STATE-OF-THE-ART PAPER

The Usefulness of Brain Natriuretic Peptide in Complex Congenital Heart Disease

A Systematic Review

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Brain natriuretic peptide (BNP) and N-terminal pro–brain natriuretic peptide (NT-proBNP) are well-established markers for heart failure in the general population. However, the value of BNP as a diagnostic and prognostic marker for patients with structural congenital heart disease (CHD) is still unclear. Therefore, the purpose of this study was to evaluate the clinical utility of BNP in patients with CHD. We executed a PubMed literature search and included 49 articles that focused on complex congenital heart defects such as tetralogy of Fallot, systemic right ventricle, and univentricular hearts. Data on BNP measurements and cardiac function parameters were extracted. In all patients after correction for tetralogy of Fallot, BNP levels were elevated and correlated significantly with right ventricular end-diastolic dimensions and severity of pulmonary valve regurgitation. Patients with a systemic right ventricle had elevated BNP levels, and positive correlations between BNP and right ventricular function were seen. In patients with a univentricular heart, elevated BNP levels were observed before completion of the Fontan circulation or when patients were symptomatic; a clear association between BNP and New York Heart Association functional class was demonstrated. In conclusion, this review shows an overall increase in BNP values in complex CHD, although differences between types of congenital heart anomaly are present. As BNP values differ widely, conclusions for individual patients should be drawn with caution. Further investigation with sequential BNP measurement in a large, prospective study is warranted to elucidate the prognostic value of BNP assessment in patients with CHD.   (J Am Coll Cardiol 2012;60:2140–49) © 2012 by the American College of Cardiology Foundation

Congenital heart disease (CHD) is the most prevalent form of congenital abnormality with an incidence of approximately 9 cases per 1,000 live births (1). The number of adult patients with a congenital heart disease is steadily increasing due to the success of pediatric cardiology and open-heart surgery. However, few cardiac surgical repairs are curative. At adult age, many patients will have complications as valvular dysfunction and arrhythmias. The increasing number of adult CHD patients also brings an increasing number of patients at risk of late ventricular dysfunction and heart failure. That is mainly seen in the more complex congenital heart diseases, such as tetralogy of Fallot (TOF), defects with a systemic right ventricle (RV), and univentricular hearts.

Brain natriuretic peptide (BNP) and N-terminal pro–B-type natriuretic peptide (NT-proBNP) have gained a lot of interest in the last 20 years (2). These hormones are synthesized and released into the circulation by the ventricular myocytes in response to pressure overload, volume

expansion, and increase in myocardial wall stress. Within the myocytes, the precursor pro-BNP is divided in the biologically active form BNP and the inactive NT-proBNP fragment. Once in the circulation, BNP has natriuretic, diuretic, and vasodilatory effects on the internal climate (2). Both markers show a comparable clinical utility for assessing cardiac impairment and are well-established markers of heart failure in the general population (3).

Natriuretic peptides might be of clinical importance in the congenital heart disease population because of their proven usefulness in acquired heart disease and the simplicity of assessment. Their role in the diagnostic approach and clinical decision making in patients with CHD is not well defined. In this systematic review, we evaluate the recent literature on BNP and NT-proBNP activation and the relationship between these biomarkers and cardiac function in patients with complex congenital heart disease.

Methods

Search strategy, selection criteria, and data extraction. On September 1, 2011, a PubMed literature search with focus on complex cardiac defects (including TOF, systemic RV, and univentricular hearts) was conducted. Data from

January 1990 to September 2011 were included. The following Medical Subject Headings and text key words were used: "natriuretic peptide, brain" or "pro-brain natriuretic peptide" and "heart defects, congenital" or "tetralogy of Fallot" or "transposition of great vessels" or "Fontan procedure" or "Norwood procedure" or "congenitally corrected transposition of the great arteries."

Each article title and abstract was screened to identify relevant studies. The search strategy was limited to articles concerning human subjects that were published in the English language. Articles concerning both children and adult patients were included. The BNP levels had to be reported per cardiac diagnosis. Consequently, articles that presented BNP levels for a group of CHD diagnoses were excluded. We focused on complex cardiac defects because of the relative high incidence of adverse events as heart failure in these groups. Atrial septal defects and ventricular septal defects, aortic coarctation, congenital aortic stenosis, and persistent ductus arteriosus, although also of interest, were excluded in the current study. References of selected papers were crosschecked with the same inclusion and exclusion criteria to identify articles missed by the search strategy.

