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" *The Utility of B-type Natriuretic Peptide (BNP) for Evaluating Left to Right Shunts Effects in Pediatric Patients*"

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ABSTRACT:

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Background: Congenital heart disease (CHD) with left-to-right shunts, including atrial septal defect (ASD), ventricular septal defect (VSD), and patent ductus arteriosus (PDA), is a leading cause of pediatric morbidity. Echocardiography remains the diagnostic standard for defining anatomy and shunt magnitude, yet repeated imaging can be resource-intensive. B-type natriuretic peptide (BNP), a ventricular stress biomarker, has emerged as a potential adjunct for assessing shunt severity, guiding management, and monitoring outcomes in infants and children. This review aims to synthesize current evidence on the prognostic and diagnostic value of BNP in pediatric left-to-right shunts.

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Methods: PubMed, Scopus, and Web of Science databases were searched without language restriction, focusing on studies evaluating BNP or NT-proBNP in VSD, ASD, and PDA. Key outcomes of interest included correlations with shunt fraction (Qp/Qs), chamber enlargement, hemodynamic significance, and changes following pharmacological or interventional closure. Additional literature on neonatal BNP physiology and confounding factors was also examined to contextualize biomarker interpretation.

Conclusion: Evidence consistently demonstrates that BNP levels rise with increasing shunt burden, particularly in hemodynamically significant PDA, and decline following closure, highlighting its role as a dynamic marker of ventricular volume overload. BNP offers practical advantages as a bedside, minimally invasive tool to complement echocardiography in diagnosis and follow-up. However, age-dependent reference ranges, assay variability, and non-specific elevations (e.g., renal dysfunction, cardiomyopathy) limit its standalone use. Future studies are needed to establish standardized pediatric cut-offs and to integrate BNP into multimodal diagnostic algorithms for CHD.

Keywords: Congenital heart disease; B-type natriuretic peptide; left-to-right shunt; pediatric cardiology; patent ductus arteriosus.

List of Abbreviations

Abb.	Full term
ASD	atrial septal defects
VSD	ventricular septal defect
BNP	b-type natriuretic peptide
CHD	congenital heart disease
HF	heart failure

Abb.	Full term
PDA	Patant ductus arteriosus
HCM	hypertrophic cardiomyopathy
Qp/Qs	Pulmonary-to-systemic flow ratio
PVR	Palmonary vascular resistance
RV	Right ventricle
LV	Left ventricle
RCM	restrictive cardiomyopathy
PH	Pulmonary hypertention
TTE	Transthoracic echocardiography
TEE	Transesophgeal echocardiography
LVOT	Left ventricular outflow tract
RVOT	Right ventricular outflow tract
CSA	Cross sectional area
VTi	Velocity time integrals
ISHLT	International society for heart and lung transplantation
m-PAP	Mean pulmonary artery pressure
RV EDV	Right ventricular end diastolic volume
LV EDP	Left ventricular end diastolic pressure
hs-PDA	Hemodynamically significant patent ductus arteriosus
NT-pro BNP	N-terminal pro-B-type natriuretic peptide
Pro BNP	pro brain nateruretic peptide

Introduction

Congenital heart disease (CHD) encompasses a diverse group of structural cardiac malformations that significantly contribute to morbidity and mortality in the pediatric population. These defects originate from abnormal development of the fetal heart and great vessels during intrauterine life [(1)].

Nearly 60% of pediatric heart failure (HF**)** occurs within the first year of age, underscoring the importance of timely recognition and accurate diagnosis of CHD for improving outcomes [(2)].

Among circulating biomarkers, B-type natriuretic peptide (BNP) has attracted increasing attention as a potential screening and monitoring tool. Beyond reflecting the magnitude of intracardiac shunting, BNP levels provide valuable information on ventricular loading conditions, systolic and diastolic dysfunction, and impending decompensation in children with CHD [(3)].

BNP, a cardiac neurohormone primarily released from the ventricular myocardium in response to wall stress, is regarded as a sensitive and relatively specific marker of ventricular function [(3)].

This narrative review aims to synthesize the available evidence on diagnostic and prognostic utility of BNP in pediatric left-to-right shunt lesions, with a particular focus on its correlation with echocardiographic parameters and its potential role in guiding clinical management.

