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The potential and limitations of plasma BNP measurement in the diagnosis, prognosis, and management of children with heart failure due to congenital cardiac disease: an update

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Abstract The aim of this article is to review the diagnostic and prognostic relevance of measurement of brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) in pediatric patients with heart failure caused by various acquired and congenital heart diseases (CHD). In January 2013, we performed a computerized literature search in the National Library of Medicine (PubMed access to MEDLINE citations; http://www.ncbi.nlm.nih.gov/PubMed/). The search strategy included a mix of Medical Subject Headings and free-text terms for the key concepts, starting from *BNP assay* and '*NT-proBNP assay*', *children*, *CHD*. The search was further refined by adding the keywords *neonate/s*, *newborn*/s, *heart failure*, *cardiomyopathy*, *screening*, *prognosis*, *follow-up*, and *management*. BNP values are age and method dependent, even in pediatric populations. Regardless of age, there is great variability in BNP/NT-proBNP values within CHD characterized by different hemodynamic and clinical conditions. There is enough evidence to support the use of BNP/NT-proBNP as an adjunctive marker in the integrated evaluation of patients with congenital and acquired heart disease to help define severity and progression of heart failure as well in the monitoring of response to treatment. BNP/NT-proBNP can also be used for the screening of heart failure and as a prognostic marker in children undergoing cardiac surgery; however, to date, there are studies with heterogeneous patient groups, and diverse outcome measures selected are still few. BNP/NT-proBNP can be used as adjunctive markers in the integrated screening, diagnosis, management, and follow-up of children with heart failure caused by various acquired and congenital heart disease.

Keywords Biomarker · Natriuretic peptides · BNP · Children · Neonates · Congenital heart disease · Heart failure

Abbreviations

BNP	Brain natriuretic peptide
CHD	Congenital heart disease
HF	Heart failure
MCS	Mechanical circulatory support
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association (NYHA)
POCT	Point-of-care test
RV	Right ventricle
SV	Single ventricle
UH	Univentricular heart

Background

Cardiac natriuretic peptides, which include the atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) and their related peptides, constitute a complex family of peptide hormones produced and secreted by the human heart [1, 2]. The active peptide BNP is produced in human cardiomyocytes by cleavage of the COOH-terminal

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part of the pro-hormone (NT-proBNP), while the N-terminal fragments of the pro-hormone, NT-proBNP, are currently considered inactive [1]. To date, international guidelines are recommending measurements of circulating BNP and NT-proBNP [3, 4] as a biomarker for diagnosis, prognosis, and therapeutic monitoring in adults with cardiac diseases, especially those with acute and chronic heart failure. Accordingly, there has been a growing interest to incorporate the use of BNP/NT-proBNP also in the management of children with cardiomyopathy and congenital cardiac disease (CHD) [2, 5]. However, despite the inflation of single-center pediatric studies, better definition of normative values in children, and the strength of evidence in clinical trials in adults, there still are no large scale or definitive studies to substantiate its utility in the various aspects of heart failure management in children. Here, we will discuss the caveats and challenges to its applicability.

Aims

The overall objective of this article is to provide a critical review of published studies concerning the diagnostic accuracy and prognostic relevance of BNP/NT-proBNP measurements in children with heart failure caused by different types of congenital and acquired cardiac disease. Another purpose is to suggest some pathophysiologic and clinical considerations for future studies in diagnosis, risk stratification, follow-up, and management of pediatric patients with CHD.

Methods

In January 2013, we performed a systematic search for potential publications in the National Library of Medicine (PubMed access to MEDLINE citations; http://www.ncbi.nlm.nih.gov/PubMed/). Potential publications were identified from a systematic search in the National Library of Medicine (PubMed access toMEDLINE citations; http://www.ncbi.nlm.nih.gov/PubMed/) conducted in January 2013. The search strategy included a mix of medical subject headings and free-text terms for the key concepts, starting from BNP assay NT-proBNP assay children, congenital heart disease. The search was further refined by adding the keywords neonate/s, newborn/s, heart failure, cardiomyopathy, screening, prognosis, follow-up, and management. In addition, we identified other potentially relevant publications using a manual search of references from all eligible studies and review articles as well as from the Science Citation Index Expanded on the Web of Science. All reports identified were assessed independently by two authors (i.e., MC and YL) and underwent a consensus procedure before being included in the present study. Exclusion criteria for titles and abstracts of articles identified by the search strategy were as follows: case reports, abstracts from meetings, articles concerning children without congenital or acquired heart disease, or reports were in languages other than English. Of the two-hundred and twenty-four publications identified for potential inclusion in the study, seventy-eight studies were excluded, leaving 146 publications for analysis.

Following is brief introduction on the most important biochemical and physiological issues of natriuretic peptide production and secretion by cardiac tissue, the first part of this review will take into consideration the critical importance of using reliable references values for BNP in children. In particular, we will focus on the difficulties in establishing reliable cutoff values for CHD. In the second part of our study, we will discuss how plasma BNP concentrations can vary in children with heart failure due to acquired and congenital heart disease according to different hemodynamic conditions and how BNP may aid in the diagnosis, stratification, and prognosis of such diseases.