Data were extracted on type of CHD, age, sex, plasma BNP levels, and BNP immunoassay method. Furthermore, when reported in the article, BNP levels of controls, type of controls, and correlations between BNP and cardiac function parameters measured with echo, cardiac magnetic resonance (CMR) imaging, exercise test, New York Heart Association (NYHA) classification, reinterventions, and adverse events were collected. In all potentially relevant articles, eligibility was assessed by 2 authors (J.A.E. and J.W.R.H.). Disagreements were resolved by discussion. Because of the heterogeneity in functional tests and result presentation, a formal meta-analysis linking BNP levels with functional parameters and outcome could not be conducted. In this article, both markers, BNP and NT-proBNP, will further be referred to as "BNP" unless a separate use is needed for clarification.

Results

The literature search yielded 200 potential eligible studies (Fig. 1). We excluded 51 articles because BNP levels for >1 CHD were reported without specification of BNP levels per diagnosis or age at time of assessment. In addition, 38 reports focusing on relative mild cardiac defects including atrial septal defect, ventricular septal defect, aortic coarctation, and persistent ductus arteriosus were excluded. Finally, 49 studies concerning TOF (n = 20), systemic RV (n = 13), or single ventricle morphology (n = 16) were included in this systematic literature review. The main diagnostic tools used to quantify cardiac function were physical examination, echocardiography, and CMR imaging. Further, occasionally results of cardiopulmonary exercise tests, cardiac catheterization, or cardiac computed tomography scan were reported. Longitudinal data were available in 6 of the 49 studies.

Tetralogy of Fallot. The value of BNP in patients with surgically repaired TOF has been studied in 20 articles describing a total of 770 patients with a median/mean age ranging from 4.2 to 30.9 years (4–23). The BNP levels were significantly higher in Fallot patients (mean/median values of BNP and NT-proBNP ranging from 19 to 85 pg/ml and from 85 to 231 pg/ml, respectively) when compared to age- and sex-matched controls (mean/median values of BNP and NT-proBNP ranging from 6 to 15.4 pg/ml and from 38 to 111 pg/ml, respectively), although most patients were asymptomatic or only mildly symptomatic (Fig. 2) (5–10,12,14,16,17). Patients with NYHA functional class II revealed significantly higher BNP values than patients with NYHA class I (p = 0.01) (Table 1) (12,15).

