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*Original Research Article*

# N Terminal Pro B Type Natriuretic Peptide as a Tool to Diagnose Hemodynamically Significant Patent Ductus Arteriosus in Older Infants

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## ABSTRACT

B type natriuretic peptide (BNP) is a pre-pro hormone secreted from the ventricular myocardium in response to myocardial stretching due to pressure or volume overload. N terminal pro B type natriuretic peptide (NT pro BNP) is a biologically inactive form of BNP. The measurement of plasma NT pro BNP has been found to be effective in diagnosing hemodynamically significant patent ductus arteriosus (hsPDA) in neonates. The role of plasma NT pro BNP measurement in diagnosing hsPDA in older infants has not been studied much.

**Objectives:** To evaluate the usefulness of the measurement of plasma NT pro BNP level in diagnosing hsPDA in older infants.

**Methods:** The patients referred from primary or secondary level health care centres with the clinical diagnosis of PDA and our out-patient-department-basis follow up cases of PDA were enrolled into our study. All these patients were made to undergo echocardiography by expert Pediatric Cardiologist to assess the hemodynamic significance of PDA as well as to exclude other clinical mimickers of PDA. Subsequently plasma NT pro BNP of each patient of PDA was measured within one hour of echocardiographic assessment.

**Results:** A total number of 40 patients (3 months to 9 months of age) of PDA were evaluated. 24 out of them fulfilled the echocardiographic criteria of hsPDA. NT pro-BNP level was measured in 24 patients with hsPDA, and in 16 patients with hemodynamically insignificant PDA. The median NT pro-BNP value of infants of 3 months or older with hsPDA was 1245.0 pg/ml, range 90-7998 pg/ml, and 95th percentile was 7693.75 pg/ml. It was significantly greater than that of infants with hemodynamically insignificant PDA ($p<0.0001$). The area under the receiver operator characteristic (ROC) curve for the detection of hsPDA was 0.966 with 95% CI (0.914 to 1.018) which is significant ($p<.0001$) The measurement of plasma NT-proBNP level was highly sensitive predictor of hsPDA (sensitivity 91%; specificity 94%) at a cutoff value of 220 pg/ml.

**Conclusion:** The measurement of plasma NT pro BNP, in conjunction of clinical suspicion, can serve as a supplemented tool to echocardiography in diagnosing hsPDA in older infants.

***Keywords:*** natriuretic peptides, BNP, NT pro BNP, patent ductus arteriosus, hsPDA

## INTRODUCTION

B type natriuretic peptide (BNP) is secreted from the ventricular myocardium in response to myocyte stretching due to volume or pressure overload. BNP is secreted as a prepro hormone which is

cleaved to pro BNP. This pro BNP is further cleaved to a biologically active form of BNP and an inactive form N-terminal pro BNP (NT-pro BNP) which has got a longer half- life(60 minutes) than its biologically active counterpart. [1,2] Studies have shown the importance of measuring plasma BNP & NT-pro BNP in diagnosing many congenital cardiac diseases including atrial septal defect (ASD), ventricular septal defect (VSD), & hemodynamically significant patent ductus arteriosus (hsPDA) and congestive cardiac failure also. [3,4]

Early detection of hsPDA is of utmost importance as it can cause significant amount of morbidity & mortality. [5] Till date echocardiography is used as a reference standard in diagnosing hsPDA which is defined as one that is widely patent (>3 mm) with left to right shunt with retrograde or no post-ductal aortic diastolic flow. [6] But it is noteworthy here that there is no well defined echocardiographic criteria for assessment of the degree of shunting in PDA. [7] Moreover interpretation of echocardiography has certain amount of intra-observer & inter-observer variability, hence echocardiography basically provides a subjective interpretation of hemodynamic status in PDA. Measurement of plasma BNP can be used as an alternative to echocardiography or at least in conjunction with echocardiography in the assessment of hemodynamic status in PDA patients as shown by some studies in the peer reviewed literature. [8] Plasma BNP can accurately predict the presence and magnitude of PDA, and a plasma level > 300 pg/ml predicts the presence of a hsPDA while plasma level of BNP <105 pg/ml predicts the absence of that in case of pre term neonates. [9,10]

BNP is a non-specific marker of cardiac disease as it is found to be elevated in a number of conditions namely cardiomyopathy, congenital arrhythmias and many congenital cardiac anomalies. It is also influenced by the concomitant presence of other conditions like increased pulmonary vasculature resistance, right ventricular overload, associated renal impairment, hydration status and effect of medical therapy with corticosteroid & inotropic agents. [11] It is also important to note that BNP and NT pro BNP play a key role in the circulatory changes during the transition from fetal to neonatal period. Pro BNP levels are found to be very high in healthy infants during the first few days of life and it rapidly falls during the first week of life due to neonatal circulatory transitions including increased pulmonary blood flow, decreased pulmonary vasculature resistance and gradually maturing renal functions. It further declines through early infancy reaching almost constant adult value after 3 months of the age. [12]

