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B-type Natriuretic Peptide: A Diagnostic Biomarker for a Hemodynamically Significant PDA

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Abstract

BACKGROUND: B-type natriuretic peptide (BNP), it has been reported to be a useful biomarker for the severity of hemodynamically significant patent ductus arteriosus (HsPDA) in premature infants.

AIM: The objective of the study was to assess serum levels of BNP in premature neonates with echocardiographically-confirmed hemodynamically significant and non-significant PDA (HnsPDA) and to explore the effect of PDA on left ventricular function. We also aimed to detect the level of BNP that differentiates between HsPDA and HnsPDA.

PATIENTS AND METHODS: This was a cross-sectional observational study conducted on 73 randomly selected preterm neonates with HsPDA or HnsPDA, between May 2017 and May 2018. Echocardiography was done. BNP was measured using enzyme linked immunosorbent assay.

RESULTS: There was no affection of left ventricular function in either group (LA/Ao ratio, FS, LVESD and LVEDD). PDA size, PFO size, and PAP were significantly larger in HsPDA ($p < 0.001$, $p = 0.001$, and $p < 0.001$ respectively). Levels of BNP were significantly higher in HsPDA and correlated with the size of the PDA. At a cutoff value of 160.5 pg/ml, BNP had 80.49% sensitivity, and 90.62% specificity with a positive predictive value of 91.7% and a negative predictive value of 78.04%, (AUC: 0.923, 95% C.I. 0.837–0.973).

CONCLUSION: Levels of BNP in preterm babies with hemodynamically significant PDA rise early in neonatal life and correlate well with the size of the PDA. BNP can be used to screen for this condition. Ventricular dysfunction may not appear in the first 3 days of life.

Introduction

A third of premature infants with gestational ages <32 weeks experience cardiac dysfunction with a hemodynamically significant patent ductus arteriosus (HsPDA) [1]. The left-to-right shunt which occurs results in an increase in pulmonary blood flow and a simultaneous decrease in systemic blood flow (steal phenomenon). A reduction in intestinal and renal blood flows as well as congestive heart may ensue causing pulmonary or intracranial hemorrhage and exacerbation of chronic lung diseases [2].

Persistent PDA may result in a hyperdynamic left ventricle and alteration of the right ventricle (RV) function, with the latter being a determinant of long-term outcome in preterm infants [3]. Once HsPDA is suspected clinically by the presence of tachycardia, heart murmur and a large pulse pressure, diagnostic confirmation and visual assessment of the ductus are sought by echocardiography. Doppler flow studies confirm ductal patency and help assess the direction of ductal flow, cardiac anatomy, ventricular function, the ratio of estimated pulmonary to systemic blood flow and pulmonary artery pressures (PAP) [4].

Conventional echocardiography, however, has limitations because of the complex anatomy of the RV and the physiological hemodynamic changes that take place in the 1st week of life [5].

Brain natriuretic peptides are hormones synthesized by the heart, brain and other organs in response to heart failure. By inducing vasodilatation and diuresis, B-type natriuretic peptide (BNP) decreases systemic vascular resistance and reduces arterial pressure [6]. BNP has been used as a biomarker for the diagnosis and response to the treatment of chronic heart failure in adults [7]. In premature infants, it has been reported to be a useful biomarker for the severity of HsPDA [8].

We aimed to assess serum levels of BNP in premature neonates with echocardiographically-confirmed hemodynamically significant and non-significant PDA (HnsPDA) and to explore the effect of PDA on the left ventricular function. We also aimed to detect the level of BNP that differentiates between HsPDA and HnsPDA.

Patients and Methods

This cross-sectional observational study was conducted on randomly selected preterm neonates with HsPDA or HnsPDA in the neonatal intensive care unit of the Obstetrics and Gynecology hospital, Kasr Al-Aini Hospital, Cairo University, between May 2017 and May 2018.

Sample size was calculated using PASS version 11 program, setting the type1 error (α) at 0.05 (95% Confidence Interval) and power (1-β) at 0.8. Results from a previous study [9] showed that the area under the curve (AUC) for BNP to differentiate between HsPDA from non-HsPDA was 0.83. Calculation according to these values produced a minimal sample size of 40 cases (including ten cases with HsPDA).

Inclusion criteria

Preterm newborns ≤35 weeks gestational age, on 1st–3rd days of life with echocardiographic confirmation of PDA.

