www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2017;6(2):e060213
doi: 10.7363/060213
Received: 2017 Feb 20; revised: 2017 May 25; accepted: 2017 Jun 02; published online: 2017 Aug 15

Original article

Serial serum brain-type natriuretic peptide (BNP) identifies compromised blood flow in infants with hemodynamically significant patent ductus arteriosus

Yasser Elsayed, Mary Seshia, Ronald J. Baier, Shyamala Dakshinamurti

Section of Neonatology, Department of Paediatrics and Child Health, University of Manitoba, Winnipeg, Manitoba, Canada

Abstract

Background: The physiological correlates of elevated serum brain-type natriuretic peptide (BNP) in hemodynamically significant patent ductus arteriosus (HSPDA) are unclear.

Objective: To determine if serial BNP measured at 48-72 hours of age, before and after non-steroidal anti-inflammatory drugs (NSAID) treatment of HSPDA reflect compromised blood flow indices, in infants < 31 weeks of gestational age (GA).

Design/methods: In a prospective blinded study, 70 infants < 31 weeks GA, admitted to Winnipeg NICUs from August 2010 to September 2011, had serum BNPs and echocardiograms at 48-72 hours of age, before and after medical treatment of HSPDA. All BNP and logarithm of BNP (logBNP) were correlated by linear regression with contemporaneous blood flow indices for: 1) systemic hemodynamic indices (corrected left and right ventricular outputs [LVO, RVO], RVO/LVO ratio, superior vena cava flow [SVCF], SVCF/LVO); 2) regional blood flow indices (middle cerebral artery flow [MCAF], MCAF/LVO ratio, middle cerebral artery resistive index [MCARI], middle cerebral artery pulsatility index [MCAPI]; celiac artery flow [CAF], CAF/LVO ratio, celiac artery resistive index [CARI], and celiac artery pulsatility index [CAPI]).

Results: Twenty-six of 70 infants developed HSPDA at 6 ± 2 days. Both BNP and logBNP had similar correlations with all indices, but logBNP showed better goodness of fit. The best correlation was at 48-72 hours of life. Analyzing systemic hemodynamics, logBNP best correlated with SVCF (β -0.49, R^2 0.24, $p < 0.0001$), SVCF/LVO (β -0.55, R^2 0.31, $p < 0.0001$), RVO/LVO (β -0.59, R^2 0.35, $p < 0.0001$), LVO (β 0.4, R^2 0.16, $p < 0.0001$), and RVO (β -0.35, R^2 0.12, $p < 0.0001$). For regional blood flow, logBNP best correlated with MCARI (β 0.6, R^2 0.35, $p < 0.0001$), MCAPI (β 0.5, R^2 0.29, $p < 0.001$), and MCAF (β -0.34, R^2 0.12, $p < 0.0001$).

Conclusions: BNP correlates with blood flow indices in preterm infants with HSPDA mainly at 48-72 hours reflecting the value of pre-symptomatic physiologic prediction by BNP.

Keywords

Brain-type natriuretic peptide, PDA, preterm, blood flow, targeted neonatal echo.

Corresponding author

Yasser Elsayed, MD, PhD, Section of Neonatology, WS012 Women's Hospital, 735 Notre Dame Ave, Winnipeg Manitoba, Canada R3E 0L8; phone: (204) 787-1853; fax: (204) 787-1587; email: yelsayed@exchange.hsc.mb.ca.

How to cite

Elsayed Y, Seshia M, Baier RJ, Dakshinamurti S. Serial serum brain-type natriuretic peptide (BNP) identifies compromised blood flow in infants with hemodynamically significant patent ductus arteriosus. J Pediatr Neonat Individual Med. 2017;6(2):e060213. doi: 10.7363/060213.

Introduction

Patent ductus arteriosus (PDA) is the most common cardiovascular problem in preterm neonates, with an incidence as high as 33% in infants < 31 weeks gestation, and was reported to be associated with adverse outcomes. Determination of whom to treat and when to treat to minimize PDA-related morbidity remains challenging for neonatologists [1, 2].

Current studies are focusing on the acute physiologic changes and subsequent neonatal morbidity which are more likely to be related to the shunt volume across the PDA, rather than merely its patency [3, 4]. A more comprehensive and standardized assessment of the PDA shunt, including biochemical, clinical and blood flow indices, may assist in refining the early diagnosis of hemodynamically significant PDA (HSPDA), allowing for accurate estimation of its significance [5]. The likelihood of operator-dependent error from individual measurements could be minimized through this more comprehensive approach [6]. Ascertainment of the hemodynamic significance of a PDA may benefit from the inclusion of biochemical markers, together with clinical and echocardiographic evaluation [7]. A potential candidate is the brain-type natriuretic peptide (BNP), secreted by ventricular myocytes in response to volume overload of the ventricles [8]. BNP measurements have been reported useful for the diagnosis and assessment of PDA in preterm infants [9]. The half-life of BNP is 20 minutes; it causes diuresis, natriuresis, and arterial dilatation. The expected effect is a compensatory reduction of intravascular volume, and ventricular preload [10]. BNP was reported in prior studies to be useful in evaluating HSPDA and correlated with the magnitude of shunt volume, but the physiologic correlation with blood flow indices is not yet examined [9, 11]. BNP levels are variable at different time points of measurement, limiting the generalizability of this method for routine use [8, 12, 13]. We proposed to explain this phenomenon by studying the physiologic correlation of BNP levels with indices reflecting systemic and regional blood flow, considering the presence of HSPDA requiring treatment as a reference standard for a perturbed hemodynamic state [14]. We hypothesized that BNP is correlating with blood flow indices at different times of assessment in infants with HSPDA.