There is hardly any study of serum NT pro BNP measurement for the assessment of hemodynamic significance of PDA in older infants in India. The purpose of our study is to see whether serum NT pro BNP level correlates with the hemodynamic significance of PDA or not. If it does, then we can say that measurement of serum NT pro BNP can guide us in early detection of hsPDA. In centres where expert pediatric echocardiographical assessment is not available, it may help us to have a better triage in referring patients of hsPDA to tertiary care centres.

## METHODS

The population in our study comprises of the cases referred from primary or secondary level health care centres with the clinical diagnosis of PDA as well as our out-patient-department-basis follow up cases of PDA. As the exact prevalence of hsPDA in India is not known due to scarcity of data, a pilot study has been taken and 46 patients have been recruited & evaluated.

As mentioned earlier, pro BNP level reaches adult value after 3 months of the age, we have taken 3 months to be our lower age limit.

This study was purely observational and non-therapeutic and it was approved by the Ethics Committee of the IPGMER &

SSKM Hospital. Informed consent was obtained from the parents before recruiting each child to our study. Out of these 46 patients, 18 infants were our out-patient-department-basis follow up patients and the remaining 28 patients were referred from various primary health centres with the clinical diagnosis of PDA.

All these patients were made to undergo echocardiography by expert Pediatric Cardiologist to assess the hemodynamic significance of PDA as well as to rule out other conditions that may mimic PDA clinically. The Siemens accuson CV 90 echocardiography machine with 3-7 Mhz pediatric cardiology transducer was used. Echocardiography of each patient was separately done by one of our experts in pediatric echocardiography to minimize interobserver bias.

Some previously established criteria were taken into consideration for the diagnosis of hsPDA, like left atrium to aortic root (LA/AO) ratio more than 1.5, left ventricular to aortic root(LV/AO) ratio more than 2.1, narrowest ductal diameter > 3mm, left ventricular end diastolic diameter(LVEDD), fractional shortening greater than or equal to 40% and evidence of aortic run off assessed by left ventricular systolic time interval (pre-ejection period/ejection period) ratio less than or equal to 0.28. [13,14] The LA/AO ratio was determined in the parasternal long-axis view at the level of the aortic valve and the PDA diameter was measured in the ductal view.

Subsequently blood sample was taken from each patient within 1 hour of his/her echocardiographic assessment. Sample was taken via peripheral venous puncture and collected in tubes containing EDTA. All the samples were examined by Roche COBAS 8232 machine. Each pro-BNP kit required 3ml of blood. Testing time was about 10 minutes. Measurable range of NT proBNP with that kit was upto 9000 pg/ml.

**STASTICAL ANALYSIS:**

Analysis was performed using SPSS, version 15 (SPSS Inc, Chicago, Illinois, USA). The Mann–Whitney rank-sum test was used to calculate the differences between the groups where applicable. Simple linear regression was done to see the changing pattern of NT pro BNP with age.
p value of 0.05 was considered significant.
Receiver operator characteristic (ROC) analysis was performed to determine the best cut-off values of plasma NT-proBNP levels for the detection of hsPDA.

## RESULTS

Out of the 28 patients that were referred from different health centres with the clinical diagnosis of PDA, 22 were actually found to have PDA, and the rest included 2 cases of ruptured sinus of Valsalva, 1 VSD with aortic regurgitation, 1 case of VSD, 1 case of AS and AR and 1 case of venous hum.

So, a total number of 40 patients of PDA remained in our study, and 24 out of them fulfilled the echocardiographic criteria of hsPDA. NT pro-BNP was measured in 24 patients with hsPDA, and in 16 patients with hemodynamically insignificant PDA. Age-matched infants aged 3 months to 9 months (24 with hsPDA and 16 with hemodynamically insignificant PDA) were compared. There was no significant difference between NT pro-BNP levels of females (n = 19) and males (n = 21), (p = 0.86)

NT pro-BNP level does not differ significantly through the age in infants from age 3 months to 9months ($R^2$= 0.015;) In 16 infants with hemodynamically insignificant PDA above 3 months of age, the mean (±SE) plasma NT pro-BNP level was 103.06 (±20.004) pg/ml, median 94 pg/ml, range 15–323 pg/ml, and 95th percentile was 323.0 pg/ml.