The physiological role of BNP

Natriuretic peptides are mainly produced and secreted by cardiomyocytes from the atria (atrial natriuretic peptide, ANP) and ventricles (BNP and NT-proBNP) [1]. Human BNP is synthesized as a 134-amino acid (aa) precursor protein (pre-NT-proBNP) and subsequently processed during secretion to form a 108-aa peptide, NT-proBNP (Fig. 1). The hormone precursor NT-proBNP is cleaved enzymatically by corin, a convertase produced in cardiomyocytes, to form the 76-aa N-terminal peptide (i.e., NT-proBNP) and the C-terminal biologically active 32-aa BNP.

Normal ventricular myocardium may produce only a limited amount of BNP in response to an acute stimulation such as through myocardial stretch, probably via a constitutive secretory pathway, while upregulation and the secretion of additional amounts occur after chronic stimulation through the interaction of the myocardium with the neurohormonal and immunological systems in heart failure [1]. Accordingly, BNP plasma concentrations fluctuate widely and according to patho-physiologic stimuli and cardiovascular hemodynamic both in healthy subjects and in patients with heart failure [1]. However, the bioactive hormone BNP has shorter plasma half-life compared to NT-proBNP. Consequently, BNP also has lower plasma concentration [1, 6]. In particular, it is estimated that BNP has a plasma half-life of about 15–20 min, while that of NT-proBNP is more than 60 min in healthy subjects [1, 6]. Furthermore, there is likely significant infra-individual

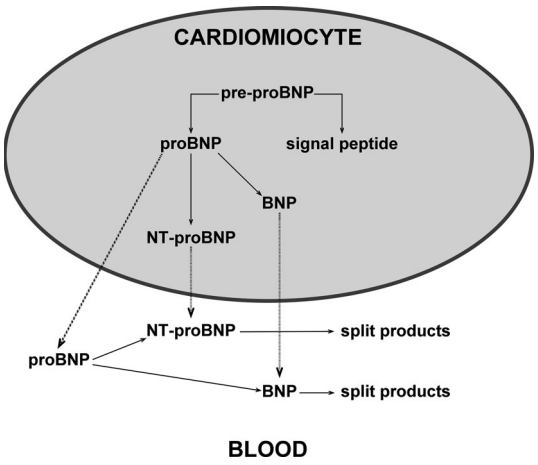

Fig. 1 Schematic representation of production/secretion pathways of B-type natriuretic hormone and its related peptides. Human BNP is synthesized as a 134-amino acid (aa) precursor protein (pre-NT-proBNP) and is subsequently processed during secretion to form the 108-aa peptide, NT-proBNP. The pro-peptide hormones of the cardiac natriuretic peptides can be enzymatically cleaved by at least two pro-protein convertases produced in the cardiomyocytes, such as corin and furin. In particular, NT-proBNP is processed to form the 76-aa N-terminal peptide (i.e., NT-proBNP), and then the biologically active 32-aa C-terminal peptide (i.e., BNP). BNP has a shorter plasma half-life (about 15–20 min vs. 1 or 2 h) and consequently lower plasma concentration, compared to NT-proBNP. Moreover, the intact NT-proBNP 108-aa peptide is also present in plasma, especially of patients with heart failure, in both glycosylated and non-glycosylated form

biological variability (CVi), ranging from 30 to 50 % which may have clinical relevance [6].

Reference range values

Plasma BNP and NT-proBNP values highly depend on age [1, 2, 6–33]. In particular, considering the pediatric age, plasma BNP concentrations are very high during the first 4 days of life and then rapidly fall during the first week, with a further slower progressive reduction throughout the first month of life (Table 1; Fig 2). After the first month of life, BNP concentrations remain steady, without any significant changes, between 31 days and 12 years of age. Up to 10–14 years of age, there are generally.

In contrast to adults, no gender-related differences in BNP values were reported up to 10–14 years of age [1, 13]. The gender-related effects observed during adolescence and sexual maturation are probably due to the action of steroid sex hormones [9, 20, 21, 34].

BNP/NT-proBNP concentrations can however be affected by several confounding factors. In particular, higher plasma peptide concentrations were reported in newborn twins compared with singletons, as well as in infants of mothers with type 1 diabetes [28–30], with prematurity, intrauterine growth retardation, caesarian section following uterine contraction, and antenatal stress conditions [31]. Moreover, it is well known that circulating concentrations of BNP and NT-proBNP in pediatric and adult patients can be affected by several extra-cardiac conditions including pulmonary diseases, endocrine and metabolic disorders, liver cirrhosis with ascites, renal failure, inflammatory diseases, use of cardiotoxic drugs, anemia, obesity, severe infections, and cardiac trauma. It is also important to note that BNP levels are strongly method dependent because different immunoassays methods use different antibodies and calibration materials; as a result, the reference ranges change according to the method used (Table 1).), whereas reference ranges for NT-proBNP measurements are not affected—since all immunoassays use the same antibodies and calibration materials (Roche Diagnostics), providing comparable values across studies (Table 1).

