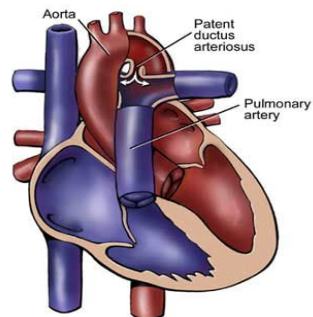


Measuring BNP for patent ductus arteriosus: Exploring a new marker for monitoring treatment

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Ductus Arteriosus



Patent Ductus Arteriosus

- Rate:
 - 30% of infants <1500g
 - >80% of infants born <750g will have a PDA after three days
- 60% of infants <28 weeks require medical/surgical intervention

Patent Ductus Arteriosus

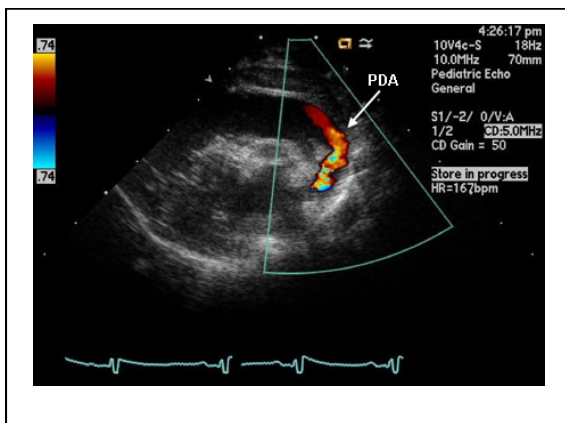
- Excessive pulmonary blood flow:
 - Increased ventilator dependence
 - Bronchopulmonary dysplasia
- Complications:
 - Respiratory distress syndrome (RDS)
 - Pulmonary hemorrhage
 - Prolonged ventilation
 - Bronchopulmonary dysplasia
 - Renal dysfunction
 - Necrotizing enterocolitis
 - Mortality

Treatment Options

- Conservative/Supportive Management
 - Ventilator strategies – adequate oxygenation
 - Mild fluid restrictions – 110-130mL/kg/day
 - Heme – maintain HCT 35-40%
- Pharmacotherapy
 - IV Indomethacin/Ibuprofen
- Surgery
 - Ligation

Diagnosis & Assessment

- Echocardiography
 - Allows direct visual assessment of ductus originating from descending aorta and connecting to pulmonary artery
 - Measure ratio of ductal diameter to ostium of left pulmonary artery
 - Assess clinical course (hemodynamically significant PDA)
 - Gold Standard for diagnosing PDA



Diagnosis & Assessment

- CXR
 - Increased pulmonary vascular markings
 - Cardiomegaly

- BNP
 - New marker useful for diagnosing PDA?

Natriuretic Peptides

- Ring-shaped amino acids of various shape divided into 4 families (A, B, C, and D)
- B-type natriuretic peptides (BNP) synthesis occurs mainly in ventricles of heart
- Release of BNP due to pressure and volume loading, and ventricle distress
- Causes: diuresis, natriuresis, arterial and venous vasodilatation, and it antagonises the renin-angiotensin system
- Net effect: reduction of intravascular volume, and ventricular preload and afterload

B-type Natriuretic Peptide

- Uses:
 - Assess cardiac dysfunction in adults

- Studies for PDA:
 - BNP useful screening tool for hemodynamically significant PDA
 - BNP levels appear to decrease after closure of PDA

Early Hum Dev 2009;85(3):147-9
J Perinatol 2005;25(11):709-13

Clinical Question

P	Neonate with Patent Ductus Arteriosus
I	BNP monitoring
C	Gold standard echocardiogram
O	Closure of PDA Magnitude and change of shunt Treatment adjustment Reduction in clinically significant outcomes of PDA

Literature Search

Databases	Pubmed, Medline, Embase, Cochrane, Google Scholar, IPA, clinicaltrials.gov
Search Terms	B-type natriuretic peptide, Brain natriuretic peptide, Patent Ductus Arteriosus, Neonate
Limits	English, Human
Results	2 RCTs 1 prospective cohort 1 retrospective analysis

B-Type Natriuretic Peptide to Predict Ductus Intervention in Infants <28 Weeks

CHRISTOPH CZERNIK, JULIA LEMMER, BORIS METZE, PETRA S. KOEHNE, CHRISTIAN MUELLER,
AND MICHAEL OBLADEN

Pediatr Res 2008;64:286-90

Czernik et al.