Methods

This was a prospective cohort study of premature neonates (< 31 weeks gestation) admitted to the Neonatal Intensive Care Units (NICUs) of Health Sciences Center and St. Boniface General Hospitals in Winnipeg (Manitoba, Canada) between August 2010 and November 2011. With institutional Research Ethics Board approval, infants were recruited, independent of clinical suspicion for PDA, and following informed parental consent. Infants with right-to-left PDA shunt or congenital heart disease (other than patent foramen ovale) were excluded. Prophylactic indomethacin was not used, and treatment given only for symptomatic PDA. In all study infants, blood flow indices were evaluated by targeted neonatal echocardiography (TNE) and Doppler techniques, which were performed after 48 and before 72 hours of age, before and within 12 hours after medical treatment of a PDA; serum BNP was measured concurrently with each TNE and Doppler assessment of blood flow indices.

Management of patent ductus arteriosus

The clinical team, blinded to blood flow indices and BNP findings, independently determined whether the PDA was symptomatic; their decision to treat was based on clinical features and independent echocardiographic confirmation of an unrestrictive left-to-right shunt by the pediatric cardiologist.

The reference standard for HSPDA diagnosis was PDA diameter > 1.5 mm with a left-to-right non-restrictive shunt, as reported by the pediatric cardiologist, and subsequently received treatment for ductal closure. Clinical features considered by the clinical team for treating PDA included (but not limited to) signs of pulmonary over-circulation (pulmonary hemorrhage), extubation failure, or need for re-intubation due to increased respiratory work, persistent apnea requiring stimulation, pH < 7.25 and/or pCO_2 > 60 mmHg, and signs of systemic hypoperfusion (hypotension requiring inotropic support). The medical treatment strategy was intravenous indomethacin or ibuprofen for a maximum of 2 consecutive or separate courses together with reduced fluid intake; surgical ligation of the PDA was considered if medical treatment failed or was contraindicated.

Measurement of serum brain-type natriuretic peptide

Blood was drawn from an indwelling catheter or heel poke. BNP was determined in 0.3 ml whole blood by Triage® BNP bedside immunoassay (Biosite Diagnostics Inc., San Diego, CA, USA), measuring BNP in filtered serum using a murine polyclonal fluorescence-tagged anti-BNP antibody with detection range 5-5,000 pg/ml [7].

Targeted neonatal echocardiography and Doppler techniques

Targeted neonatal echocardiographic studies were performed using Vivid-7® (GE Healthcare, Waukesha, WI, USA) or HP SONOS® 5500 (Phillips, Andover, MA, USA) echocardiographic systems with 7-10 MHz transducers. TNE and Doppler studies were performed by a trained single operator (Y.E.) as per published guidelines [15]. Imaging data were stored digitally; off-line echocardiography analysis was performed 1-3 months after the study, to avoid recall bias of neonatal outcomes.

TNE and Doppler assessment were performed at 48-72 hours of age, irrespective of clinical symptoms. If a PDA was suspected by the clinical team, echocardiography for evaluation and management of the PDA was independently performed by the Pediatric Cardiology consultation service; in cases of PDA, TNE and Doppler assessment were independently performed by the study team before and after PDA treatment. No enrolled infant received medical treatment of the ductus before 72 hours of age.

Measurement of systemic and regional blood flow parameters

The aortic diameter was measured using the parasternal long axis view proximal to and just below the aortic valve annulus while aortic Doppler was performed using the apical long axis view [16]. Pulmonary valve annulus was measured while pulmonary Doppler was performed using the parasternal short axis view. Superior vena cava (SVC) diameter was measured using a high parasternal view and measured close to the entrance to the right atrium (average of maximum and minimum diameters). SVC Doppler was evaluated using the subcostal sagittal view [17]. Middle cerebral artery (MCA) diameter and Doppler were measured at the right parietal region. Celiac artery (CA) Doppler and diameter were assessed at the subcostal sagittal view just at its exit from the aorta [18-20]. Pulsatility and resistive indices (PI and RI) were calculated from peak systolic flow velocity, minimum diastolic blood flow velocity, and mean velocity [21-23]. Left ventricular output (LVO), right ventricular output (RVO), superior vena cava flow (SVCF), middle cerebral artery flow (MCAF) and celiac artery flow (CAF) were measured by the following equation [22, 24]: flow or output = velocity time integral × {π × (mean vessel diameter^2/4) × heart rate}/body weight. PI was calculated according to the following equation: PI = (PSV-MDV)/MV, and RI was calculated as follows: RI = (PSV-MDV)/PSV, where PSV = peak systolic velocity, MDV = minimum diastolic velocity, MV = mean velocity (time averaged velocity).

Features of patent ductus arteriosus

Ductal diameter: using 2-D mode at high parasternal (ductal view), the narrowest transductal diameter was obtained, expressed as the mean of 3 measurements. Color Doppler was used to identifying flow across the PDA. The scale of the color was adjusted upwards to remove aliasing [25], according to the assessment of the PDA published by Tavera et al. [26].

Peak PDA flow velocity: the direction and peak velocity of transductal flow was assessed by pulse- and continuous-wave Doppler [3, 16].