Exclusion criteria

Infants with signs of sepsis or dehydration, gross congenital malformations or those with heart diseases other than PDA or patent foramen ovale (PFO) or those whose mothers received medications that can affect the heart, for example, non-steroidal anti-inflammatory drugs or selective serotonin inhibitors.

Methodology

Patients were subjected to the following:

a) History-taking: Maternal, antenatal, and intranatal with emphasis on maternal risk factors for preterm labor, gestational age (according to maternal dates and/or ultrasound information), mode of delivery and whether singleton or multiple pregnancy. Other data included APGAR score at 1, 5, and 10 min after delivery and oxygen therapy in NICU (none, nasal oxygen, nasopharyngeal continuous positive airway pressure [CPAP] or synchronized intermittent mandatory ventilation [SIMV]).

b) Clinical examination for assessment of gestational age [10], birth weight, chest, cardiovascular, and other system examination.

Laboratory investigations on day 1–2 of life after establishing vascular access. All patients were on intravenous fluids at the time of venipuncture: Four milliliters venous blood were withdrawn aseptically using a sterile disposable syringe at the time of routine sampling of the neonates and were divided into: 2 ml of whole blood in a sterile EDTA tube for complete blood count (CBC) and 2 ml of blood in a plain sterile vacutainer for BNP assay.

i. CBC (Bechman Coulter LH-750 hematology analyzer). Normal CBC values in preterm babies on day 1–3: Hb: 15.6 gm/dL, TLC: 9.4–34 × 10^9, PLT: 150–350 × 10^9 [11].

ii. BNP on the same day as, but after, echocardiography following manufacturer instructions (measured by solid-phase sandwich enzyme linked immunosorbent assay NOVA ELISA, Bioneovan Company, Beijing, China). The optical density was detected at 450 nm with microplate reader.

c) Radiological investigation:

Echocardiography using portable echocardiography “sonosite-180 plus” using probes 5-7mHz for assessment of PAP, chamber size (Left Ventricular End Systolic Diameter [LVESD] Left Ventricular End Diastolic Diameter [LVEDD]), Fractional shortening (FS), Left atrium/aorta ratio (LA/Ao), PDA size, presence and size of PFO and/or mitral regurgitation (MR), and tricuspid regurgitation (TR) (and degree).

Pulmonary pressure: Less than 35 mmHg = normal pulmonary pressure, 35–50 mmHg = mild hypertension, 51–70 mmHg = moderate pulmonary hypertension, >70 mmHg = severe pulmonary hypertension [12].

PDA size >2 mm is considered significant [13].

LA/Ao ratio was calculated by dividing left atrium diameter by aortic diameter. A value >1.5 indicates left atrium dilation [14].

FS was calculated by the following formula: LVEDD–LVESD/LVEDD × 100. A value > 28% indicates normal left ventricular function [15].

The study was approved by the Institutional review board of Cairo University and conducted in accordance with the Helsinki Declaration for biomedical research. Consent was obtained from parents.

Statistical analysis

Data were revised, coded, tabulated, and introduced to Statistical package for the Social Science 20. Mean, Standard deviation (± SD) and range were used for parametric numerical data, median and interquartile range (IQR) for non-parametric numerical data, frequency, and percentage of non-numerical data. Mann–Whitney Test was used to assess the difference between non-parametric variables. Spearman’s rho method was used to assess the strength of association between quantitative and qualitative variables. P-value was significant when < 0.05.

Results

The total patient number included 85 singletons, six of whom died before an echocardiogram could be done and another six were withdrawn due to incomplete laboratory data meaning 73 patients remained in the study. Thirty-two had HnsPDA (four later died) while 41 had HsPDA (nine later died).

Demographic, pregnancy, delivery, and neonatal data

There was no difference between the two groups with regard to male: female ratio, pregnancy history of relevance, mode of delivery, gestational age (weeks) at birth, birth weight (kg), or age at testing (days). APGAR score at 5 min was significantly lower in HsPDA group (p = 0.006) and significantly more children in this group needed oxygen (95.1%, of whom 51.2% were on nasopharyngeal CPAP) compared to 87.5% in HnsPDA (43.8% on SIMV) (p = 0.032). Hemoglobin levels were lower (but normal) in HsPDA group. A left shift was observed in some which is not uncommon in preterm infants [11] (Table 1).

