that the beneficial role of medical/surgical treatment is questionable.<sup>4,5</sup> Thus, it is important to identify and discriminate infants with hemodynamically significant ductus arteriosus (hsPDA). A growing body of evidence has investigated the role of several methods in the identification of hsPDA. Biomarkers, as natriuretic peptides and ischemia-modified albumin, were reported to significantly correlated with early hsPDA and have a good predictive value.<sup>6,7</sup> Other reports showed high diagnostic accuracy of clinical scores for the detection of hsPDA infants who needs treatment.<sup>8</sup> However, there is no consensus about a grading system for hsPDA; functional echocardiography is considered as gold standard in the early diagnosis of significant PDA and focus on early targeted treatment.<sup>9</sup> McNamara & Sehgal,<sup>10</sup> proposed a staging system with a comparison between clinical and echocardiographic criteria of hsPDA.

On the other hand, hsPDA was reported to be associated with

a significant reduction in regional blood flow, hsPDA reduced blood flow velocity (BFV) in the cerebral, renal, and mesenteric arteries.<sup>11,12</sup> Freeman-Ladd and colleagues<sup>13</sup> noted a significant absence or reversal of diastolic flow in the superior mesenteric artery (SMA) among preterm infants with hsPDA. Another report showed that retrograde diastolic flow in the descending aorta may act as a potential marker of high-volume shunt and hypoperfusion of lower body segment.<sup>14</sup> Additionally, SMA and celiac artery (CA) BFV increased dramatically after ductal closure in ELBW infants, which may predispose to oxidative stress and reperfusion injury of the gut.<sup>15</sup> Therefore, the hemodynamic effects of hsPDA on the SMA and CA blood flow may play critical role in targeted treatment strategies. Our aim was to do the accurate estimation of blood flow velocities in both SMA and CA in high risk infants with PDA with a cohort. This relationship may provide an accurate estimate of compromise to intestinal circulation due to duct and provide a rationale for treatment to reduce the intestinal morbidity.

## Methods

### Subjects

- Infants admitted to tertiary neonatal intensive care unit with GA less than 32 week and birth weight less than 1kg were enrolled for the study. Exclusion criteria were major congenital malformations, critical congenital heart disease and evidence of perinatal asphyxia requiring significant resuscitation (need of drugs).
- The demographic data of study population is shown in Table 1.

c. This study was approved by Dubai health authority (DHA) ethical committee and written informed consent was obtained from the parents before the subject enrollment.

### Study design

50 infants fulfilling the inclusion criteria were included in this prospective trial, who underwent bedside ultrasound twice at 24hr

**Table 1** Subject characteristics of the study population (50 new-born)

PDA category (total no=50)					
Subject characteristics	Large PDA (N=12)	Moderate PDA (N=3)	Small PDA (N=22)	NO PDA (N=13)	P value
Birth weight(gm)	854.25±103.24	788.33±212.74	844.68±157.13	846.15±187.56	0.93
Gestational age(weeks)	26.83±1.46	25.33±1.15	27.0±2.46	27.15±2.19	0.61
Gender (% male)	33.3	33.3	63.6	53.8	0.34
Delivery method (% C-section)	75.0	33.3	77.3	69.2	0.45
Clinical measures					
Mean blood pressure (mmhg)	35.5±7.90	35.33±4.16	38.55±9.11	42.00±7.23	0.23
Haematocrit (%)	45.58±6.24	42.67±4.61	46.45±6.26	45.46±6.96	0.80
Duration to full feeds	25.43±10.83	33.50±6.36	24.38±14.32	27.11±19.87	0.868
(n=34)	(N=7)	(N=2)	(N=16)	(N=9)	
Confounding factors					
Umbilical artery catheter (%)	25	33.3	18.2	23.1	0.98
Caffeine (%)	100	100	100	100	-
Antenatal steroid 2 doses (%)	58.3	33.3	59.1	38.5	0.57

Values showing percentage of patients are labelled with % sign. Otherwise, values are reported as means and SDs, mean± SD

**Table 2** SMA blood flow velocities

SMA Variables	Large PDA (N=12)	Moderate PDA (N=3)	Small PDA (N=22)	NO PDA (N=13)	P value
	(N=12)	(N=3)		(N=13)	
PSV(cm/s)	45.62±13.68	38.50±9.96	38.27±10.88	37.65±6.47	0.219
EDV(cm/s)	6.21±2.71	6.83±0.76	8.61±3.61	7.95±1.74	0.148
TAV (cm/s)	18.50± 7.55	17.0±2.59	16.05±5.02	15.38±3.05	0.485
RI	0.85± 0.04	0.80±0.03	0.77±0.04	0.77±0.05	0.000**
PI	2.11±0.25	1.78±0.42	1.83±0.32	1.76±0.40	0.058