The severity of pulmonary valve regurgitation and RV end-diastolic volume showed a positive correlation with BNP in 7 of 9 studies (Table 1) (6,9,11,12,15–19). A great variety between correlations of BNP with RV function was seen, ranging from nonsignificant correlations up to highly significant correlations of 0.60 in comparable study populations using the same diagnostic tools. In none of the studies was a correlation observed between BNP and left ventricle (LV) function or LV end-diastolic volume.
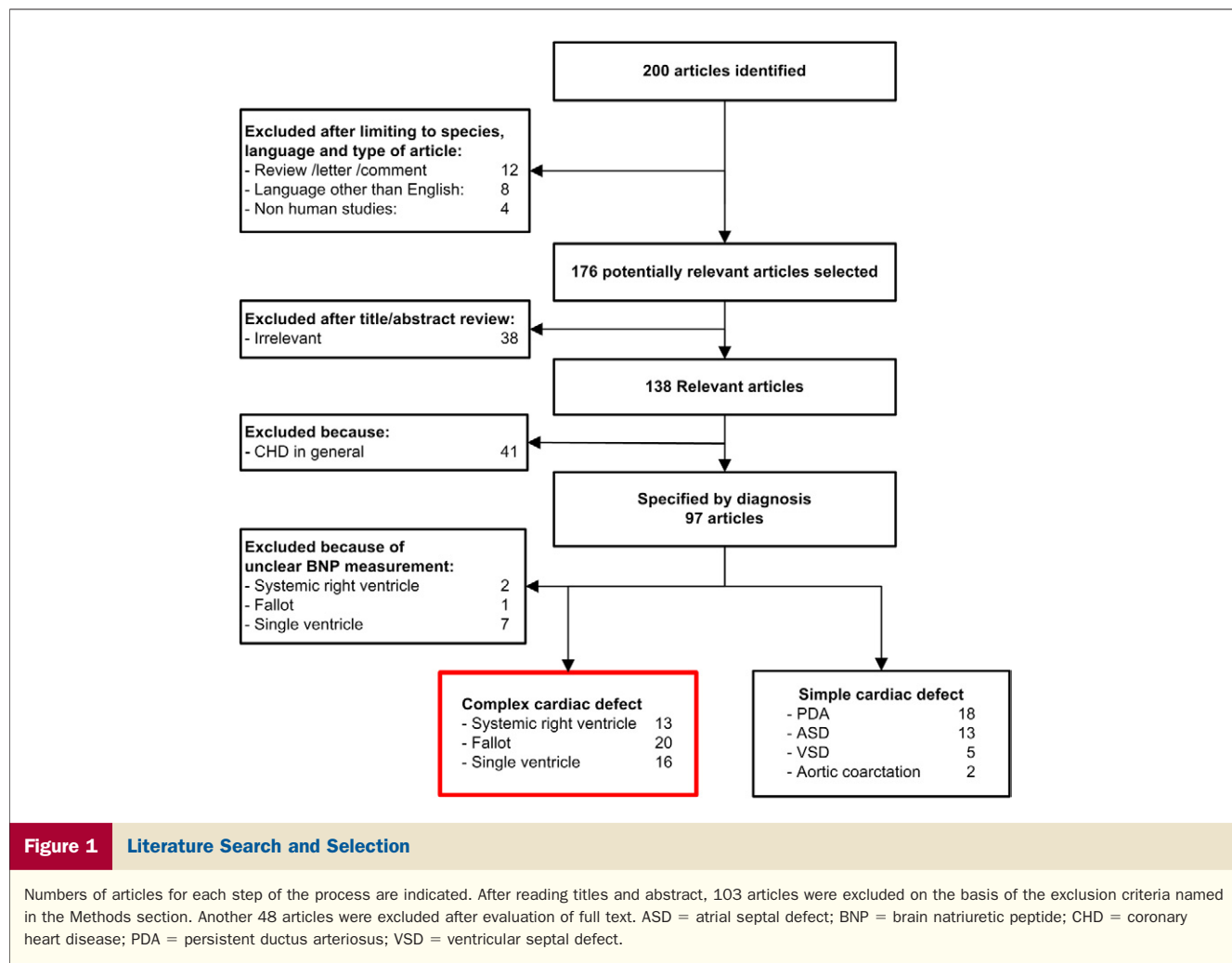
In 7 studies, an exercise test was performed (6,7,9,15–18). Plasma BNP correlated negatively with exercise capacity and peak oxygen uptake (8,15–17). Furthermore, TOF patients had more pronounced increases in BNP levels post-exercise compared with healthy controls (17).

Three studies with longitudinal data revealed a significant decrease of BNP levels 6 months or longer after pulmonary valve replacement compared with BNP levels before the intervention, mirroring the smaller RV end-diastolic volume and/or improved RV ejection fraction (4,15,23).

Systemic RV. In 13 studies (24–36), levels of BNP were reported for patients with a systemic RV, including patients with transposition of the great arteries (TGA) after atrial switch operation (Mustard or Senning) and congenitally corrected TGA. A total number of 469 patients with a systemic RV were studied for BNP levels. All patients were included at adult age (mean/median age ranging from 19 to 35 years). The BNP levels were higher in systemic RV patients (mean/median BNP and NT-proBNP values ranging from 13.5 to 98 pg/ml and from 200 to 654 pg/ml, respectively), compared with controls (median BNP 17 pg/ml, range of mean NT-proBNP 48 to 57 pg/ml) in most studies, even when no signs or symptoms of heart failure

Figure 1   Literature Search and Selection

Numbers of articles for each step of the process are indicated. After reading titles and abstract, 103 articles were excluded on the basis of the exclusion criteria named in the Methods section. Another 48 articles were excluded after evaluation of full text. ASD = atrial septal defect; BNP = brain natriuretic peptide; CHD = coronary heart disease; PDA = persistent ductus arteriosus; VSD = ventricular septal defect.

were present (Fig. 2). In addition, an association between BNP levels and NYHA functional class was reported in 3 studies (Table 2) (27,29,33).