Table 1: Demographic, pregnancy, delivery and laboratory data of the study group (n = 73)

	HnsPDA (n = 32)	HsPDA (n = 41)	p value
Gestational age (weeks) mean ± SD	30.9 ± 2.4	31.1 ± 2.4	0.67
Sex (n, %)			
Male	17 (53.1)	22 (53.7)	0.96
Female	15 (46.9)	19 (46.3)	
Birth weight (kilograms) mean ± SD	1.53 ± 0.45	1.57 ± 0.42	0.69
APGAR score (mean ± SD)			
1 min	5 ± 1.5	4.2 ± 1.8	0.053
5 min	7.3 ± 1.3	6.3 ± 1.8	0.006
10 min	8.3 ± 0.9	7.8 ± 1.1	0.054
Pregnancy history of relevance (n, %)			
None	28 (87.5)	25 (61)	0.12
Rupture uterus	0	1 (2.4)	
PROM	2 (6.3)	4 (9.8)	
Cord prolapsed	0	1 (2.4)	
Pre-eclampsia	2 (6.3)	9 (22)	
Chorioamnionitis	0	1 (2.3)	
Mode of delivery (n, %)			
Vaginal	11 (34.4)	14 (34.1)	0.98
Cesarean section	21 (65.6)	27 (65.9)	
Mode of ventilation on day of tests			
No oxygen	4 (12.5)	2 (4.9)	0.032
Nasal oxygen	8 (25)	6 (14.6)	
NP CPAP	6 (18.8)	21 (51.2)	
SIMV	14 (43.8)	12 (29.3)	
Day of life at testing	2.2 ± 0.9	1.9 ± 0.8	0.143
Hemoglobin (gm/dL) (mean ± SD)	16.9 ± 2.8	15.5 ± 3.2	0.043
Hematocrit % (mean ± SD)	51.8 ± 10.6	47.6 ± 10.6	0.094
Platelet s ($\times 10^9$/L) (mean ± SD)	184.8 ± 66.2	220.5 ± 133.7	0.170
Total leukocytic count ($\times 10^9$/L) (mean ± SD)	12.6 ± 8.5	12.9 ± 6.7	0.873
Left shift	27 (84.4)	30 (73.2)	0.251
No (n, %)			
Yes (n, %)	5 (15.6)	11 (26.8)	

PROM: Premature rupture of membranes, NP CPAP: Nasopharyngeal continuous positive airway pressure, SIMV: Synchronized intermittent mandatory ventilation.

Echocardiographic findings

There was no left ventricular function affection in either group (LA/Ao ratio, FS, LVESD and LVEDD). PDA size, PFO size and PAP were significantly larger in HsPDA (p < 0.001, p = 0.001, p < 0.001 respectively). Mean PAP in HsPDA was in mild hypertension level (42.4 ± 9.5 mmHg). MR, PFO and pulmonary hypertension occurred significantly more frequently in HsPDA (p = 0.002, p = 0.002, and p = 0.006, respectively) (Table 2).

Table 2: Echocardiographic findings in patients with HnsPDA and HsPDA (n = 73)

	HnsPDA (n = 32)	HsPDA (n = 41)	p value
	Mean ± SD	Mean/N	
Size of PDA (mm)	0.9 ± 0.6	3.1 ± 0.9	<0.001
Left atrium/aorta ratio	1.04 ± 0.13	1.09 ± 0.18	0.188
Fractional Shortening %	40.8 ± 6.0	41.4 ± 10.2	0.784
End Systolic Diameter (mm)	0.84 ± 0.623	0.96 ± 0.73	0.344
End Diastolic Diameter (mm)	1.38 ± 0.21	1.61 ± 1.12	0.255
Pulmonary Artery Pressure (mmHg)	35.2 ± 7	42.5 ± 9.4	<0.001
Size of Patent Foramen Ovale (mm)	2.8 ± 1.1	3.7 ± 0.8	0.001
	n, %	**n, %**	
Mitral Regurgitation			
None	31 (96.9)	27 (65.9)	0.002
Grade 1	0	6 (14.6)	
Grade 2	1 (3.1)	8 (19.5)	
Pulmonary Artery Pressure (mmHg)			
Normal	15 (46.9)	6 (14.6)	0.024
Mild	15 (46.9)	29 (70.8)	
Moderate	2 (6.3)	6 (14.6)	
Tricuspid Regurgitation			
None	29 (90.6)	40 (97.6)	0.391
Grade 1	2 (6.3)	1 (2.4)	
Grade 2	1 (3.1)	0	
Patent Foramen Ovale			
None	12 (37.5)	3 (7.3)	0.002
Present	20 (62.5)	38 (92.7)	

BNP

Levels of BNP were significantly higher in HsPDA (median: 536, IQR 193–2468, range: 36–5665) than in HnsPDA patients (median: 59.25, IQR: 25.5–111, range: 11.5–331) p < 0.001.