Specific blood BNP measurements

From an analytical standpoint, it is important to be aware that not only are BNP and NT-proBNP not the same analyte and cannot be converted using a formula, but that the methods of detection can produce different results both in pediatric and adult subjects [9–36]. Considering with specific reference to pediatric subjects, BNP values reported by Soldin et al. [20] obtained with a point-of-care test (POCT) method (TRIAGE BNP test, Biosite, Alere Inc., USA.) showed a similar time course, although with greatly higher values than those reported by Cantinotti et al. [32], who measured BNP using an automated platform (TRIAGE BNP assay by Access platform, Beckman Coulter, Inc. Brea, CA, USA) despite both assays had used the same antibodies for BNP detection. Moreover, NT-proBNP values measured with the same ECLIA method (Roche Diagnostics, Basel, Schweiz) are very similar among the reported studies [8, 13, 15–17], while the results obtained with the dimension platform (Siemens Healthcare Diagnostics Inc. Tarrytown, NY, USA) by Soldin et al. [20] show significantly higher values. Therefore, clinicians should use great care when comparing results obtained by laboratories using different methods.

BNP in CHD and cardiomyopathy

From a patho-physiologic standpoint CHD may be characterized by: (1) increased volume overload (i.e., defects characterized by left-to-right shunt, such as ventricular septal defect, patent ductus arteriosus, truncus arteriosus, atrial septal defect, atrio-ventricular septal defects); (2) pressure overload involving the left ventricle (i.e., aortic stenosis, aortic coarctation) or the right ventricle (i.e., tetralogy of Fallot, pulmonary stenosis); (3) complex

Table 1 Reference values for BNP and NT-proBNP immunoassay in healthy neonates, infants, and children

Part A: BNP assays (M: males, F: females)

References	Assay method	BNP (ng/L)				
		Age, subjects (no.)	Median	Range	Percentile	Percentile
Cantinotti et al. [19]		0–24 h (57)	224	41–837	342 (75th)	521 (90th)
		25–48 h (49)	242	53–866	344 (75th)	457 (90th)
	Automated access	49–96 h (50)	152	23–862	229 (75th)	315 (90th)
	Platform	97–192 h (32)	45	10–739	90 (75th)	224 (90th)
	Beckman-Coulter	8–30 days (34)	27	9–63	45 (75th)	55 (90th)
		31 days–12 months (69)	19	1–53	28 (75th)	36 (90th)
		1–12 years (142)	14.5	1–46	20 (75th)	28 (90th)
		0–192 h (188)	–	10–866	714 (97.5th)	853 (99th)
		2 weeks–12 years (245)	–	1–739	37 (97.5th)	40 (99th)

		Age, subjects (no.)	97.5th percentile
Soldin et al. [20]		0–<31 days (50)	1,585
		31–<90 days (38)	1,259
	POCT method	3–<6 months (26)	759
	Biosite, inverness medical	6 months–<1 year	263
		1–<3 years (M = 60, F = 51)	M = 173–F = 158
		3–<10 years (M = 89, F = 72)	M = 132–F = 120
		10–<15 years (M = 91, F = 51)	M = 120–F = 115
		15–<18 years (M = 63, F = 66)	M = 100–F = 107

		Subjects (no.)	Mean ± SD
Koch et al. [11]		0–1 days (12)	231.6 ± 197.5
	POCT method	4–6 days (12)	48.4 ± 49.1
	Biosite, inverness medical	<10 years (M = 43, F = 42)	M = 8.3 ± 6.9–F = 8.5 ± 7.5
		>10 years (M = 31, F = 36)	M = 5.1 ± 3.5–F = 12.1 ± 9.6

		Subjects (no.)		Mean ± SD
Kunii et al. [14]	IRMA BNP	Neonates (11)	12–24 h after birth	118.8 ± 83.2
			7 days	15.3 ± 7.8
	Shionogi & Co. Ltd	Children (242)		5.3 ± 3.8

Part B: NT-proBNP assays (M: males, F: females)

Reference	Assay method	NT-proBNP (ng/L)				
		Age, subjects (no.)	Median	Range	95th percentile	97.5th percentile
Nir et al. [8]		0–2 days (43)	3,183	260–13,224	11,987	13,222
		3–11 days (84)	2,210	28–7,250	5,918	6,502
	ECLIA method	>1 month–≤1 year (50)	141	5–1,121	646	1,000
	Roche diagnostic	>1–≤2 years (38)	129	31–657	413	675
		>2–≤6 years (81)	70	5–391	289	327
		>6–≤14 years (278)	52	5–391	157	242
		>14–≤18 years (116)	34	5–363	158	207

Table 1 continued

Part B: NT-proBNP assays (M: males, F: females)