Statistical analysis

SPSS® v. 21 (SPSS Inc, Chicago, IL, USA) was used to perform the statistical analysis.

Pearson correlation was used to correlate BNP with systemic and regional blood flow indices. Data are presented as mean ± SD, or median with interquartile range, as appropriate; $p < 0.05$ was considered significant. The logarithm of BNP (logBNP) was used for a better fit of transformed smaller number to the correlation graphs.

Results

Seventy-one of 132 eligible infants were enrolled in the study. The main reason for non-enrollment was a lack of parental consent before 72 hours of age. One infant was withdrawn from the study after enrollment due to the parental request. Thirty-seven infants of the enrolled group were males (53%). Mean ± SD of gestational age (GA) and birth weight of the enrolled group were 28 ± 1.6 weeks and 1,101 ± 280 grams respectively, the lower limit for GA was 24 weeks and for birth weight was 520 grams. A PDA was present in 56 of 70 (80%) infants at 48-72 hours of life, 31 of them were on CPAP support during the time of initial TNE study, 18 were on conventional mechanical ventilation, and 7 were on high-frequency jet ventilation support. Fourteen infants had PDA closed at 48-72 hours of life (20%), 12 of them were on CPAP support, and 2 were on conventional ventilation. Twenty-six of 70 infants developed HSPDA at 6 ± 2 days. PDA closed after one non-steroidal anti-inflammatory drug NSAID course in 8/26 (31%). Seven (27%) of neonates with clinical PDA received 2 courses of medical treatment, and after failure to close underwent surgical ligation. Infants with HSPDA were of lesser birth weight and lower gestation (**Tab. 1**). They also had a significantly higher BNP level. Infants with HSPDA had LVO, middle cerebral artery resistive index (MCARI), middle cerebral artery pulsatility index (MCAPI), celiac artery resistive index (CARI), and celiac artery pulsatility index (CAPI) significantly higher than infants with no HSPDA; they had significantly lower RVO, RVO:LVO ratio, SVCF, MCAF, CAF, CAF:LVO ratio; SVCF:LVO and MCAF:LVO ratios were not statistically different between both groups.

BNP and logBNP had similar correlations with all hemodynamic indices, but logBNP showed the better goodness of fit. Positive correlations can be determined from **Tab. 2** as β values not preceded by any sign, and negative correlations with β values preceded by (-) sign. The best time-related

Table 1. Comparison between hemodynamically significant patent ductus arteriosus (HSPDA) and non-HSPDA groups.

	HSPDA n = 26	No HSPDA n = 44	p-value
GA (weeks)	26 (27, 28)	29 (29, 30)	**0.0001**
Birth weight (gm)	927 ± 190	1,191 ± 292	**0.0001**
BNP (pg/ml)	178 (103, 605)	17 (10, 33)	**0.0001**
Days on oxygen	71 ± 20	23 ± 13	**0.001**
LVO (ml/kg/min)	358 (300, 387)	295 (251, 332)	**0.001**
RVO (ml/kg/min)	225 (199, 269)	280 (259, 298)	**0.001**
RVO:LVO	0.68 (0.59, 0.89)	0.94 (0.86, 1.0)	**0.001**
SVCF (ml/kg/min)	87 (73, 107)	120 (97, 129)	**0.001**
SVCF:LVO	0.36 (0.33, 0.42)	0.4 (0.34, 0.46)	0.055
MCAF (ml/kg/min)	9.9 (8, 13.8)	12 (10.2, 13.5)	**0.001**
MCARI	0.64 (0.62, 0.81)	0.57 (0.45, 0.7)	**0.001**
MCAPI	1.3 (1.2, 2.5)	1.2 (0.9, 1.7)	**< 0.05**
MCAF:LVO	0.04 (0.03, 0.058)	0.043 (0.03, 0.05)	0.48
CAF (ml/kg/min)	23.3 (18.5, 23.9)	26.9 (21.4, 32)	**0.001**
CARI	0.82 (0.62, 0.96)	0.56 (0.51, 0.63)	**0.001**
CAPI	1.4 (1.3, 2.2)	1.2 (1.1, 1.4)	**0.01**
CAF:LVO	0.09 (0.07, 0.11)	0.1 (0.07, 0.12)	**< 0.05**

Data is presented as mean ± standard deviation or median (interquartile range); p-value is bolded where significant.
HSPDA: hemodynamically significant patent ductus arteriosus; GA: gestational age; BNP: brain-type natriuretic peptide; LVO: left ventricular output; RVO: right ventricular output; SVCF: superior vena cava flow; MCAF: middle cerebral artery flow; MCARI: middle cerebral artery resistive index; MCAPI: middle cerebral artery pulsatility index; CAF: celiac artery flow; CARI: celiac artery resistive index; CAPI: celiac artery pulsatility index.

Table 2. Correlation of logarithm of brain-type natriuretic peptide (logBNP) with blood flow indices at the 3 time points.