There were no significant differences in BNP levels with regard to sex, mode of delivery, pregnancy history of relevance, or outcome (death/discharge) between patients with HnsPDA or HsPDA.

Table 3 shows BNP levels in relation to different echocardiographic findings in patients with HnSPDA and HsPDA. There were no differences related to the presence of MR, TR, or high PAP. In HnsPDA, higher BNP levels were found in children with PFO (p = 0.045).

Table 3: BNP levels in relation to echocardiographic findings in neonates with HnSPDA and HsPDA (n = 73)

	BNP (pg/ml)			p-value
	N	Median (IQR)	Range	
HnsPDA (n = 32)				
MR				
None	31	59.5 (26–114)	11.5–331	0.176
Present	1	20.5 (20.5–20.5)	20.5–20.5	
TR				
None	29	59 (25–108)	11.5–331	0.286
Present	3	104.5 (41–189.5)	41–189.5	
PAP				
Normal	15	46 (25–104.5)	20.5–200	0.706
Mild	15	59.5 (21–117)	11.5–331	
Moderate	2	90.5 (67–114)	67–114	
PFO				
None	12	31.25 (23–60.25)	18–154	0.045
Present	20	97.75 (37.25–131.75)	11.5–331	
HsPDA (n = 41)				
MR				
None	27	262 (170–2024)	36–5665	0.058
Present	14	845 (536–3164)	87–5327	
TR				
None	40	558 (203–2622.5)	36–5665	0.353
Present	1	170 (170–170)	170–170	
PAP				
Normal	6	1433.5 (256–2648)	120–2922	0.306
Mild	29	472 (213–2024)	69–5665	
Moderate	6	464.5 (150–4299)	36 – 5327	
PFO				
None	3	737 (472–930)	472–930	0.652
Present	38	435.5 (170–2777)	36–5665	

Correlations

BNP levels correlated positively with PDA size (r = 0.57, p < 0.001) but showed no correlation with (Figure 1). A/Ao, FS, PAP, LVEDD, LVESD, or size of PFO (Figure 2).

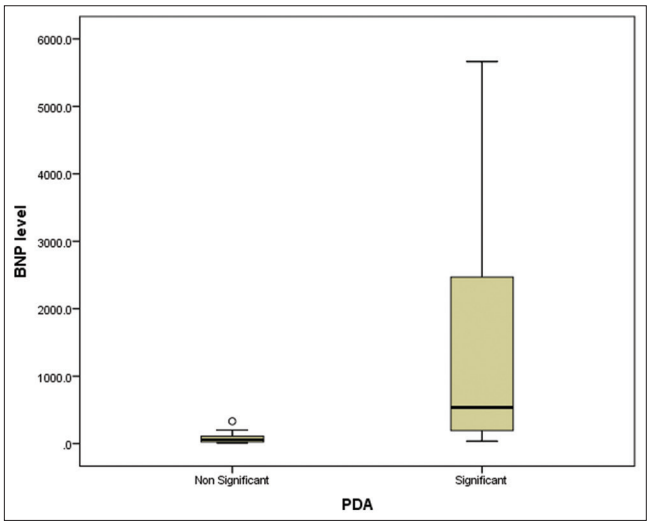

Figure 1: BNP levels in HnsPDA and HsPDA patients

Sensitivity and specificity of BNP levels

At a cutoff value of 160.5 pg/ml, BNP had 80.49% sensitivity, and 90.62% specificity with a positive predictive value of 91.7% and a negative predictive value of 78.04%, (AUC: 0.923, 95% confidence interval 0.837–0.973) (Figure 3).