Reference	Assay method	NT-proBNP (ng/L)				
		Age, subjects (no.)	Median	Range	95th percentile	97.5th percentile
Albers et al. [17]	ECLIA method Roche diagnostic	1–3 years (13)		5–391.5		319.9
		4–6 years (21)				189.7
		7–9 years (32)				144.7
		10 years (11)				112.4
		11 years (69)				317.1
		12 years (21)				186.4
		13 years (23)				369.9
		14 years (18)				362.8
		15 years (24)				216.7
		16 years (24)				206.0
		17 years (24)				134.9
		18 years (12)				114.9
Nir et al. [8]	ECLIA method	1–5 days (20)	1,638			
	Roche diagnostic	4 months–15 years (58)	780	5–391	348.6	
Rauh et al. [15]	ECLIA method	<1 month (13)		1,121–7,740		229 (1 year)
	Roche diagnostic	4 months–18 years (78)	62.3	11–379		48 (16 years)
Schwachtgen et al. [16]	ECLIA method Roche diagnosti	Umbilical cord (62)	668	281–2,595		
		0–1 days (8)	4,558	273–13,224		
		2–3 days (40)	2,492	621–8,122		
		4–8 days (11)	1,321	243–4,130		
		9–365 days (26)	157	48–739		
		10–13 years (55)	77	5–675		
		10–13 years F (16)	43	5–157		
		10–13 years M (14)	30	8–150		
		13–18 years F (11)	68	9–162		
		13–18 years M (15)	23	5–161		
		0–<31 days (M = 46, F = 53)				M = 28,183, F = 35,481

cyanotic CHD (i.e., univentricular heart, transposition of the great arteries) [2].

Several studies [32, 33, 37–39] indicate that BNP concentrations are high in neonates and children with CHD and are higher in those with left ventricular volume overload as compared to those with right ventricular volume or pressure overload. Furthermore, BNP values are higher in diseases characterized by left ventricular pressure overload than in diseases with right ventricular pressure overload. In diseases with volume overload, BNP values are generally positively correlated with the magnitude of left-to-right shunt, pulmonary artery pressure, pulmonary vascular resistance, and end-diastolic volume [37, 40, 41].

In neonates, BNP/NT-proBNP values may be employed for the diagnosis of significant left-to-right shunts and to determine the need for intervention as in the case of ductal closure [42–47]. On average, pediatric patients with complex CHD show significantly higher BNP concentrations compared with those with simple cardiac defects, such as patent ductus arteriosus and atrial or ventricular septal defects [2, 32, 37]. It is still unclear, however, whether there is a difference in BNP expression and production between univentricular heart (UH) defects of right ventricular versus left ventricular morphology [48, 49].

As to BNP values in children with various cardiomyopathies, data are few [44–62]. BNP values are usually higher with decreased ejection fraction, enlarged left ventricular dimensions, and abnormal diastolic indices assessed by echocardiography [50, 52]. In children with hypertrophic cardiomyopathy, BNP values were able to predict disease severity, independently correlated with various echocardiographic parameters including indices of diastolic function and maximal left ventricular wall thickness [51]. In a study considering children with heart failure

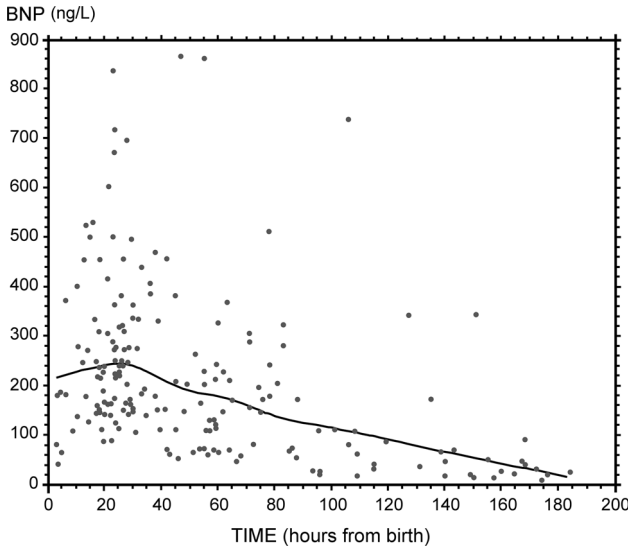

Fig. 2 Plasma BNP in healthy newborns throughout the first days of life. Plasma BNP values were measured in 188 healthy newborns throughout the first days of life. Plasma BNP concentrations are very high during the first 4 days of life, then values fall rapidly during the first week with a further slower progressive reduction throughout the first month of life. Plasma BNP was measured with the automated Access platform (Triage BNP reagents, Access Immunoassay Systems, REF 98200, Beckman Coulter, Inc., Fullerton, CA 92835). The trend was indicated by a continuous line, assessed by smooth spline analysis (data modified from references [19, 32, 33])

of various etiologies, including 14 cases of dilated cardiomyopathy, NT-proBNP levels were significantly higher than in controls and showed correlation with the ejection fraction and with the clinical heart failure (HF) score [53]. Children with dilated cardiomyopathy appeared to have higher BNP values than those with hypertrophic and restrictive forms [53]. BNP and NT-proBNP may be helpful in detecting latent left ventricular impairment in children with doxorubicin-induced cardiomyopathy [54–59] as well as in those with iron-overload cardiomyopathy in beta thalassemia major [58].

BNP as a diagnostic tool

Data discussed in the previous paragraphs clearly indicate that reliable age-related pediatric reference values for BNP/NT-proBNP are available, and natriuretic peptides correlate with various indexes of disease severity in children with congenital and acquired heart defects. In the following section, another relevant question that is whether BNP may be helpful for the diagnosis of heart failure of various etiologies will be discussed.