A significant negative correlation between BNP levels and RV function measured by either CMR or echocardiography was found in 5 of 8 studies (correlation coefficients ranging from r = −0.42 to r = −0.54) (Table 2) (24,25,29,33,34). Secondly, a weaker but still significant positive correlation between BNP and end-diastolic RV volume was observed (24,25,29,33). Furthermore, a positive correlation was found between the severity of tricuspid valve regurgitation (TR) and BNP (27,35). In contrast, LV function did not correlate with BNP in any of the studies.

In 5 studies, exercise tests were performed (25,27,28,32,34). Plasma BNP correlated negatively with peak oxygen consumption in 3 of these studies. When comparing atrial switch patients with congenitally corrected TGA, no significant differences in BNP levels were found (26,27,31). Furthermore, 1 study reported longitudinal data of 14 patients (median follow-up 1.4 years) and observed no differences in BNP levels (no changes in clinical findings were identified either) (27).

Single ventricle. Sixteen studies reported data on BNP in patients with univentricular hearts and Fontan physiology (37–52), including a total of 1,185 patients. The studied Fontan patients mainly comprised children (mean/median age ranging from 0.6 to 33.1 years). Patients treated with a classic Fontan procedure had significantly higher levels of BNP compared with patients who had undergone the currently used Fontan approach (Fig. 2, Table 3) (40,42,48). Young patients after the first palliative operation revealed higher BNP levels than patients after the bidirectional Glenn procedure or completion of the Fontan circulation with a total cavopulmonary connection (TCPC) (39,41). After completion of the Fontan procedure by TCPC, the BNP values of asymptomatic patients were comparable to those of healthy age-matched controls (39–41,44,47,48). However, symptomatic patients defined as NYHA class ≥2 or New York University Pediatric Heart Failure Index ≥5 had significantly higher levels of BNP than did asymptomatic patients (Table 3) (38,40,49,50). The New York University Pediatric Heart Failure Index score is an alternative instrument for measuring heart failure severity in children (53).
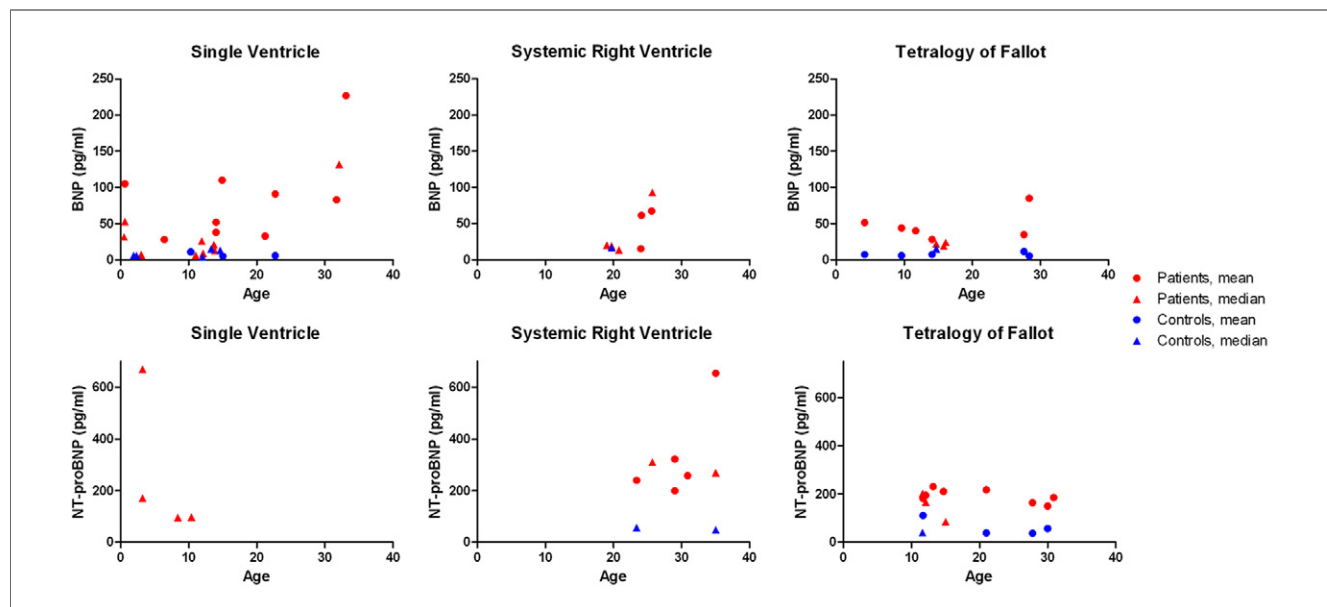
Figure 2 | **BNP and NT-proBNP Measurements per Cardiac Diagnosis**