	At 48-72 hours			Pre-treatment			Post-treatment		
	R^2	β	p-value	R^2	β	p-value	R^2	β	p-value
LVO (ml/kg/min)	0.16	0.4	**< 0.0001**	0.02	0.14	0.5	0.19	0.43	**0.03**
RVO (ml/kg/min)	0.12	-0.35	**< 0.0001**	0.1	-0.32	0.06	0.24	-0.5	**< 0.05**
RVO:LVO	0.35	-0.59	**< 0.0001**	0.2	-0.45	**0.02**	0.42	-0.65	**0.001**
SVCF (ml/kg/min)	0.24	-0.49	**< 0.0001**	0.35	-0.59	**0.002**	0.34	-0.58	**0.002**
SVCF:LVO	0.31	-0.55	**< 0.0001**	0.15	-0.39	0.056	0.26	-0.51	**0.01**
MCAF (ml/kg/min)	0.12	-0.34	**< 0.0001**	0.18	-0.43	**0.01**	0.24	-0.49	**< 0.05**
MCARI	0.35	0.6	**< 0.0001**	0.46	0.68	**0.0001**	0.59	0.77	**0.0001**
MCAPI	0.29	0.5	**< 0.001**	0.32	0.57	**0.002**	0.38	0.62	**0.001**
MCAF:LVO	0.017	-0.13	0.11	0.1	-0.31	0.066	0.1	-0.32	0.11
CAF (ml/kg/min)	0.15	-0.38	**< 0.0001**	0.02	-0.04	0.8	0.22	-0.47	**0.01**
CARI	0.29	0.54	**0.0001**	0.09	0.29	0.15	0.4	0.63	**0.001**
CAPI	0.18	0.42	**0.0001**	0.06	0.07	0.7	0.12	0.35	0.09
CAF:LVO	0.03	-0.17	**0.03**	0.2	0.17	0.5	0.15	-0.22	0.3

P-value is bolded where significant.
LVO: left ventricular output; RVO: right ventricular output; SVCF: superior vena cava flow; MCAF: middle cerebral artery flow; MCARI: middle cerebral artery resistive index; MCAPI: middle cerebral artery pulsatility index; CAF: celiac artery flow; CARI: celiac artery resistive index; CAPI: celiac artery pulsatility index.

correlation of serial BNP measurements with systemic and regional blood flow indices was at 48 to 72 hours of life (**Fig. 1**). Post PDA treatment logBNP also correlated with many hemodynamic parameters; BNP measured before medical treatment had little correlation with the measured parameters (**Tab. 2**). Analyzing systemic blood flow indices, logBNP best correlated for all the three-time points of measurements with SVCF and RVO/LVO; LVO, RVO, and SVCF:LVO ratio were significant at 48-72 hours and post treatment (**Tab. 2**). For regional blood flow logBNP best correlated with MCAF, MCARI, and MCAPI at all the three-time points of measurements; CAF and CARI were significant at 48-72 hours and post treatment; logBNP was correlated with CAPI and CAF:LVO only at 48-72 hours. **Tab. 3** shows mean ± SD of all systemic and regional blood flow indices at 48-72 hours, pre-treatment and post-treatment; BNP was not significantly different between the 3-time points, but most of the blood flow indices were significantly different. The intra-observer variability of the TNE and Doppler measurements was good (k = 0.87, 95th CI: 0.72-94).

Discussion

In this study, we examined the correlation between BNP and both systemic and regional blood flow Doppler indices, in preterm infants < 31 weeks with HSPDA. Although there is not a universally accepted definition of HSPDA, for purposes of this study we considered a clinically symptomatic and non-restrictive PDA shunt requiring treatment as our reference definition of HSPDA [27, 28]. We recently published the pre-symptomatic prediction of morbidities related to PDA in preterm infants by BNP at 48-72 hours, but to date no studies have examined its physiologic correlation with echocardiographic blood flow indices [3]. We examined the correlation between BNP and blood flow indices at 3 different time points and found that the best correlation occurred at 48-72 hours after birth. Once the PDA is clinically symptomatic, this correlation became less significant. These data are consistent with our previous finding that BNP measured at 48 to 72 hours was a better predictor of neonatal morbidities related to PDA than other echocardiography parameters [3]. We speculate that BNP may play a temporary role in clinical compensation of systemic hypoperfusion due to HSPDA during the pre-symptomatic period [11]. This compensation may diminish at a variable period beyond 72 hours of age for unknown reasons, which would make the ductus more likely symptomatic at or beyond 48 to 72 hours of life [29]. This speculation is supported by animal studies which showed improvement in congestive heart failure with BNP infusion [30].