According to the Evidence-Based Laboratory Medicine (EBLM) principles, the development of a medical test like the BNP assay is a multiphase process [63]: The first phase includes the evaluation of the analytical performance of the test, as well as the set up of reference limits, whereas the remaining phases concern the efficacy and efficiency of the biomarker as a clinical laboratory test. The clinical impact of BNP/NT-proBNP assay has been tested through four prospective studies with control groups. Aiming to diagnose an at-risk population, these selected studies differ from other studies that identify an association of hemodynamical significant heart disease with a BNP increases. The study by Koulouri et al. [64], in acute care setting, enrolled 49 children with acute respiratory distress; of these, 29 turned out to have HF. A BNP of 40 pg/mL produced a sensitivity of 91 % and specificity of 77 %. However, the study had also included patients who had an acknowledged condition of heart disease prior to presentation. Another study with similar design again allowed enrollment of patients with known heart disease of which 17 with heart failure, 18 with lung disease, and 13 healthy controls [65]. There was significant differentiation between the groups with the HF subgroup having a NT-proBNP of 26,344 pg/mL and lung disease of 458 pg/mL. A prospective study by Maher et al. [148] considered 2 groups of sick children, a critically sick cohort with heart disease and less compromised cohort comprising patients presenting at the emergency department for respiratory distress or infection and found BNP to be higher in the first group. The 33 patients with newly discovered heart disease had were 3290 pg/mL vs. 17.4 pg/mL for the 70 sick subjects in the comparison group.

To date, the most rigorous study done to date in pediatrics enrolled all-comers who were equally sick presenting to the acute care setting where the front-line physician queried whether hemodynamically significant cardiovascular disease was present [66]. Clinicians were not aware on patient's history of heart disease and were blinded to the BNP result and relied on the cardiology consult alone as the official diagnosis. The study differentiated two cutoff values that best discriminated hemodynamically significant cardiovascular disease from other disease processes with a similar presentation. For neonates 0–7 days of age ($n = 42$), a cutoff of 170 pg/mL produced a sensitivity of 94 % and specificity of 73 %. For the older age group ($n = 58$), a cutoff of 41 pg/mL produced a sensitivity of 87 % and specificity of 70 %. Nonetheless, the study presented a great limitation as to sample size and heterogeneity of age groups.

Generally speaking higher accuracy measures, for example, may be attained if multiple cutoffs are determined by age group, especially during the early infancy when BNP and NT-proBNP decrease over the first few months of life—which could explain why BNP underperforms compared to accuracy values reported in studies of adults with possible HF or ventricular dysfunction ([67], see Table 2).

Table 2 Diagnostic accuracy of BNP and NT-proBNP assays in pediatric patients suspected to have CHD assessed by ROC analysis

Study	Peptide measured	Number of subjects	Age	AUC (95 % CI)	Sensitivity % (95 % CI)	Specificity % (95 % CI)	Cutoff value (ng/L)
Koulouri et al. [64]	BNP	49	Infants and children (age not specified)	0.92 (0.88–0.96)	91 (72–99)	77 (56–91)	40
					83 (61–95)	77 (56–91)	60
					78 (56–93)	81 (61–93)	80
					78 (56–93)	85 (65–96)	100
Cantinotti et al. [33]	BNP	306	1–30 days of life	0.84 ± 0.02[a]	73	78	281
		160	1–3 days of life	0.77 ± 0.04[a]	66	84	417
		146	4–30 days of life	0.94 ± 0.02[a]	80	91	206
Davlouros et al. [62]	BNP	75	Neonates	0.996	93.1	100	132.5
Law et al. [66]	BNP	42	Neonates	0.90 ± 0.05[a]	94	73	170
		58	Infants and children	0.81 ± 0.06[a]	87	70	41
		100	Combined group	0.84 ± 0.04[a]	81	76	99
Hammerer-Lercher et al. [28]	NT-proBNP	142	33–1,070 days	0.87 (0.76–0.94)	74 (51–89)	95 (89–98)	2,000
Sahin et al. [69]	BNP	70	4 months–17 years	0.97	88	100	100
	NT-proBNP	70		0.96	100	71	400

AUC area under the ROC curve, *95 % CI* confidence interval

[a] AUC ± standard error (SE)

BNP in the assessment of heart failure

In addition to the prospective studies aimed at diagnosing new HF mentioned in the previous section, numerous other studies have been performed to make the correlation between BNP and various forms of heart disease in children. For example, several pediatric studies made the association of HF with increased BNP using healthy children as a comparative group in their analysis [66–72]. Attempts from retrospective and prospective studies have also determined BNP's diagnostic accuracy, of which some are lesion specific (Table 2).

Data reported in Tables 3 and 4 indicate that on average BNP/NT-proBNP immunoassay methods share a good (or even very good in some studies) clinical accuracy in the diagnosis of heart failure in children with CHD, showing AUC values from 0.77 to 0.97 (on average approximately 0.88) using the ROC curve analysis.

Overall, studies demonstrate there is a correlation with the severity of heart failure in most cases [52, 53, 69, 70, 73] with few exceptions [71, 74, 75]. In particular, there appears to be an association between BNP levels and NYHA functional class in adults with systemic morphological right ventricle [76–88], as well as in patients with transposition of the great arteries after atrial switch operation (Mustard or Senning) and congenitally corrected transposition of the great arteries [79, 81, 85]. BNP values, however, were higher than controls even when no signs or symptoms of HF were present.