Mean/median values of brain natriuretic peptide (BNP), N-terminal pro–B-type natriuretic peptide (NT-proBNP), and age for patients and controls per cardiac diagnosis. Each symbol reflects 1 study patient population or control population. **Red circles** indicate patients, mean; **red triangles** indicate patients, median; **blue circles** indicate controls, mean; **blue triangles** indicate controls, median. One result was left out of the figure to retain clarity (mean BNP 399 pg/ml by Law et al. [41] for single ventricle patients).

Echocardiographically measured severity of atrioventricular valve regurgitation showed a positive correlation with BNP values (38). There was 1 study reporting a correlation between variables of diastolic function and BNP (44). No correlations were found between ventricular systolic function and BNP (44,45). When focusing on ventricular morphology, 2 studies found higher BNP levels in patients with an anatomical RV compared with patients with LV morphology (39,49), whereas 4 other studies, including a large study of 510 Fontan patients, did not find this anatomy-based difference (38,40,48,50).

In 7 of the 16 studies, an exercise test was performed. Only 1 study demonstrated a significant correlation between BNP and peak oxygen consumption in Fontan patients (40), whereas 3 other studies found no significant correlation (39,49,51). Mixed results were also found for pulse oxymetric saturation and plasma BNP.

Follow-up data revealed significantly higher levels of BNP in 5 patients who died from heart failure during the study period (38). Another study, however, found no prognostic value of BNP during 4 years of follow-up, including events in 11 patients (46).

Discussion

This systematic review demonstrates that BNP is a potential robust clinical marker for functional status and cardiac function in congenital heart disease. Although most studies were performed cross-sectional and originally not designed to assess BNP, some conclusions can be drawn. Plasma BNP was increased in complex CHD compared with controls or reference values, even when patients were asymptomatic. Exceptions to this finding are asymptomatic patients after TCPC; their BNP levels were comparable to those of healthy control patients. This review shows that, despite the overall increase in BNP, a wide range of BNP values is measured in most studies, and therefore, conclusions for individual patients should be drawn with caution. The studies with TOF and systemic RV patients mainly included asymptomatic and mildly symptomatic patients (NYHA I and II), and therefore, BNP values of more symptomatic patients (NYHA III to IV) are still uncertain. In contrast, in Fontan patients, strong positive correlations were found between BNP and NYHA class when all functional classes were studied.

Natriuretic peptides are known to be age and sex dependent (54), and accordingly, reference values for BNP and NT-proBNP were mainly obtained from age- and sex-matched controls. In line with this assumption, the majority of the studies found higher BNP values in older patients, and female patients revealed higher levels of BNP than men (48). However, age-adjusted reference values of BNP were not always used, which could explain discrepancies between study conclusions. Also, inappropriate controls subjects were used, including patients with (repaired) left-to-right shunts (8,24,44) or Kawasaki disease (40).

Another potential direct cause of increased BNP production, hypoxia, could influence the results in single ventricle patients, as cyanosis is a common finding in uncorrected or partially corrected patients (55). However, correlations be-