Ventricular Septal Defect (VSD)

Pathophysiology

In VSD, an opening in interventricular septum permits abnormal communication between the right and left ventricles. When the defect is large, blood flows unrestrictedly across septum, leading to pressure equalization and generating a significant left-to-right shunt [(4)].

The hemodynamic impact of lesion is determined by defect's size, pulmonary vascular resistance (PVR), and presence of any RV outflow tract obstruction. Shunt volume and direction are influenced by interplay of these factors, as well as by precise location of septal defect [(5)]

If a substantial shunt persists, progressive changes ensue: pulmonary arterial hypertension develops, PVR rises, and RV undergoes hypertrophy with pressure overload. Eventually, sustained elevation in PVR can reverse shunt to right-to-left, producing systemic desaturation and cyanosis characteristic of Eisenmenger syndrome [(1)]. Echocardiography remains the diagnosis cornerstone, providing visualization of the defect, measurement of its dimensions, and quantification of shunt flow [(6)].

Patent Ductus Arteriosus (PDA)

Persistence of ductus arteriosus beyond neonatal period results in a left-to-right shunt analogous to that seen in VSD. The magnitude and direction of shunting depend on ductal size and relative balance between systemic and PVR [(7)].

Echocardiographic findings of increased transmitral flow, often resembling relative mitral stenosis, usually signify a large PDA. Such lesions are commonly associated with congestive HF (CHF) and demonstrate right ventricular hypertrophy, LV enlargement, and left atrial dilatation as a consequence of chronic volume overload [(8)].

Atrial Septal Defects (ASD)

An ASD represents an abnormal communication across interatrial septum, allowing blood flow between the atria. The size and direction of shunt largely depend on relative compliance of left and right ventricles [(9)].

In early infancy, RV is relatively noncompliant, resulting in only a modest left-to-right shunt. As RV becomes more compliant with growth, shunting typically increases. Later in adulthood, when RV compliance declines, the shunt volume diminishes. Over time, sustained pulmonary over-circulation may lead to pulmonary hypertension (PH), and as PVR rises, reversal of the shunt can occur, culminating in Eisenmenger physiology and cyanosis after several decades [(10)].

Echocardiographic evaluation typically reveals RV dilatation, right atrial enlargement, and evidence of right axis deviation, serving as key indicators of hemodynamic significance [(10)].

Significance of the shunt and Diagnosis

Multiple echocardiographic modalities can be applied to detect intracardiac shunts, including transthoracic echocardiography (TTE), trans-esophageal echocardiography (TEE), and transcranial Doppler; among these, TTE is generally the most practical and widely used technique [(11)].

Quantification of shunt significance is often based on the ratio of pulmonary (Qp) to systemic (Qs) blood flow, which reflects balance of flows in opposite directions across defect and is used to derive the shunt fraction [(11)].

In left-to-right shunts, oxygenated pulmonary venous blood is recirculated into the pulmonary circulation, thereby augmenting pulmonary blood flow. The magnitude and direction of shunting are influenced by systemic and pulmonary vascular

resistances, which in turn are modulated by autonomic tone, neurohumoral mediators, heart rate, ventricular contractility, and chamber volumes [12].

Flow calculations rely on measuring volume of blood passing through the left or right ventricular outflow tract (LVOT, RVOT) over time. This is obtained by multiplying the cross-sectional area (CSA) of respective outflow tract by velocity of blood flow. Echocardiographic measurements include diameters of RVOT and LVOT in parasternal short- and long-axis views. With pulse-wave Doppler interrogation, velocity–time integrals (VTIs) are derived from spectral Doppler envelopes, enabling calculation of Qp/Qs ratio as a robust, noninvasive estimate of shunt severity [11].

Qp/Qs = (CSA RVOT) x (RVOT VTI) / (CSA LVOT) x (LVOT VTI)

- **Shunt fraction (Qp/Qs) > 1**
    - Left-to-right shunt present
    - Right-sided (pulmonary) flow surpasses left-sided (systemic) flow when oxygenated blood from left heart is shunted into systemic venous return, thereby increasing blood volume directed to pulmonary circulation
    - Hemodynamic significance is generally observed when shunt fraction is above 1.5, at which point right atrial and ventricular enlargement and dysfunction become apparent
- **Shunt fraction (Qp/Qs) < 1**
    - Shows the presence of a RT-to-LT shunting of blood, in which a portion of SVR systemic venous return passes directly into left-sided circulation
- **Shunt fraction (Qp/Qs) = 1**
    - Shows no shunting of blood through defects, or coexistence of equal right-left and left-right shunting.