Significant correlations between BNP levels and right ventricular (RV) function [76, 77, 80, 84, 85], end-diastolic volume [77, 78, 81, 86], and severity of tricuspid valve regurgitation [79, 87] measured by either cardiac magnetic resonance or echocardiography were also observed. Furthermore, plasma BNP correlated negatively with peak oxygen consumption [78–80, 84, 86].

BNP may also be employed in the management of children with univentricular heart [46, 47, 87–107]. Despite data being still controversial in this patient setting, a recent study involving a cohort of 510 children (6–18 years old at a median of 8.2 years after Fontan) found BNP to be variable but within a normal range in the majority of patients and only weakly correlated with clinical and functional status [91].

Some studies suggest that plasma BNP and NT-proBNP may be employed as adjunctive tests for the diagnosis of HF in children with single-ventricle (SV) physiology [89, 90, 149]. Other studies have shown Fontan patients with a better functional capacity to have lower values compared to those with a lower level of functional capacity using either the New York Heart Association (NYHA) or the New York University Pediatric Heart Failure Score [48, 92, 96, 103].

Table 3 Diagnostic accuracy and prognostic value of BNP in children with HF of various etiology

	Study	Disease	Method	Number of subjects	Age	Cutoff value (ng/L)	AUC	Sensitivity	Specificity	PPV	NPV
HF diagnosis	Sugimoto et al. [73]	Various CHD and acquired HD	Biosite Triage	102	4 m–3y	CHF ≥ II 31.2	CHF ≥ II 0.894	CHF ≥ II 0.830	CHF ≥ II 0.836		
						CHF ≥ III 52.1	CHF ≥ III 0.860	CHF ≥ III 0.810	CHF ≥ III 0.848		
						CHF = IV 209.5	CHF = IV 0.837	CHF = IV 0.714	CHF = IV 0.932		
				79	3–14y	CHF ≥ II 29.7	CHF ≥ II 0.964	CHF ≥ II 0.947	CHF ≥ II 0.830		
						CHF ≥ III 201.5	CHF ≥ III 0.994	CHF ≥ III 1.000	CHF ≥ III 0.986		
						CHF = IV 313.0	CHF = IV 0.987	CHF = IV 1.000	CHF = IV 0.976		
	Sahin et al. [69]	Various CHD	Biosite Triage	70	4 m–17y	100	0.90	0.88	1.00	1.00	0.96
						16.95	0.94	0.95	0.66	0.57	0.97
	Kalouri et al. [64]	HF versus lung disease in respiratory distress	Biosite Triage	49	Infants and children	40	0.84	0.91	0.77	0.78	0.91
						60	0.80	0.83	0.77	0.76	0.83
						80	0.80	0.78	0.81	0.78	0.81
						100	0.82	0.78	0.85	0.82	0.81
	Law et al. [66]	Hemodynamically significant HD	Biosite Triage	42	Neonates	170	0.90	0.94	0.73	0.91	0.80
				58	Older age	41	0.81	0.87	0.70	0.77	0.83
	Law et al. [94]	SV ventricular disfunction versus nondisfunction	Biosite Triage	33	3 m–154 m	40		0.85	0.81	0.92	0.68
	Wu et al. [72]	Normal versus HF due to CHD	NR	118	Children	349 (pg/ml)	0.88				
	Shah et al. [90]	HF versus non-HF; SV physiology; 9 HF, 20 not HF	Biosite Triage	29	1 m–7y	30	0.603	0.889	0.75		
Prognosis	Price et al. [50]	49 IDM, 19 LVNC, 9 myocarditis, 8 DND, 6, IC, 3 AT, 3 MM, 2 other	Biosite Triage	64	2.7–15.1y	≥300[b]		0.93	0.95	0.88	0.97
	Auerbach et al. [74]	60 % cardiomyopathy, 40 % CHD	Beckman Coulter	138	1.1–11y	140[a]	0.71	0.63			38

AT antracicline therapy, *AUC* area under the ROC curve, *CHD* congenital heart disease, *CHF* congenital heart failure, *IC* ischemic cardiomyopathy, *DCM* Duchenne muscular dystrophy, *HD* heart disease, *HF* heart failure, *IDM* idiopathic dilated cardiomyopathy, *LVCN* left ventricular noncompaction, *m* month, *MM* mitochondrial myopathy, *NPV* negative predictive value, *PPV* positive predictive value, *SV* single ventricle, *y* year

[a] Composite outcome of hospitalization for worsening HF, death or transplantation

[b] Adverse cardiovascular event at 90 days defines as cardiac death (pump failure or cardiac death), hospitalization for cardiac reasons (new onset or worsening of heart failure symptoms), or new listing for cardiac transplantation