\*P <0.05, \*\*p<0.01

Data are mean± SD unless otherwise indicated

**Abbreviations:** PSV, peak systolic velocity; EDV, end-diastolic velocity; TAV, time-averaged mean velocity; RI, resistive index; PI, pulsatile index; PDA, patent ductus arteriosus; SMA, superior mesenteric artery

### Doppler ultrasound studies and evaluation of PDA:

- a. SMA and CA BFV were measured using pulsed Doppler ultrasound (vivid q GE, USA) and a 10MHz transducer. A real-time two-dimensional image and colour flow mapping was used to identify the arteries. SMA was identified as the second major branch of the abdominal aorta, originating just below the CA. The sampling volume of the pulsed Doppler was placed 3mm distal to the origin of the SMA and CA using a real-time two-dimensional image from a longitudinal abdominal approach. Angle correction was used when necessary.
- b. When stable waveforms measurements were obtained, the curves were traced and the blood flow variables in each artery were calculated from at least three consecutive cardiac cycles of optimal quality. The recorded blood flow variables were the peak systolic velocity (PSV), end-diastolic velocity (EDV), time-averaged mean velocity (TAV). At least two sets measurements were taken at each time point, and the mean of these readings was used for the final analysis. The resistance index (RI): (PSV-EDV)/PSV. The pulsatility index (PI): (PSV-EDV)/TAV
- c. Assessment of PDA was done by measurement of PDA size, LA to aortic ratio and descending aortic end diastolic flow. PDA was defined as small, moderate and large on the basis of above variables.
  - A. Ductal diameter: ductal diameter  $\geq 1.5$ mm was considered significant.<sup>7,8</sup>  
Large  $> 3$ mm, moderate 1.5-3mm, small  $< 1.5$ mm
  - B. LA: Ao: we used a cut-off ratio of  $\geq 1.5$  to define significance.<sup>7,8</sup>  
Large:  $> 2$ , moderate 1.5-2, small  $< 1.5$
  - C. Descending aortic end diastolic velocity: absent or reversed end diastolic flow.<sup>8,9</sup>  
Large: reversal DA flow, Moderate: absent DA flow, small: normal DA flow

**Table 3** CA blood flow velocities

CA variables	Large PDA (N=12)	Moderate PDA (N=3)	Small PDA (N=22)	NO PDA (N=13)	P value
PSV (cm/s)	56.70 $\pm$ 13.56	64.33 $\pm$ 13.05	47.35 $\pm$ 10.65	46.76 $\pm$ 11.36	0.022*
EDV (cm/s)	11.66 $\pm$ 6.09	19.66 $\pm$ 4.75	14.21 $\pm$ 5.12	15.65 $\pm$ 4.18	0.076
TAV (cm/s)	26.87 $\pm$ 6.77	36.66 $\pm$ 8.80	25.97 $\pm$ 9.46	26.73 $\pm$ 7.35	0.237
RI	0.77 $\pm$ 0.08	0.68 $\pm$ 0.01	0.69 $\pm$ 0.07	0.65 $\pm$ 0.05	0.001**
PI	1.73 $\pm$ 0.52	1.20 $\pm$ 0.10	1.37 $\pm$ 0.29	1.17 $\pm$ 0.21	0.001**

\*P <0.05, \*\*p<0.01

Data are the mean $\pm$  SD unless otherwise indicated.

**Abbreviations:** PSV, peak systolic velocity; EDV, end-diastolic velocity; TAV, time-averaged mean velocity; RI, resistive index; PI, pulsatile index; PDA, patent ductus arteriosus; CA, celiac artery

### Statistical analysis

Blood flow variables readings at 48 hr, were compared using ANOVA test for different PDA groups. Subject characteristics and clinical variables were recorded for four PDA groups: large, moderate, small and no PDA. ANOVA and chi-square test were used to detect statistically significant difference (alpha=0.05) based on continuous or categorical nature of the item. Statistical analysis was performed by using SPSS (statistical Package for Social Sciences) version 20.0.

### Result

Fifty infants were enrolled. The mean birth weight and GA of enrolled patients was 844 $\pm$ 153gm and 27 $\pm$ 2.1 week respectively. Out of the total study population, 15 infants were diagnosed with significant PDA (large: 12, moderate: 3) as per the predefined echocardiography criteria. Table 1 summarizes the demographic and clinical data. Birth weight and gestational age were similar between the groups, and the mean blood pressure values were low in the significant PDA group. Caffeine, hematocrit and presence of UAC (known modifiers of SMA and CA blood flow velocities) did not differ between the groups. 34 infants were followed for duration to reach full feeds, which was not influenced by the type of PDA. Large PDA was associated with high PSV and low EDV, whereas moderate PDA was associated with low EDV in superior mesenteric artery circulation. This flow pattern was associated with significantly high SMA RI (large 0.85 $\pm$ 0.04, moderate 0.80 $\pm$ 0.03) and PI (large 2.11 $\pm$ 0.25) in significant PDA groups compared to others. SMA blood flow velocities (Table 2) and indices were comparable between small and no PDA groups. SMA TAV was not influenced by PDA type. Neonates with large PDA had low EDV (11.66 $\pm$ 6.09) and moderate PDA had significantly high PSV (64.33 $\pm$ 13.05) compared to other groups in celiac artery circulation. The velocity pattern in CA (Table 3) was associated with significantly high RI (0.77 $\pm$ 0.08) and high PI (1.73 $\pm$ 0.52) in large PDA infants compared to other three groups. CA RI and PI in moderate PDA group were comparable with small/no PDA groups. CA TAV was comparable in all PDA groups.