Design	Prospective, non-randomized trial Single Centre (2005-2007)
Population	67 patients < 28 weeks GA BNP collected at 24-48 hours ECHO performed at 24-48 hours
Intervention	24 patients Mechanically ventilated PDA diameter >2mm
Comparator	42 patients Control
Outcomes	Predict ductus intervention Correlation between BNP and ductal diameter

Pediatr Res 2008;64:286-90

Czernik et al.

Table 2. Cutoff values for prediction of ductus intervention

BNP (pg/mL)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
>380	88	65	58	90
>450	83	74	65	89
>500	83	84	74	90
>550	83	86	77	90
>600	71	88	77	84
>650	71	91	81	85
Ductal diameter >1.5 mm	96	32	55	90
Ductal diameter >1.5 mm and BNP >550	83	93	91	86

Correlation between BNP plasma concentrations and ductal diameter
R = 0.46 (p < 0.001)

Pediatr Res 2008;64:286-90

• Conclusion

- Increasing BNP level can be useful for prediction of early PDA treatment
- BNP >550pg/mL have high sensitivity and specificity to predict need for therapy in ventilated preterm neonates

• Limitations

- Need for treatment based on ECHO, not BNP
- Clinical outcomes not measured
- Lack of follow-up >48 hours

B-type natriuretic peptide concentrations to guide treatment of patent ductus arteriosus

J T Attridge,¹ D A Kaufman,¹ D S Lim²

Arch Dis Child Fetal Neonatal Ed 2009;94:F178–F182.

Design	Prospective, randomized, controlled trial Single-center (US hospital) referral neonatal intensive care unit
Population	60 infants with echocardiographic diagnosis of PDA with intent to treat and: receiving positive airway pressure, feeding intolerance, or requiring high supplemental oxygen Exclusion: congenital heart defects, renal failure
Intervention	BNP-guided therapy Indomethacin held if BNP<100 pg/mL at 12 or 24 hours
Comparator	Conventional treatment 3 doses of Indomethacin (0.2mg/kg/dose) BNP measured at baseline and at 48 hours
Outcomes	Primary: Number of doses of indomethacin during the primary course of treatment (three doses every 12 hours) Secondary: Rate of PDA ligation Post-treatment SCR Death

Arch Dis Child Fetal Neonatal Ed 2009;94:F178–F182.

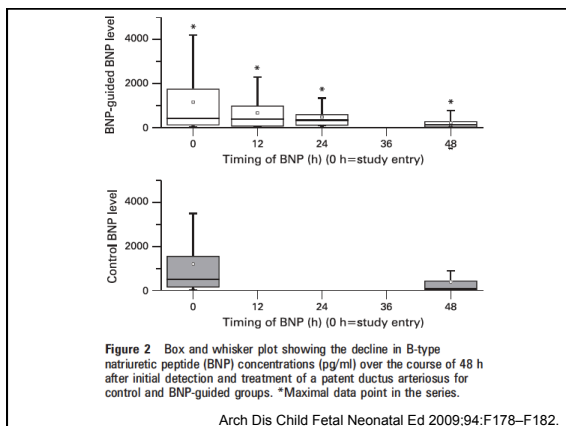


Table 3 Primary and secondary outcomes of infants with a patent ductus arteriosus assigned to a control or B-type natriuretic peptide (BNP)-guided indomethacin treatment group

	Control	BNP-guided	p Value
Number of study doses of indomethacin	88	70	<0.01
Non-study number of doses of indomethacin	84	98	0.51
Persistent PDA after initial indomethacin course	19 (63%)	17 (57%)	0.79
PDA ligation	11 (37%)	14 (48%)	0.43
Timing of PDA ligation (days)	19	26	0.03
Isolated intestinal perforation	3 (10%)	3 (10%)	1.00
Necrotising enterocolitis (surgical)	1	2	0.60
Chronic lung disease*	18 (62%)	19 (73%)	0.41
Died	0	3	0.24

*Data available for 57 patients at 36 weeks' corrected gestational age (three deaths). PDA, patent ductus arteriosus.