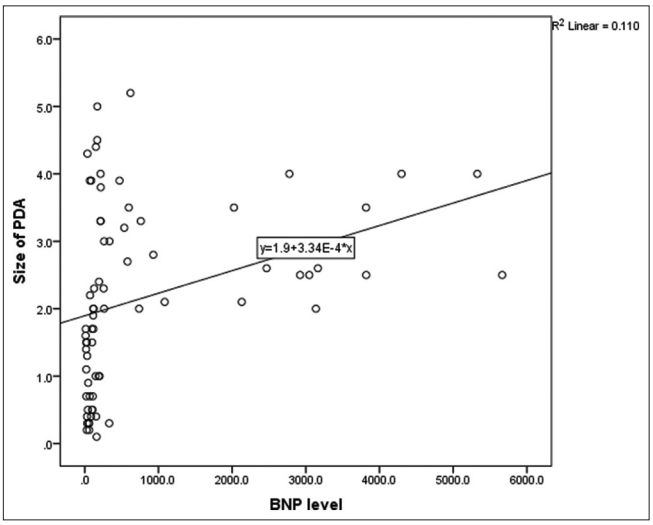

Figure2: Correlation between BNP levels and PDA size

Discussion

The normal ductal closure observed in healthy full-term infants is delayed or fails to occur in preterm babies with up to 60% of preemies born <28 weeks needing some sort of intervention to prevent complications of PDA [16], [17].

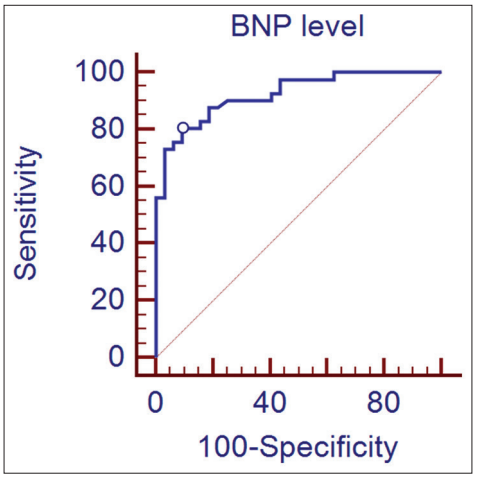

Figure 3: Sensitivity and specificity of BNP

During the 1st days after birth, a rise in BNP levels occurs in healthy newborns during the transition from fetal to adult circulation with a gradual fall thereafter [18]. Excess BNP is secreted into the circulation from the cardiac ventricles in response to cardiac stress and this may play a role in maintaining ductal patency after birth [8].

Diagnosis of PDA based on the clinical features alone has low sensitivity and a delay in detection of 1–4 days compared to echocardiography. Left ventricular hypertrophy and left atrial enlargement increase as shunt size increases [4]. Correlating BNP with left ventricular output (assessed by echocardiography) may provide a noninvasive method that yields much information about cardiac performance [19].

We found no differences between neonates with HsPDA or HnsPDA with regard to male: female ratio, pregnancy data, mode of delivery, gestational age, and birthweight. This was in agreement with previous studies Van der Laan *et al.* [20] and Nizarali *et al.* [21]. However, we did observe significantly lower APGAR scores at 5 min in the HsPDA group. Nizarali *et al.* [21] suggested that higher APGAR scores at 1 and 5 min decreased the risk of PDA. Lower APGAR scores may be a manifestation of asphyxiating conditions that are in themselves a risk factor for HsPDA. In contrast, Van der Laan *et al.* [20] found no differences in APGAR scores between HsPDA and HnSPDA neonates.

In our study, as with others Flynn *et al.* [22] and Kim and Shim [6], BNP levels were significantly higher in HsPDA patients (median = 536 pg/ml) than in HnSPDA (median = 59.25 pg/ml, p < 0.001). As found in the study of König *et al.* [23], BNP levels in our patients strongly correlated with ductal size (p < 0.001).

Different cutoff values for BNP have been reported. In our study, a cutoff level of 160.5pg/ml BNP had a sensitivity of 80.49% and a specificity of 90.62%

(AUC = 0.923) for the diagnosis of an HsPDA. This was closest to the cut-off value of 123 ng/L of Kalra *et al.* [24] who constructed their curve based on a treat/no treat option, lower than those of Flynn *et al.* [22] where BNP >300 pg/mL predicted significant PDA and <105 pg/mL predicted absence of significant PDA and much lower than findings of Byung *et al.* [25] who concluded that the best cutoff of BNP concentration for the diagnosis of HsPDA was 1110 pg/mL (sensitivity = 100%; specificity = 95.3%). We believe that these differences are due to different ages at sampling, differences in gestational ages of infants enrolled in the studies the more immature the myocardium, the lower the ability, at least initially, to produce BNP in response to cardiac stress [26], higher levels for specificity and sensitivity sought and perhaps because in some studies children were followed up to disappearance of ductal flow. Using a cutoff value for all preterm infants regardless of gestational age therefore may not be appropriate.