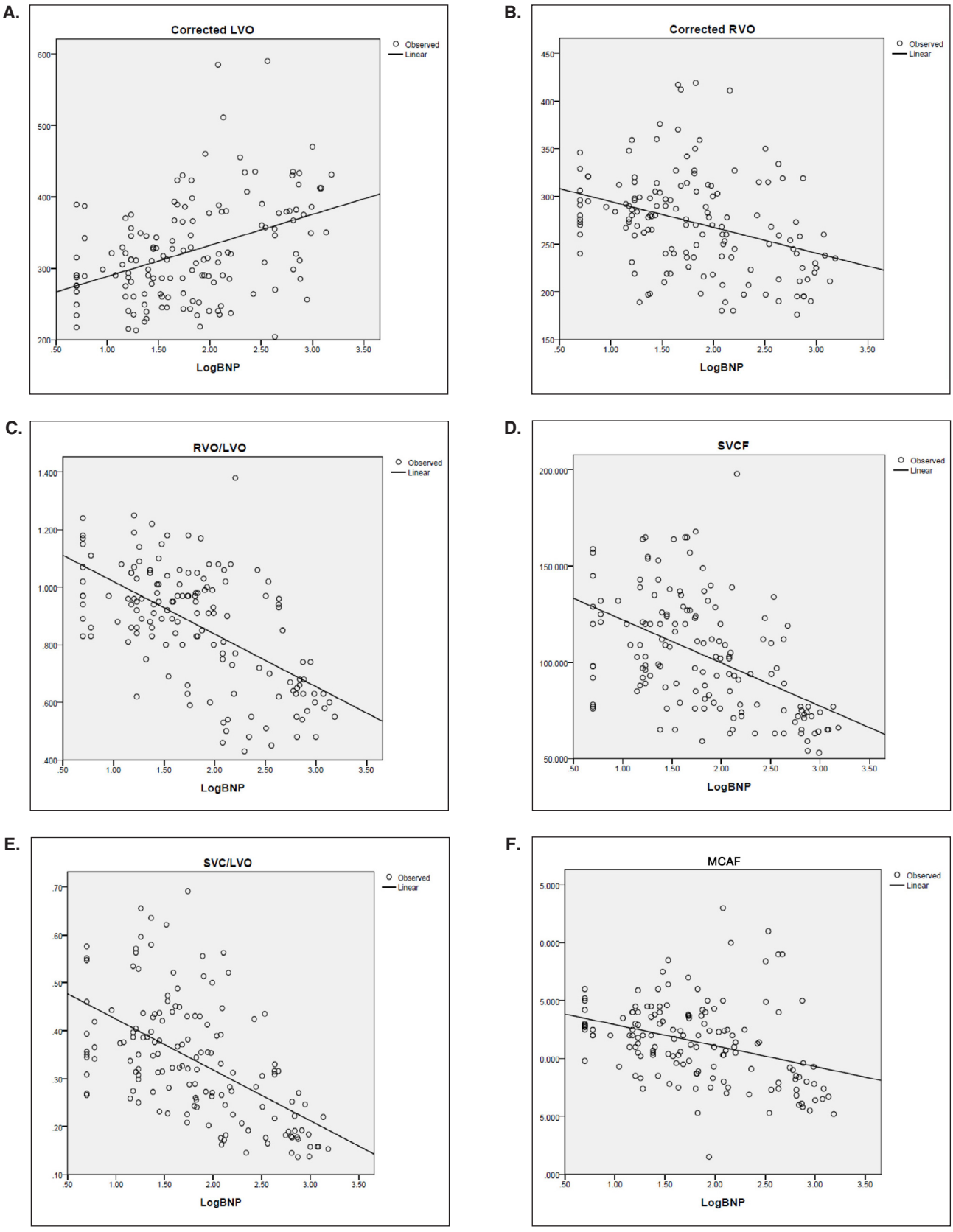

Figure 1. Correlation between logarithm of brain-type natriuretic peptide (logBNP) and different blood flow indices at 48-72 hours of age (continues on the next page).

Please refer to **Tab. 2** for R^2 and slop (β) values. Y axis is representing flow (ml/kg/min) for LVO, RVO, CAF, MCAF, ratio for RVO:LVO and SVC:LVO, and index (resistive or pulsatility) for the rest.

LogBNP: logarithm of brain-type natriuretic peptide; LVO: left ventricular output; RVO: right ventricular output; SVCF: superior vena cava flow; MCAF: middle cerebral artery flow; MCARI: middle cerebral artery resistive index; MCAPI: middle cerebral artery pulsatility index; CAF: celiac artery flow; CARI: celiac artery resistive index.