Arch Dis Child Fetal Neonatal Ed 2009;94:F178-F182.

Attridge et al.

Conclusion

- BNP-guided therapy allowed for fewer doses of indomethacin in the initial course (every 12 hours) without change in rate of PDA closure or complications
- No change in total number of doses of indomethacin including prophylaxis, treatment, and follow-up

Attridge et al.

Limitations

- No PDA size cut-off
- No indication for timing or criteria for ECHO (determined by practitioner)
- Use of indomethacin over ibuprofen??
- No regulation for prophylactic and follow-up doses of indomethacin
- Change of assay type during study period

How useful are B-type natriuretic peptide measurements for monitoring changes in patent ductus arteriosus shunt magnitude?

S Chen¹, T Tacy¹ and R Clyman^{1,2}

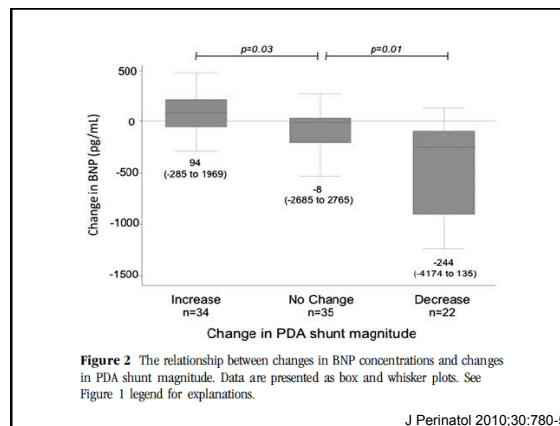
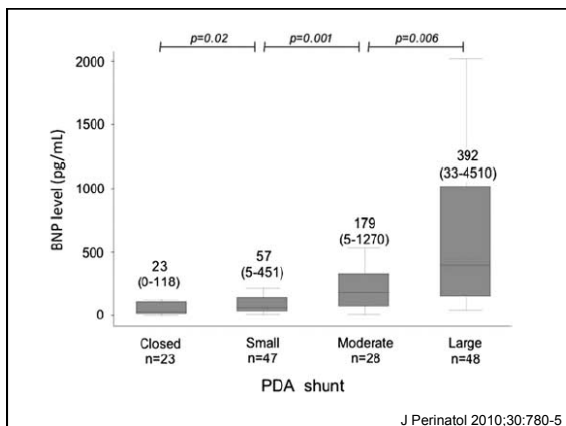
¹Department of Pediatrics, University of California, San Francisco, CA, USA and ²Cardiovascular Research Institute, University of California, San Francisco, CA, USA

J Perinatol 2010;30:780-5

Chen et al.

Design	Retrospective analysis, single centre, data collection 2004-2008
Population	797 infants 24-32 weeks gestation At least one BNP measurement with ECHO pair Exclusion: < 5 days old, congenital heart disease, pulmonary hypertension, hypotension requiring vasopressor support, sepsis, NEC, renal impairment
Intervention/Comparator	ECHO interpreted by one blinded cardiologist PDA scored as open or closed (subjective) Magnitude of Left to Right shunt (subjective)
Outcomes	Magnitude of PDA shunt Monitoring changes in PDA shunt magnitude

J Perinatol 2010;30:780-5



Chen et al.

- **Conclusion:**
 - BNP concentrations are related to magnitude of a PDA shunt
 - BNP <40pg/mL indicates low likelihood of large left to right shunt
 - High degree of variability in measurements, monitoring BNP likely not useful for monitoring changes in magnitude of shunt
 - BNP low predictive value for determining shunt magnitude

Chen et al.