The median NT pro-BNP value of infants of 3 months or older with hsPDA was 1245.0 pg/ml, range 90-7998 pg/ml, and 95th percentile was 7693.75 pg/ml. It is significantly greater than that of infants with hemodynamically insignificant PDA

(p<0.0001). 3 out of the 24 patients with hsPDA older than 3 months had NT pro-BNP levels below the 95th percentile of the infants with hemodynamically insignificant PDA (323.0 pg/ml). Their NT pro-BNP values were 90, 176, 235 pg/ml. (fig-1)

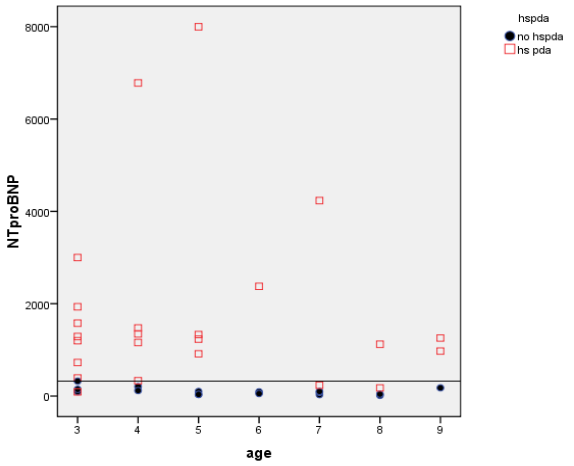


**Figure 1. Plasma NT pro-BNP levels in infants with (blank square) and without (filled circle) hsPDA.**
The line represents the 95th percentile of normal (323.0 pg/ml) for hemodynamically insignificant PDA in infants of 3 months and older.

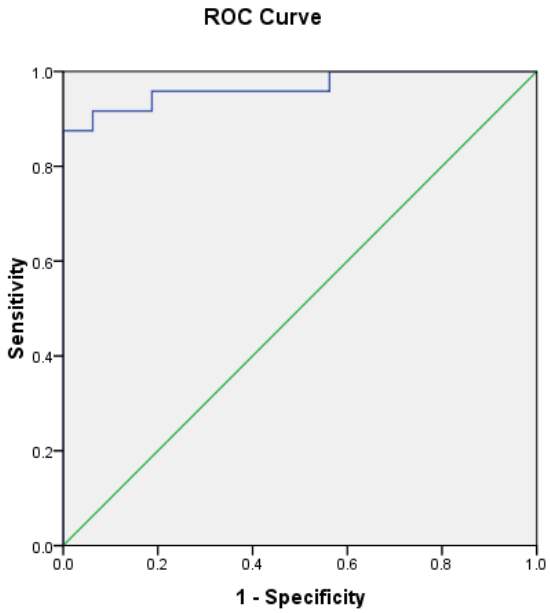


**Figure 2 Receiver operator characteristic (ROC) curve for determination of NT-proBNP cut-off value for detecting hsPDA.**
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The area under the ROC curve for the detection of hsPDA is 0.966 with 95% CI (0.914 to 1.018). The area under the curve is significant (p<.0001) The measurement of plasma NT-proBNP level was highly sensitive predictor of hsPDA (sensitivity 91%; specificity 94%) at a cutoff value of 220 pg/ml (fig 2).

## DISCUSSION

Hemodynamically significant PDA is associated with considerable morbidity. [15,16] As we have already discussed that echocardiographic criteria to diagnose hsPDA are not well defined and at the same time it needs certain amount of expertise, echocardiography still serves as the only measure to diagnose hsPDA.

On the other hand the NT pro BNP assay requires only a small amount of blood and can be easily performed at the bedside with immediate result. A significant left to right shunt from a hsPDA imposes volume overload of the left ventricle and thus it causes secretion of BNP from the ventricular myocardium. Therefore BNP or NT pro BNP level correlates with the degree or severity of the shunt, and this fact has been validated in case of preterm infants with hsPDA in previous studies. [1,9]

In our study, we have found that the plasma NT pro BNP level is significantly higher amongst the infants who have hsPDA than those without hsPDA. Plasma NT pro BNP levels above the cutoff value of 220 pg/ml are strongly predictive of hsPDA with a sensitivity of 91% and specificity of 94%.

3 out of the 24 patients with hsPDA older than 3 months had NT pro-BNP levels below the 95th percentile of the infants with hsPDA (323.0 pg/ml). The reason for this false negative result was not entirely clear, possible cause being all of them received heart failure treatment outside.

## CONCLUSION

Our study showed that measurement of spot NT pro-BNP can be useful to diagnose hsPDA in conjunction with clinical suspicion. It can serve as a supplementive tool to echocardiography for early detection of hsPDA, and also help in

decision making in centres where expert pediatric echocardiographical assessment is not available.

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