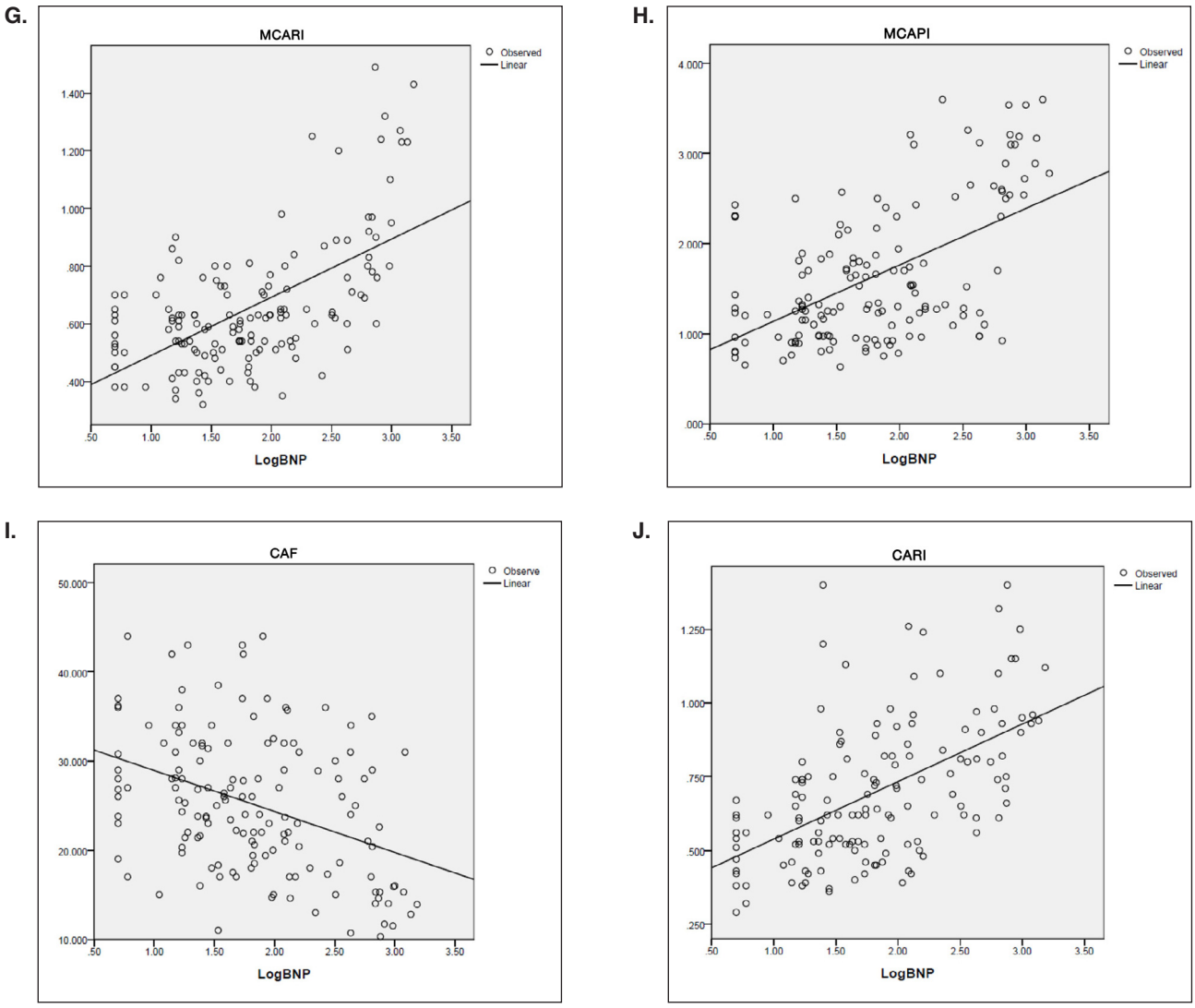

Figure 1. Correlation between logarithm of brain-type natriuretic peptide (logBNP) and different blood flow indices at 48-72 hours of age (continues from the previous page).

Please refer to **Tab. 2** for R^2 and slop (β) values. Y axis is representing flow (ml/kg/min) for LVO, RVO, CAF, MCAF, ratio for RVO:LVO and SVC:LVO, and index (resistive or pulsatility) for the rest.

LogBNP: logarithm of brain-type natriuretic peptide; LVO: left ventricular output; RVO: right ventricular output; SVCF: superior vena cava flow; MCAF: middle cerebral artery flow; MCARI: middle cerebral artery resistive index; MCAPI: middle cerebral artery pulsatility index; CAF: celiac artery flow; CARI: celiac artery resistive index.

Pilot studies of nuclear magnetic resonance (NMR)-based urinary pharmacometabolomics can distinguish neonatal populations of ibuprofen responders from non-responders, and thus have been proposed to predict which HSPDA may be amenable to closure by medical therapy, though this approach has not yet been tested in clinical trials [31-33]. Echo-based studies cannot predict responsiveness to therapy, but can be used to answer the distinct question of urgency of need for therapy, based on an assessment of hemodynamic consequences of the PDA.

Evaluating systemic and regional blood flow indices have been described in previous studies with significant correlations in infants with HSPDA, both before and after medical treatment, but this is the first study describing quantitation of blood flow through Doppler indices of CA and MCA and correlating these indices with BNP levels during the pre-symptomatic and symptomatic periods [30]. Our data are consistent with other published studies showing variations of BNP values at different time points [8]. This makes standardization of BNP monitoring difficult in practice, and limits its reliability as a single parameter. Our study data was included in a recently published systematic review which showed the same variation between studies and at

Table 3. Comparison of all indices at the 3 time points.

	At 48 -72 hours Mean ± SD	Pre-treatment Mean ± SD	Post-treatment Mean ± SD	p-value
BNP (pg/ml)	321.2 ± 190	484.5 ± 166	283.2 ± 102	0.13
LVO (ml/kg/min)	355 ± 84	377 ± 79	329 ± 58	0.09
RVO (ml/kg/min)	240 ± 47	253 ± 44	281 ± 56	**0.02**
RVO:LVO	0.7 ± 0.1	0.68 ± 0.15	0.88 ± 0.2	**0.001**
SVCF (ml/kg/min)	89.6 ± 20	82.4 ± 19	97 ± 31	0.1
SVCF:LVO	0.37 ± 0.06	0.32 ± 0.06	0.34 ± 0.07	0.07
MCAF (ml/kg/min)	11.4 ± 4	9 ± 3	11.9 ± 4	**0.04**
MCARI	0.72 ± 0.17	0.91 ± 0.29	0.64 ± 0.19	**< 0.0001**
MCAPI	1.7 ± 0.5	2.5 ± 0.6	1.6 ± 0.82	**< 0.0001**
MCAF:LVO	0.4 ± 0.01	0.03 ± 0.01	0.04 ± 0.02	**0.03**
CAF (ml/kg/min)	22 ± 6	18 ± 5	26 ± 8	**< 0.0001**
CARI	0.85 ± 0.26	0.860.18	0.72 ± 0.21	**0.036**
CAPI	1.7 ± 0.5	1.99 ± 0.4	1.4 ± 0.4	**< 0.01**
CAF:LVO	0.08 ± 0.03	0.07 ± 0.02	0.09 ± 0.03	**< 0.05**