- **Limitations:**
 - Identifying healthy patients
 - Exclusion diseases associated with elevations in BNP
 - ECHO and BNP conducted at different times
 - May have not reflected the same hemodynamic state
 - Data collection over 5 years
 - Changes in precision of instruments used to measure BNP
 - Imprecision of both tests <12%

B-Type Natriuretic Peptide Predicts Responses to Indomethacin in Premature Neonates with Patent Ductus Arteriosus

Jong-Hau Hsu, MD, San-Nan Yang, MD, PhD, Hsiu-Lin Chen, MD, Hsing-I. Tseng, MD, Zen-Kong Dai, MD, PhD, and Jiunn-Ren Wu, MD

J Pediatr 2010; 157:79-84

Design	Prospective, single-center (tertiary hospital/15-bed NICU) Data collection over 1 year
Population	31 infants (mean gestational age, 30 weeks; range, 25-35 weeks; mean body weight, 1393 g; range, 670-2250 g). Echocardiographically large and clinically significant PDA >1.5mm diameter; positive pressure ventilation; worsening cardiopulmonary status Indomethacin x 3 doses (1 or 2 courses given) Exclusion: congenital heart defects, possible infection
Intervention/Comparator	Echocardiography baseline and 24 hours after each indomethacin dose: PDA diameter B-type Natriuretic peptide: Collected at same time as ECHO
Outcome	Responder: PDA closed or insignificant after indomethacin therapy (per ECHO) Non-responder: Persistent significant PDA after indomethacin therapy, requiring surgical ligation during the same hospital stay

J Pediatr 2010; 157:79-84

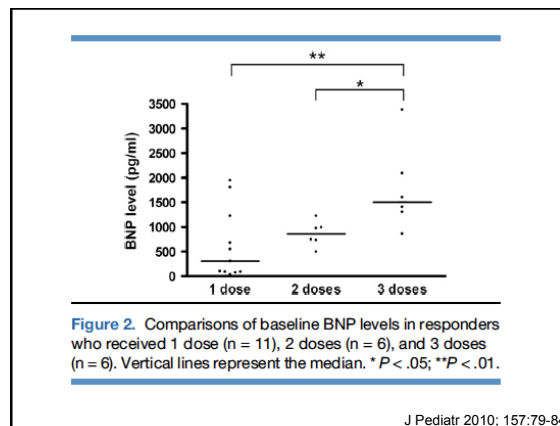
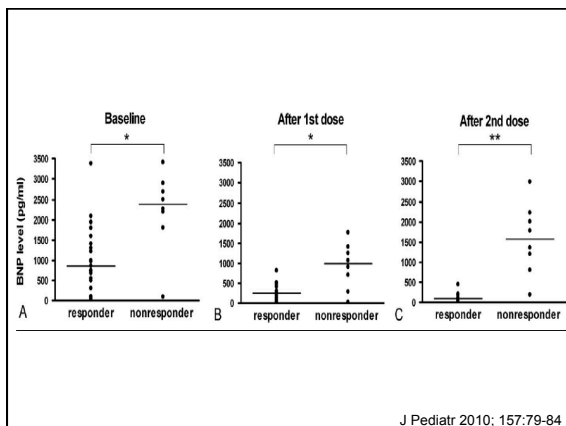


Figure 2. Comparisons of baseline BNP levels in responders who received 1 dose (n = 11), 2 doses (n = 6), and 3 doses (n = 6). Vertical lines represent the median. *P < .05; **P < .01.

Conclusions

Cutoff baseline BNP level >1805 pg/mL was predictive of non-responsiveness to indomethacin and the need for surgical ligation in premature neonates

- sensitivity rate of 88%, a specificity rate of 87%, a positive predictive rate of 70%, and a negative predictive rate of 95% (P = .003, area under the curve = 0.85)

Higher baseline BNP levels were associated with the requirement of more doses in responders

- sensitivity rate of 75%, a specificity rate of 95%, a positive predictive rate of 86%, and a negative predictive rate of 92% (P = .01, area under the curve = 0.83).

J Pediatr 2010; 157:79-84

Hsu et al.

Limitations

- Relevance to current practice
 - Most PDA treated with 3 doses, then repeat ECHO
- Practicality of findings
 - Disregard indomethacin, straight to surgical ligation
- No clear suggestion for monitoring
- Exclusion criteria

Conclusion

Monitoring BNP in PDA

Closure of PDA	✓
Degree of shunt	?
Treatment adjustment/ need for surgical ligation	✓
Reduction in clinically significant outcomes of PDA	?

Recommendation

- BNP monitoring does not replace ECHO
- Additional research needed to investigate use of BNP monitoring to identify patients at high risk of treatment failure with indomethacin/ ibuprofen