Natriuretic Peptide B Type

BNP is a 32–amino acid peptide hormone secreted primarily by ventricular myocardium in response to volume and pressure overload. Its biological actions include promoting diuresis and natriuresis, suppressing aldosterone release, inducing

vasodilation, and inhibiting renin–angiotensin–aldosterone system. Collectively, these effects lower preload and afterload while improving stroke volume [3].

Circulating BNP concentrations are influenced by presence and treatment of congenital heart disease, intracardiac shunts, cardiomyopathies, and HF. Plasma levels have been shown to correlate closely with ventricular loading conditions, particularly left ventricular volume, across a range of congenital lesions such as ASD, tetralogy of Fallot, VSD, and several cyanotic heart diseases [3].

Furthermore, dynamic changes in BNP can be used to monitor cardiac load following catheter-based interventions, providing a less invasive alternative to direct hemodynamic assessment [12]. Importantly, BNP can be measured rapidly at bedside, even in neonatal patients, making it a practical biomarker in acute and routine pediatric cardiac care [13].

Normal Value of BNP in Neonates

In term neonates, plasma BNP levels increase sharply immediately after birth, remain relatively high throughout the first week of life, and then decline substantially. Thereafter, concentrations continue to fall gradually, stabilizing by around one month of age [13].

This early surge reflects perinatal circulatory changes, as blood flow shifts from placental to pulmonary circulation, creating increased ventricular volume and pressure loads that stimulate BNP release from both atrial and ventricular myocardium [14].

Fetal BNP concentrations are typically higher than those measured in placenta, suggesting that placental clearance mechanisms may partially account for neonatal BNP regulation. The subsequent decline in circulating levels is attributed to progressive adaptation of pulmonary vascular resistance and enhanced renal maturation, which augments diuresis [15].

Variability in neonatal BNP is further influenced by prematurity, intrauterine growth restriction, and plurality of gestation (singleton vs twin). Nevertheless, despite these differences, overall trajectory of BNP decline remains consistent, reflecting shared physiological adaptations to extrauterine life [(31)]. Importantly, because no universally accepted reference ranges for neonatal BNP currently exist, interpretation should always be contextualized within individual clinical and environmental factors [(16)].

BNP in Cardiac Disease

Pediatric HF is defined by International Society for Heart and Lung Transplantation (ISHLT) as a clinical and pathophysiological syndrome arising from ventricular dysfunction and/or hemodynamic overload due to pressure, volume, or both [(17)].

In Neonates, structural CHD is the predominant etiology, with the type of lesion dictating both likelihood and severity of HF. Circulating levels of BNP serve as a marker of ventricular wall stress and have been investigated as a diagnostic tool for detecting HF in this population [(18)].

Importantly, BNP concentrations in neonates correlate with type and severity of CHD, particularly in conditions characterized by volume overload, pressure overload, or intrinsic myocardial disease. Measurement of BNP therefore provides a non-invasive means of assessing cardiac function in neonates, allowing for timely recognition of decompensation, initiation of therapy, reduction of mortality risk, and improvement of long-term outcomes [(19)].

Cardiac Insufficiency Caused by Volume Overload

BNP elevation is well documented in children with left-to-right shunts, where it shows a direct relationship with shunt magnitude, RV systolic pressure, mPAP, and

PAR [20]. VSD, one of the most common CHDs, exemplifies this mechanism: in large defects without established pulmonary vascular disease, the left atrium and ventricle are subject to significant volume loading [20].

Clinical studies further confirm that plasma BNP levels in children with VSD correlate with pulmonary-to-systemic flow ratio (Qp/Qs) as well as left and RV EDV [21].

In neonates, BNP concentrations are markedly higher in those with hemodynamically significant volume-loaded shunts compared with infants whose shunts are clinically insignificant. Accordingly, BNP provides a valuable biochemical indicator of extent of ventricular dysfunction resulting from neonatal volume overload [22].