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Table 1 Tetralogy of Fallot

First Author (Ref. #)	n	Age (Yrs)	NYHA Class	Function Assessment	Age at Repair (yrs)	BNP (pg/ml)	NT-proBNP (pg/ml)	RV Function (r)	RVEDV (r)	TR Vmax (r)	PR Severity (r)	NYHA Class (r)	Peak VO$_2$ (r)
Apitz (13)	16	14.2 (9.8–24.9)	I	MRI	1.2 (0.2–4.5)	19 (7–42)		NS					
Brili (10)	25	28.4 ± 8.3	I, II	Echo	18.8 ± 6.7	85 ± 87		NS					
Cheung (16)	32	14.7 ± 3.1	I, II, III	Echo	4.6 ± 2.5	21.9 (7.8–470)		NS	0.72 $p < 0.001$	NS			−0.43 $p = 0.03$
Cheung (16)	32	14.7 ± 3.1	I, II, III	MRI	4.6 ± 2.5	21.9 (7.8–470)		NS	0.6 $p = 0.009$		0.46 $p = 0.01$		−0.43 $p = 0.03$
Cetin (12)	25	14.1 ± 4.4	I, II	Echo	4.9 ± 5.1	28.3 ± 24.1		−0.60 $p = 0.0001$	0.7 $p = 0.0001$		0.6 $p = 0.0001$	+ $p = 0.0001$	
Dodge-Khatami (23)	23	13.2 (5.3–19.6)	I, II	MRI	1.6 (0.3–4.6)		231 ± 228	−0.47 $p < 0.05$	NS				
Festa (9)	70	21 ± 1	I, II	MRI/Echo	3.4 ± 0.3		218 ± 30	−0.32 $p < 0.01$	0.40 $p < 0.001$	0.27 $p < 0.05$	NS		−0.57 $p < 0.001$
Ishii (17)	26	9.6 ± 3.3		Echo	2 to 3	44 ± 34		−0.42 $p = 0.03$		NS	+ $p < 0.05$		
Khositseth (19)	21	12.1 ± 2.5	I	Echo/MRI	4.48 ± 1.68		195 ± 303	NS	0.57 $p = 0.01$				
Koch (15)	130	16.1 ± 7.1	I, II	Echo	13 ± 6.5	24 (5–196)				NS	0.20 $p = 0.029$	I vs. II $p = 0.012$	NS
Norozi (6)	50	27.8 ± 1.7	I, II	Echo	7.3 ± 0.7		166 ± 25		0.45 $p < 0.05$	0.42 $p < 0.01$	+ $p = 0.01$		−0.63 $p < 0.001$
Tatani (11)	49	14.7 ± 10	I, II	Echo	5.4 ± 5.3		211 ± 219	NS	0.41 $p = 0.003$		0.60 $p < 0.001$		
Trojnarska (7)	60	27.6 ± 8.2	I, II	Echo	7.5 ± 5.3	34.8 ± 27.1						NS	−0.29 $p = 0.03$
Van den Berg (18)	51	15 (7–26)		MRI	0.8 (0.2–2)		85 (17–355)	NS	NS		0.005 $p < 0.05$		NS
Wand (14)	21	11.6 ± 5.2	I, II	Echo	Mean 1.7 (0.1–5)		Median 202	−0.5 $p = 0.02$	NS				

Values are mean ± SD or median (range). BNP levels were determined by Triage BNP immunoassay (Biosite Diagnostics, La Jolla, California,), IRMA (Shionoria, Shionogi, Japan) and ADVIA Centaur BNP (Siemens Healthcare Diagnostics, Deerfield, Illinois). NT-proBNP was evaluated with ECLIA (Elecsys, Roche Diagnostics, Basel, Switzerland).

Echo = echocardiography; MRI = magnetic resonance imaging; NS = not significant; NYHA = New York Heart Association; + = positive correlation, not further specified; PR = pulmonary regurgitation; (r) = correlation coefficient; RV = right ventricular; RVEDV = right ventricular end-diastolic volume; TR Vmax = tricuspid regurgitation maximum velocity; VO$_2$ = volume oxygen uptake.