Data is presented as mean ± standard deviation; p-value is bolded where significant.
BNP: brain type natriuretic peptide; LVO: left ventricular output; RVO: right ventricular output; SVCF: superior vena cava flow; MCAF: middle cerebral artery flow; MCARI: middle cerebral artery resistive index; MCAPI: middle cerebral artery pulsatility index; CAF: celiac artery flow; CARI: celiac artery resistive index; CAPI: celiac artery pulsatility index.

different time points of measuring BNP [8]. For this reason, we recommend combined integrated evaluation with TNE [34, 35]. Our data suggests a benefit of using BNP during the pre-symptomatic stage, but a lesser role for using BNP as a predictor of response to therapeutic interventions. The main limitations of our study are its small sample size, and the lack of standardization of clinical team decision-making about when to intervene by medical treatment or surgical ligation. A larger cohort would allow stratification of the study group according to gestational age cut-offs.

Conclusions

BNP correlates negatively with hemodynamic parameters of systemic blood flow indices in HSPDA, and positively with both MCA and CA pulsatility and resistive indices mainly at 48-72 hours, reflecting the value of pre-symptomatic physiologic prediction of BNP.

Abbreviations

BNP: brain type natriuretic peptide
CA: celiac artery
CAF: celiac artery flow
CAPI: celiac artery pulsatility index
CARI: celiac artery resistive index
HSPDA: hemodynamically significant patent ductus arteriosus
LVO: left ventricular output
MCA: middle cerebral artery
MCAF: middle cerebral artery flow
MCAPI: middle cerebral artery pulsatility index
MCARI: middle cerebral artery resistive index
MDV: minimum diastolic velocity
MV: mean velocity
NICU: Neonatal Intensive Care Unit
NSAID: non-steroidal anti-inflammatory drug
PDA: patent ductus arteriosus
PI: pulsatility index
PSV: peak systolic velocity
RI: resistive index
RVO: right ventricular output
SVCF: superior vena cava flow
TNE: targeted neonatal echocardiography

Acknowledgements

Supported by funding from the Children's Hospital Research Foundation of Manitoba.

Declaration of interest

The Authors declare no conflict of interest.