Cardiac Insufficiency Caused by Pressure Overload

Pressure overload occurs when the ventricle must contract against abnormally high resistance, affecting either right or left ventricle. In neonates, left ventricular pressure overload most commonly arises from obstructive left-sided congenital lesions such as coarctation of aorta or aortic stenosis [23].

Obstruction at or near the LV outflow increases systolic wall stress, which drives compensatory hypertrophy. Over time, this remodeling reduces ventricular compliance, elevates LVEDP, and secondarily raises left atrial pressure. Collectively, these changes compromise ventricular filling and contractility, ultimately progressing to cardiac insufficiency [23].

Cardiac Insufficiency Due to Myocardial Disorders

BNP is also used as a biomarker for certain primary myocardial disorders, though its diagnostic utility varies by subtype. Restrictive cardiomyopathy (RCM) is characterized by impaired diastolic filling, marked myocardial stiffness, and

progressive atrial enlargement. As the disease advances, LV systolic function deteriorates. Neonates with RCM exhibit markedly elevated BNP levels, which can aid in differentiation from constrictive pericarditis; BNP values are typically much higher in RCM, and integration with tissue Doppler imaging enhances diagnostic accuracy [(24)].

Hypertrophic cardiomyopathy (HCM), an inherited disorder with asymmetric septal hypertrophy, presents a different challenge. Evidence from Öner et al. suggests that BNP levels in HCM largely mirror extent of hypertrophy but show limited correlation with LV outflow tract (LVOT) obstruction, restricting their role in distinguishing disease subtypes. Furthermore, substantially elevated BNP concentrations have been reported in neonatal myocarditis, particularly enterovirus-associated cases, supporting its potential diagnostic role in infectious myocardial injury [(25)].

BNP in brain diseases

Emerging evidence has suggested that BNP may also have utility beyond cardiology. A recent Japanese study demonstrated a strong association between elevated BNP levels and paroxysmal atrial fibrillation risk in patients presenting with ischemic stroke, indicating its potential role as a predictive biomarker in neuro-cardiac disease overlap syndromes [(26)].

Assessment of cardiac function

In the perioperative context, BNP concentrations are typically higher after neonatal cardiac surgery compared with preoperative values, reflecting transient myocardial stress and hemodynamic adaptation. Deviations from this expected pattern may carry diagnostic or prognostic implications and warrant further clinical attention [(27)].

The value of BNP in CHD

Serial BNP monitoring has proven especially valuable in management of preterm infants with patent ductus arteriosus (PDA). Plasma BNP levels reliably decrease following either pharmacological or surgical ductal closure, serving as an objective marker of hemodynamic improvement. This makes repeated BNP measurements a practical adjunct for monitoring therapeutic efficacy [(3)]. More broadly, cardiac biomarkers—particularly BNP—have become effective tools for both diagnosis and longitudinal management of children with CHD [(28)].

Determination of PDA Severity and Treatment

In neonates with PDA, BNP levels provide clinically relevant information for assessing severity and determining need for intervention. Persistently elevated BNP values suggest significant hemodynamic burden and often justify therapeutic closure to prevent complications [(29)].

Application in Patent Ductus Arteriosus (PDA)

Diagnosing Hemodynamically Significant PDA

The term *hemodynamically significant patent ductus arteriosus (hsPDA)* is used to distinguish clinically important cases from incidental findings, underscoring the value of early recognition and timely management [(30)].

In neonates with PDA, plasma BNP has emerged as a practical biomarker to support treatment decisions. Persistently elevated BNP levels reflect significant hemodynamic burden and may indicate the need for therapeutic closure to prevent adverse outcomes. Pharmacologic management remains the first-line strategy, with NSAIDs—most commonly indomethacin or ibuprofen—serving as the standard agents for ductal closure [(31)].

Several studies have explored the relationship between plasma BNP or NT-proBNP levels and the hemodynamic burden of left-to-right shunts in pediatric patients. Consistently, BNP concentrations have been shown to rise with increasing shunt fraction (Qp/Qs), chamber dilation, and the presence of HF symptoms, particularly in children with VSD, ASD, and PDA. Moreover, serial BNP measurements before and after surgical or catheter-based closure demonstrate predictable declines, underscoring its potential role in monitoring therapeutic response. A synthesis of key studies evaluating BNP in congenital shunt lesions, including sample size, lesion type, and principal findings, is summarized in **Table 1**. This evidence highlights BNP as a valuable adjunctive biomarker, complementing echocardiographic assessment in quantifying shunt severity.