## Discussion

Despite widespread use of the term, there is no consensus on the definition of hemodynamically significant PDA. The echocardiography criteria used in the literature to define HsPDA includes:<sup>2,10,11</sup> Diameter>1.5mm at the narrowest point, absent or retrograde diastolic flow in descending aorta and major arteries (superior mesenteric and anterior cerebral artery), left atrial and aorta ratio>1.5 and unrestrictive pulsatile flow PDA pattern. Considering all the previous reports, we used PDA diameter, flow in DA and LA: RO to define the PDA. Infant's characteristics, possibly affecting intestinal perfusion, were similar among groups. Recorded mean blood pressure reading was low in significant PDA group compared to other, as reported by Evan et al<sup>12</sup>. This can be explained by the ductal steal associated with significant PDA.

Left to right shunting across a PDA is associated with systemic hypoperfusion. Echocardiography assessment of the celiac and superior mesenteric arteries demonstrates reduced blood flow in the presence of a PDA compared to controls.<sup>13-15</sup> This may explain the association between PDA and NEC. Coombs et al.,<sup>16</sup> reported abnormal SMA velocities associated with PDA despite increase in left ventricular output. Studies have reported abnormal diastolic blood flow in major arteries including SMA in infants with HsPDA.<sup>5,6</sup> Frank et al.,<sup>17</sup> demonstrated high PSV and negative EDV in preterm with significant PDA and concluded that increase SMA PSV with PDA is a compensatory mechanism to maintain the intestinal perfusion. Similarly Deeg et al.,<sup>18</sup> reported significantly low EDV in newborn with PDA leading to compromised gut perfusion. Confirming previous reports, our study showed abnormal SMA BFV associated with significant PDA. We also demonstrated the influence on SMA and CA velocities as per the severity of significant PDA (large/moderate). Large PDA influences both PSV (high) and EDV (low) compared to moderate PDA, which is associated with low EDV. This pattern showed low EDV is the determining factor for compromised intestinal perfusion in high risk preterm infants with significant PDA, which indicates diastolic run-off.

EL-Khuffash et al.<sup>14</sup> reported low celiac artery blood flow (CAF) in presence of significant PDA in spite of increased left ventricular output (LVO), had a sensitivity of 93% and specificity of 78%. We reported large PDA is associated with adverse CA BFV compared to moderate PDA. Large PDA influences both PSV (high) and EDV (low) compromising the intestinal perfusion. Comparable velocity pattern in both SMA and CA associated with small and no PDA group showed similar outcome as reported previously.<sup>19</sup> Shimada et al.,<sup>5</sup> reported lower splanchnic velocities (SMA and CA) with significant PDA in extreme low birth weight preterm. This abnormal blood flow pattern in SMA and CA reflected by the increased resistance indexes in the infants with hsPDA is consistent with ductal steal phenomenon (diastolic shunt from aorta to main pulmonary artery).<sup>20,21</sup> Clyman et al.,<sup>22</sup> have shown that the decreased splanchnic and renal blood flows in preterm lambs with large left to right PDA was a consequence of both the ductal steal and localized increase in vascular resistance.

This study shows the exact influence of PDA staging on both the SMA and CA BFV in high risk preterm population. This blood flow pattern helps the clinician to limit the feeding related complications during the early postnatal life in preterm infants with significant PDA. We acknowledge that the present study has some limitations. The study was a single- center experience with relatively small sample

size which may affect the generalizability of our findings. Moreover, it was not possible to evaluate all the echocardiography parameters used to quantify the hemodynamic consequences of significant PDA.

## Conclusion

Both large and moderate PDA was associated with abnormal velocity pattern in SMA causing compromised intestinal perfusion. On the contrary, only large PDA was associated with compromised celiac artery perfusion. Low EDV was the determining factor for the abnormal velocity pattern in both the arteries. PDA diameter and abnormal DA flow determines the flow pattern.

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Written informed consent was obtained from the parents before the subject enrollment. This study was approved by Dubai health authority (DHA) ethical committee.

## Conflicts of interest

The authors have no conflicts of interest to declare.

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