References

1. Noori S. Patent ductus arteriosus in the preterm infant: to treat or not to treat? J Perinatol. 2010;30(Suppl):S31-7.

2. Benitz WE; Committee on Fetus and Newborn, American Academy of Pediatrics. Patent Ductus Arteriosus in Preterm Infants. Pediatrics. 2016;137(1):e20153730.
3. Elsayed Y, Seshia M, Soni R, Buffo I, Baier RJ, McNamara PJ, Dakshinamurti S. Pre-symptomatic prediction of morbitidies in preterm infants with patent ductus arteriosus by targeted neonatal echocardiography and brain-type natriuretic peptide. J Pediatr Neonat Individual Med. 2016;5(2):050210.
4. McNamara PJ, Sehgal A. Towards rational management of the patent ductus arteriosus: the need for disease staging. Arch Dis Child Fetal Neonatal Ed. 2007;92:424-7.
5. Sehgal A, McNamara PJ. The ductus arteriosus: a refined approach! Semin Perinatol. 2012;36:105-13.
6. Sehgal A, Paul E, Menahem S. Functional echocardiography in staging for ductal disease severity: Role in predicting outcomes. Eur J Pediatr. 2012;172(2):179-84.
7. Flynn PA, da Graca RL, Auld PA, Nesin M, Kleinman CS. The use of a bedside assay for plasma B-type natriuretic peptide as a biomarker in the management of patent ductus arteriosus in premature neonates. J Pediatr. 2005;147(1):38-42.
8. Kulkarni M, Gokulakrishnan G, Price J, Fernandes CJ, Leeflang M, Pammi M. Diagnosing significant PDA using natriuretic peptides in preterm neonates: a systematic review. Pediatrics. 2015;135:e510-25.
9. Chen S, Tacy T, Clyman R. How useful are B-type natriuretic peptide measurements for monitoring changes in patent ductus arteriosus shunt magnitude? J Perinatol. 2010;30:780-5.
10. El-Khuffash A, Barry D, Walsh K, Davis PG, Molloy EJ. Biochemical markers may identify preterm infants with a patent ductus arteriosus at high risk of death or severe intraventricular haemorrhage. Arch Dis Child Fetal Neonatal Ed. 2008;93: F407-12.
11. El-Khuffash A, Molloy EJ. Are B-type natriuretic peptide (BNP) and N-terminal-pro-BNP useful in neonates? Arch Dis Child Fetal Neonatal Ed. 2007;92:F320-4.
12. Choi BM, Lee KH, Eun BL, Yoo KH, Hong YS, Son CS, Lee JW. Utility of rapid B-type natriuretic peptide assay for diagnosis of symptomatic patent ductus arteriosus in preterm infants. Pediatrics. 2005;115(3):e255-61.
13. Sanjeev S, Pettersen M, Lua J, Thomas R, Shankaran S, L'Ecuyer T. Role of plasma B-type natriuretic peptide in screening for hemodynamically significant patent ductus arteriosus in preterm neonates. J Perinatol. 2005;25(11):709-13.
14. Pees C, Walch E, Obladen M, Koehne P. Early Human Development Echocardiography predicts closure of patent ductus arteriosus in response to ibuprofen in infants less than 28 week gestational age. Early Hum. Dev. 2010;86:503-8.
15. Mertens L, Seri I, Marek J, Arlettaz R, Barker P, McNamara P, Moon-Grady AJ, Coon PD, Noori S, Simpson J, Lai WW; Writing Group of the American Society of Echocardiography (ASE); European Association of Echocardiography (EAE); Association for European Pediatric Cardiologists (AEPC). Targeted neonatal echocardiography in the neonatal intensive care unit: practice guidelines and recommendations for training. Eur J Echocardiogr. 2011;12(10):715-36
16. Jain A, Sahni M, El-Khuffash A, Khadawardi E, Sehgal A, McNamara PJ. Use of targeted neonatal echocardiography to prevent postoperative cardiorespiratory instability after patent ductus arteriosus ligation. J Pediatr. 2012;160(4):584-9.e1.
17. Miletin J, Pichova K, Dempsey EM. Bedside detection of low systemic flow in the very low birth weight infant on day 1 of life. Eur J Pediatr. 2009;168:809-13.
18. Noori S, McCoy M, Anderson MP, Ramji F, Seri I. Changes in cardiac function and cerebral blood flow in relation to peri/intraventricular hemorrhage in extremely preterm infants. J Pediatr. 2014;164(2):264-70.e1-3.
19. Cortez J, Gupta M, Amaram A, Pizzino J, Sawhney M, Sood BG. Noninvasive evaluation of splanchnic tissue oxygenation using near-infrared spectroscopy in preterm neonates. J Matern Fetal Neonatal Med. 2011;24(4):574-82.
20. Groves AM, Kuschel CA, Knight DB, Skinner JR. Echocardiographic assessment of blood flow volume in the superior vena cava and descending aorta in the newborn infant. Arch Dis Child Fetal Neonatal Ed. 2008;93:F24-8.
21. Petersen LJ, Petersen JR, Talleruphuus U, Ladefoged SD, Mehlsen J, Jensen HA. The pulsatility index and the resistive index in renal arteries. Associations with long-term progression in chronic renal failure. Nephrol Dial Transplant. 1997;12(7):1376-80.
22. Matasova K, Dokus K, Zubor P, Danko J, Zibolen M. Physiological changes in blood flow velocities in the superior mesenteric and coeliac artery in healthy term fetuses and newborns during perinatal period. J Matern Fetal Neonatal Med. 2011;24:827-32.
23. Shimada S, Kasai T, Konishi M, Fujiwara T. Effects of patent ductus arteriosus on left ventricular output and organ blood flows in preterm infants with respiratory distress syndrome treated with surfactant. J Pediatr. 1994;125;270-7.
24. Kluckow M, Evans N. Superior vena cava flow in newborn infants: a novel marker of systemic blood flow. Arch Dis Child Fetal Neonatal Ed. 2000;82:F182-7.
25. Kluckow M, Evans N. Ductal shunting, high pulmonary blood flow, and pulmonary hemorrhage. J Pediatr. 2000;137:68-72.
26. Tavera MC, Bassareo PP, Biddau R, Montis S, Neroni P, Tumbarello R. Role of echocardiography on the evaluation of patent ductus arteriosus in newborns. J Matern Fetal Neonatal Med. 2009;22(Suppl 3):10-3.
27. Shimada S, Kasai T, Hoshi A, Murata A, Chida S. Cardiocirculatory effects of patent ductus arteriosus in extremely low-birth-weight infants with respiratory distress syndrome. Pediatr Int. 2003;45;255-62.
28. Shimada S, Kasai T, Konishi M, Fujiwara T. Effects of patent ductus arteriosus on left ventricular output and organ blood flows in preterm infants with respiratory distress syndrome treated with surfactant. J Pediatr. 1994;125:270-7.
29. Hammerman C, Shchors I, Schimmel MS, Bromiker R, Kaplan M, Nir A. N-terminal-pro-B-type natriuretic peptide in

premature patent ductus arteriosus: a physiologic biomarker, but is it a clinical tool? Pediatr Cardiol. 2010;31(1):62-5.

30. Chen HH, Lainchbury JG, Harty GJ, Burnett JC. Maximizing the natriuretic peptide system in experimental heart failure: Subcutaneous brain natriuretic peptide and acute vasopeptidase inhibition. Circulation. 2002;105:999-1003.
31. Bassareo PP, Fanos V, Deidda M, Barberini L, Mercuro G. Metabolomic approach to foetal and neonatal heart. J Matern Fetal Neonatal Med. 2012;25(Suppl 5):19-21.
32. Katsila T, Patrinos GP. The Implications of Metabotypes for Rationalizing Therapeutics in Infants and Children. Front Pediatr. 2015;3:68.
33. Hoodbhoy SA, Cutting HA, Seddon JA, Campbell ME. Cerebral and splanchnic hemodynamics after duct ligation in very low birth weight infants. J Pediatr. 2009;154:196-200.
34. Elsayed YN, Fraser D. Integrated Evaluation of Neonatal Hemodynamics, Part 2: Systematic Bedside Assessment. Neonatal Netw. 2016;35(4):192-203.
35. Elsayed YN, Fraser D. Integrated Evaluation of Neonatal Hemodynamics Program Optimizing Organ Perfusion and Performance in Critically Ill Neonates, Part 1: Understanding Physiology of Neonatal Hemodynamics. Neonatal Netw. 2016;35(3):143-50.