Table 4 Diagnostic accuracy of NT-BNP in children with HF of various etiology

	Study	Disease	Method	Number of subjects	Age	Cutoff value (ng/L)	AUC	Sensitivity	Specificity	PPV	NPV
HF diagnosis	Sugimoto et al. [73]	Various CHD and acquired HD	Biosite Triage	102	4 m–3y	CHF ≥ II 438.4	CHF ≥ II 0.955	CHF ≥ II 0.887	CHF ≥ II 0.918		
						CHF ≥ III 1,677.5	CHF ≥ III 0.984	CHF ≥ III 0.952	CHF ≥ III 0.938		
						CHF = IV 7,733.5	CHF = IV 0.999	CHF = IV 1.000	CHF = IV 0.995		
	Sahin et al. [69]	Various CHD	Biosite Triage	70	4 m–17y	400	0.79	1.000	0.71	0.58	1.000
						514	0.94	0.95	0.80	0.66	0.98
	Wu et al. [72]	Normal versus HF due to CHD	NR	118	Children	499 (fmol/ml)	0.98				

AUC area under the ROC curve, *CHD* congenital heart disease, *CHF* congenital heart failure, *m* month, *NPV* negative predictive value, *PPV* positive predictive value, *y* year

It has also been demonstrated that in the setting of SV circulation, raised BNP values may help to distinguish HF due to ventricular dysfunction from isolated cavo-pulmonary failure [94] since the synthesis of BNP resides within the ventricle not the venous–pulmonary artery circulation.

Perhaps also related to the source of production of the peptide, BNP has been shown to be higher in classic Fontan patients compared with total cavo-pulmonary connection patients [91, 96, 97].

A decrease in BNP through various stages of palliation has also been demonstrated [49, 94], and in asymptomatic children and adolescents after completion of the Fontan procedure, average BNP values were comparable to healthy age-matched controls [49, 91, 94, 96, 99, 101, 103]. Furthermore, adolescents with Fontan circulation and HF showed NT-proBNP values significantly higher than those with Fontan without HF, and natriuretic peptides values correlate with the severity of cardiac failure [103]. Moreover, adult patients with Fontan showed higher BNP values compared to those with other corrected/palliated CHD [107]. It is noteworthy to mention that BNP correlated with several echocardiographic parameters including the severity of atrio-ventricular valve regurgitation [48], systolic ventricular function [107], indices of diastolic function [99], and total ventricular mass by magnetic resonance imaging [91].

Data on the correlation between BNP and peak oxygen consumption and chronotropic index during exercise testing are conflicting [49, 92] with only a few studies showing significant correlations [7, 96]. Data on the prognostic utility of BNP in the follow-up of patients with univentricular heart are also inconclusive [89, 91]. In some studies, higher BNP values seem to be associated with poor outcome [48] and worse neurodevelopmental outcomes in infants with single-ventricle physiology [106], although data are limited and inconclusive [91, 101].

BNP has gained usage in the follow-up of patients after tetralogy of Fallot repair with the typical sequelae, i.e., residual pulmonary regurgitation and/or stenosis [2, 3, 108–125]. In the integrated follow-up of tetralogy of Fallot patients, it is important to note that right ventricular dilatation is not necessarily accompanied by a deterioration of cardiac function; indeed, in some patients, symptoms may be mild or completely absent and decision between an interventional or conservative approach is often controversial [2, 5, 7]. In this setting, the use of BNP may help provide important additional information.

In patients awaiting valvular replacement, BNP was higher in NYHA class II compared to NYHA-I [111–114] and correlated negatively with exercise time and positively with right ventricular dilatation and both tricuspid and pulmonary regurgitation. A significant reduction in BNP

values after valve replacement has also been well documented [2, 5, 7, 105, 111, 115]. In the majority of studies, BNP correlates with degree of pulmonary regurgitation, and right ventricle end-diastolic volume and systolic pressure [112–114, 119–121, 123]. In contrast, correlation between BNP and RV function was discordant among various studies [7, 112–114, 119–121, 123]. It is important to remark that the increase in BNP in tetralogy of Fallot patients may be related not only to right ventricular dysfunction but also to the involvement of left ventricle [112]. The response of cardiac endocrine function (as indicated by the measurement of plasma BNP) to stress test in patients after surgical repair of tetralogy of Fallot was more pronounced compared to normal subjects [71, 106, 110, 113]. Furthermore, significant correlations were found between BNP and cardiopulmonary parameters during stress test including peak oxygen uptake, forced vital capacity, and the minute ventilation/carbon dioxide production ratio.

BNP in monitoring response to therapy and prognosis

The utility of BNP as a prognostic marker has been tested in various cardiomyopathies including dilated [50, 53], left ventricular non-compaction [50], inflammatory [50], dystrophin [50], ischemic [50], oncologic [50, 56–58], and mitochondrial [66]. In particular, BNP values <300 pg/ml have shown to have accuracy values of sensitivity 0.93, specificity 0.95, positive predictive value 0.88, and negative predictive value 0.97 for the prediction of adverse cardiovascular events in pediatric outpatients with chronic left ventricular dysfunction due to various cardiomyopathies [50]. A post hoc analysis of the pediatric carvedilol trial included a larger group of subjects with congenital heart disease with a broader age range [74]. Similar adverse event end points of heart failure admission, death, and transplantation were chosen. The authors found a BNP cutoff of 140 ng/L to be the most accurate for risk stratification considering a composite end point (including hospitalization for worsening HF, all-cause mortality and cardiac transplantation) with a sensitivity of 71 % and specificity of 63 % [74]. Controlling for other clinical factors, this cutoff was associated with death and transplantation for children above 2 years of age.