Table 1. Summary of Key Studies on BNP/NT-proBNP in Pediatric Left-to-Right Shunts

Author, Year	Population (n)	Lesion Type	Biomarker (BNP/NT-proBNP)	Key Findings	Clinical Implication
Ozhan et al. (2007) [3]	45 children (ASD, VSD)	ASD, VSD	BNP	BNP positively correlated with Qp/Qs and shunt severity	BNP may reflect shunt burden
König et al. (2015) [20]	68 preterm infants	PDA	BNP, NT-proBNP	Strong correlation with ductal size, mPAP, and shunt flow; BNP decreased after closure	BNP useful for diagnosing hemodynamically significant PDA (hsPDA)
Khosroshahi et al. (2019) [28]	60 children	VSD, ASD	BNP	BNP significantly associated with magnitude of left-to-right shunt	BNP as adjunct to echocardiography
Parra-Bravo et al. (2021) [23]	52 neonates	PDA	BNP	BNP levels predicted hsPDA; decrease after pharmacologic closure	BNP assists in treatment decision-making
Öner et al. (2016) [25]	34 children	HCM	BNP	BNP correlated with LV hypertrophy but not obstruction	Limited specificity for CHD shunts
Noori et al. (2017) [29]	40 children	Dilated cardiomyopathy vs controls	BNP	Higher BNP in cardiomyopathy; not specific for shunts	BNP reflects general ventricular dysfunction

B-type natriuretic peptide, NT-proBNP: N-terminal pro-B-type natriuretic peptide, PDA: Patent ductus arteriosus, ASD: Atrial septal defect, VSD: Ventricular septal defect, hsPDA: Hemodynamically significant patent ductus arteriosus, LV: Left ventricle, HCM: Hypertrophic cardiomyopathy, mPAP: Mean pulmonary artery pressure.

While BNP offers clinical utility, its interpretation is strongly influenced by age, renal function, prematurity, and the presence of comorbid cardiac conditions. For example, neonatal BNP levels naturally peak in the first week of life before stabilizing, and higher baseline values are often seen in preterm infants. Similarly, impaired renal clearance can falsely elevate BNP, and pressure- or myocardial-related cardiac diseases may also confound its specificity for shunt physiology. These considerations underscore that BNP should be interpreted within the broader clinical and echocardiographic context, rather than in isolation. Key factors affecting BNP interpretation in pediatric congenital heart disease are outlined in **Table 2**, offering clinicians a practical guide to integrating biomarker data into routine practice.

Table 2. Factors Influencing BNP Interpretation in Pediatric Congenital Heart Disease

Factor	Influence on BNP	Clinical Consideration
Age (neonate vs infant)	Physiological surge after birth, decline after first month	Always use age-adjusted interpretation
Renal function	Reduced clearance → falsely elevated BNP	Rule out renal impairment before BNP-based decisions
Prematurity	Higher baseline BNP values in preterm infants	Use gestational age-specific cut-offs
Shunt magnitude (Qp/Qs)	Direct correlation with BNP in VSD, ASD, PDA	BNP may serve as biochemical surrogate of shunt burden
Post-intervention status	BNP falls after PDA/VSD/ASD closure	Serial BNP monitoring can track treatment response
Other cardiac conditions	Elevated BNP in cardiomyopathy, myocarditis, pressure overload	BNP not specific — must be interpreted with echo findings

BNP: B-type natriuretic peptide, NT-proBNP: N-terminal pro-B-type natriuretic peptide, CHD: Congenital heart disease, Qp/Qs: Pulmonary-to-systemic flow ratio, VSD: Ventricular septal defect, ASD: Atrial septal defect, PDA: Patent ductus arteriosus.

Conclusion

BNP levels in blood samples can be measured to detect left and RV significance in infants and children with VSD, ASD, or PDA. As a result, this test may be a helpful clinical tool for treating kids with CHD that involves a left-to-right shunt.

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