Although significantly more patients with HsPDA than HnsPDA had high PAP (p = 0.006) and mean PAP for HsPDA was also higher (42.4 ± 9.5 mmHg vs. 34.8 ± 7.9 mmHg normal PAP being lower than 35 mmHg), we found no correlation between BNP levels and PAP and no difference in BNP levels between different PAP groups (normal or mild/moderate increase) in either group. PAP difference may not have been high enough to cause a statistical significance in BNP between the two groups. Results of other studies have been contradictory with some describing significantly higher levels of BNP in preterm neonates with pulmonary hypertension [27] and others not [22]. A similar scenario was observed with MR.

In the present study, BNP levels were higher in PFO patients with HnsPDA than those without PFO in the same group. Surprisingly, we observed no such difference in the group with HsPDA even though mean size for PFO was significantly higher than in the HsPDA groups. This finding resulted in no correlation between PFO size and BNP which complies with findings of Flynn *et al.* [22].

There is an element of diastolic dysfunction in all neonates which, if compounded by another source of respiratory disease, may lead to heart failure. For this reason, it is important to correlate BNP levels with left ventricular function [28]. Significantly more children with HsPDA needed some sort of oxygen support as was reported in the previous studies [29]. The use of oxygen has the potential to produce reactive oxygen species that may further increase cardiac damage [30]. However, we found no differences in left ventricular function (reflected in FS) and LA/Ao ratio between the two groups in the current study and no correlations between their values and BNP levels. These findings concur with those of Lu *et al.* [31], whose extended study included days 2, 3, 5, and 7 after birth, and of others (König *et al.* [23] Van der Laan *et al.* [20]). Conversely, Van der Laan *et al.* [20] described a statistically significant difference between HsPDA and HnsPDA patients with regard to LA: Ao ratio. It has been suggested that the degree of hydration of the infant may reflect on left atrium size with dehydration reducing LA: Ao ratio and altering BNP levels [32]. Choi *et al.* [32] found a strong correlation between FS and BNP (r = 0.73). It is likely that left atrial dilatation and left ventricular dysfunction occur only after prolonged exposure of the immature myocardium to the effects of HsPDA explaining the absence of these echocardiographic findings in our study group who were investigated in their early postnatal lives. This important observation indicates that early diagnosis coupled with timely intervention may be associated with better outcome.

We found no differences in BNP levels with regard to outcome (death/discharge), whereas Cuna *et al.* [33] found significantly lower BNP levels in surviving infants than in those who died. They identified a BNP cutoff value of 220 pg/ml to have the best combination of sensitivity (90%) and specificity (65%) for predicting mortality from all causes. BNP levels are highly elevated in patients with severe sepsis or septic shock and seem to be an early predictor of myocardial dysfunction in these patients [34]. It seems likely that there are other, as yet unidentified, factors influencing BNP levels with some neonates having low BNP levels in spite of having a large HsPDA [19].

The strength of this study is that we demonstrated early rise in BNP in HsPDA patients (as early as 1–3 days of life) before significant echocardiographic findings could be observed. Although BNP may not replace echocardiography in the diagnosis of PDA, it may eliminate the need for repeated echocardiography to confirm ductal closure following treatment. It may also be employed in neonatal intensive care units where echocardiography is not readily available [35].

Conclusion

Levels of BNP in preterm babies with hemodynamically significant PDA rise early in neonatal life and correlate well with the size of the PDA. BNP can be used to screen for this condition. Ventricular dysfunction may not appear in the first 3 days of life.

Limitations

We did not record the degree of respiratory distress, a factor that might explain variability in BNP levels within similar PDA grades. The effect of respiratory distress on BNP production was suggested in a study by Da Graca *et al.* (2006). Furthermore, we did not do a follow-up echocardiogram at a later date to determine level of BNP at ductal closure or to search for late-onset ventricular dysfunction.

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