In a study involving 24 children (median age 8.7 years) with acute HF (including 17 with cardiomyopathy of various types), NT-proBNP decreased in those patients who did not required mechanical circulatory support (MCS), but not in those who were eventually placed on MCS [75]. It is important to note that a single time point (value) in NT-proBNP did not predict the need for MCS.

In a group of 41 children with cardiac failure (due to cardiac or pulmonary disease), NT-proBNP values were higher in those who died than in survivors, who instead experienced a significant decrease after treatment [124].

In a study evaluating serum and echocardiographic predictors of death and need for transplant conducted over 91 children (median age 3 years; range 0–18) with HF for various CHD, the adjunct of BNP in 51 patients did not improve the model's accuracy markedly [125].

Some recent studies suggest that BNP is a reliable prognostic biomarker in congenital heart disease surgery [126–145, 150]. In particular, these studies indicate that BNP levels (especially those measured preoperatively) are independently associated with the duration of mechanical ventilation, intensive care unit stay, need for inotropic support, and low cardiac output syndrome [126–138]. As may be expected from the foregoing sections, the postoperative use of natriuretic peptides is complicated by the heterogeneity of cardiac lesions and the age groups of patients, namely the change in BNP after pediatric cardiac surgery seems to be age and disease dependent [2, 7, 135–137]. As a group, neonates showed an opposite response to those observed in older children. Studies by Cantinotti et al. showed that BNP values tended to increase after corrective neonatal surgery while decreased in the older age patients [136, 137, 144].

This may be partly explained by the severity of disease and complexity of procedures undertaken in neonates. However, when complexity is adjusted with the Aristotle and RACHS classification, the only parameter affecting postoperative BNP levels is age. It is also apparent that natriuretic peptide levels reach peak levels at approximately 12 h after the separation from cardiopulmonary bypass [126, 127, 129, 134]. Further increases after that time can imply potential problems ahead. When compared to other bedside monitoring such as vital signs and lactate, BNP remained significant in its association with an adverse outcome when patients were subclassified by type of lesion [135]. In another large study, incorporating a comparison group of noncardiac patients undergoing similarly long noncardiac surgery, Niedner et al. [133] demonstrated BNP to correlate with the intensity of postoperative support. In smaller studies that focused on specific patient groups, natriuretic peptide in general showed positive correlation with a complicated postoperative course and composite outcome measures. Hsu et al. examined 36 consecutive neonates undergoing various repairs and showed the 24-h to preoperative BNP ratio to be predictive of an adverse outcome that included death [127]. Another study examined neonates who had the arterial switch procedure and showed BNP was associated with low cardiac output state and length of mechanical ventilation [130]. Several studies focused on the single-ventricle population as well. There was an association of 6–12 h BNP levels with more complicated clinical course after the cavo-pulmonary connection [126, 127]. The one study that is an outlier found

troponin and lactate, but not NT-proBNP, to have a better correlation with the need for more intensive support in a diverse group of 23 patients [131].

Lastly, with the introduction of mechanical circulatory assistance in children, a study by Heise et al. [143] showed NT-proBNP and BNP to decrease significantly after implantation of the Berlin EXCOR, substantiating the advantageous neurohormone response when the ventricle is unloaded; however, given the complexity of the clinical course in this small group of patients, association with outcome was not demonstrated.

The use of BNP to monitor and predict postoperative circulatory recovery is not conclusive. Despite there being a trend for higher natriuretic peptides in those who require more intensive support, research must still confirm under which conditions that occurs (which natriuretic peptide level time point, under which cardio-surgical condition) and whether it adds to conventional indicators (echocardiography, modern intensive care unit bedside monitoring, and direct physician assessment of acute and irrecoverable cardiac dysfunction).

Summary

The practice of cardiology is in continual evolution, alongside medical research progresses in understanding the pathophysiology of cardiovascular disease and in developing new therapeutic procedures [146]. Consequently, developers of cardiac biomarkers are pressed with new demands to improve the performance of the existing and the development of novel ones. However, the implementation of a novel biomarker in clinical practice according to Evidence-Based Medicine principle is a longstanding and costly process [147].

After more than 30 years of continuous studies [1], the measurement of circulating BNP and NT-proBNP is now recommended by international guidelines [3, 4] as a biomarker for diagnosis, prognosis, and therapeutic monitoring in adult patients with cardiac diseases. Unfortunately, there are fewer data of BNP/NT-proBNP in the pediatric population.

So far, the data available today can however support the use of BNP/NT-proBNP in specific cases:

1. For the integrated evaluation and monitoring of children with known heart disease, to allow the further defining of severity and progression of heart failure, and its response to therapy;
2. As an adjunctive marker, not a stand-alone test, in the screening of hemodynamically significant cardiovascular disease as well as in the prognosis of children undergoing cardiac surgery.

It must be said however that these indications are based on texts generally conducted on limited populations, single-randomized or nonrandomized trials. As a result, they may theoretically achieve a level II B according to current classification of recommendations and level of evidence [3].

Thus further prospective studies are needed to demonstrate the true benefit of the BNP/NT-proBNP assay in these various aspects in the management of children with heart disease.

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