Table 2   **Systemic Right Ventricle**

First Author (Ref. #)	n	Diagnosis/ Surgery	Age (yrs)	NYHA Class	Function Assessment	BNP (pg/ml)	NT-proBNP (pg/ml)	RV Function (r)	RVEDV (r)	RVESV (r)	TR Severity (r)	NYHA Class	Peak VO$_2$ (r)
						Natriuretic Peptides		**BNP/NT-proBNP and Cardiac Function Parameters**					
Chow (24)	44	Senning Mustard	19.7 ± 4		Echo	19 (6–522)		−0.43 p = 0.001	0.37 p = 0.009				
Dore (34)	29	Mustard ccTGA	30.9 ± 10.9	I, II	Echo		258 ± 243	−0.42 p = 0.02					NS
Garg (28)	24	Mustard ccTGA	24 (15–37)		MRI or ERNA	15.4 ± 18.2		NS	NS	NS			NS
Koch (27)	48	Mustard ccTGA	19 ± 5	I, II	Echo	20 (5–198)		NS	NS		0.5 p < 0.001	I vs. II p = 0.028	−0.35 p = 0.02
Kozelj (33)	19	ccTGA	35 ± 13.1	all	Echo MRI or CT		654 ± 1535	−0.53 p = 0.02	0.50 p = 0.026	0.61 p = 0.006	NS	0.49 p = 0.032	
Norozi (32)	33	Mustard	23.4 ± 7.4	I, II, III	Echo		240 ± 230					NS	−0.46 p = 0.03
Plymen (29)	35	Mustard Senning	29 (18–40)	I, II	MRI		322 ± 288	−0.54 p < 0.001	0.43 p = 0.01	0.53 p = 0.001		I vs. II p = 0.02	
Schaefer (25)	43	Mustard	29 ± 4		Echo/MRI		200 ± 148	−0.46 p = 0.002	0.32 p = 0.044				−0.32 p = 0.04
Vogt (35)	16	Mustard Senning	25.6 ± 3.7	I, II, III	Echo	67.3 ± 47.5		NS			0.55 p < 0.03	NS	

Values are mean ± SD or median (range). The BNP levels were determined by Triage BNP immunoassay (Biosite Diagnostics), IRMA (Shionoria), or ADVIA Centaur (Siemens). The NT-proBNP was evaluated with ECLIA (Roche Diagnostics).

ccTGA = congenitally corrected transposition of the great arteries; ERNA = equilibrium radionuclide angiography; RVESV = right ventricular end-systolic volume; other abbreviations as in Table 1.

| Table 3 | Single Ventricle |

First Author (Ref. #)	n	Surgery	Age (yrs)	NYHA Class	Function Assessment	BNP (pg/ml)	NT-proBNP (pg/ml)	VEDV (r)	LV vs. RV Morph.	AVR (r)	NYHA Class	Peak VO₂ (r)	SaO₂	RA Pressure (r)	Diastolic Function (r)
						Baseline Characteristics	**Natriuretic Peptides**		**BNP/NT-proBNP and Cardiac Function Parameters**							
Atz (48)	510	Fontan§	Mean 11.9 (6–18)		Echo MRI	13 (4–652)		+ p < 0.01	NS	NS		NS			
Holmgren (39)	38	Shunt Glenn TCPC	0.5 (0.–0.9) 3 (1.6–3.7) 12 (5.2–17.9)		Echo	32 (8–1220) 6.7 (0–16) 9 (0–39)			p = 0.02‡					NS	
Inai (46)	50	Fontan§	22.7 ± 3.6	I, II	Cardiac cath.	91 ± 14							NS		
Koch (38)	67	TCPC	13.8 ± 5.8	I, II	Echo	13 (5–290)			NS	0.38 p = 0.002	I vs. II p = 0.035	NS			
Law (41)	33	APC BDG Fontan§	5.2 (0.3–37.8)	All	Echo or cardiac cath.	Median 84 Median 38 Median 38								0.54 p = 0.04	
Lechner (50)	59	TCPC	8.4 (2.1–25)	All†	Echo		96 (11–376)		NS		r² = 0.44† p < 0.001				
Lechner (49)	78	BDG (CHF+) BDG (CHF−)	3.2 (0.9–9.8)	All†	Echo and cardiac cath.		670 (290–39,763) 171 (32–335)		p < 0.05		0.90† p < 0.001		NS	0.375 p = 0.013	
Man (44)	35	Fontan§	13.7 ± 5.3		Echo	21 (5–397)		NS							−0.31 p = 0.009
Motoki (51)	68	Fontan§ (young) Fontan§ (adult) Cyanotic SVP	21.2 ± 1.1 31.7 ± 7.8 33.1 ± 9.29	All	Echo	33 ± 27 83 ± 96 227 ± 235		+ p < 0.05					NS		
Ohuchi (40)	97	Fontan§	14 ± 5	All	Cardiac cath.	46 ± 76		β = 0.24 p < 0.0001	NS		II vs. III, IV p < 0.01	−0.21 p < 0.05	β = −0.34 p < 0.0001		
Robbers-Visser (45)	28	TCPC	10 (6.8–20.7)		MRI		98 (25–483)	NS				NS			

Values are mean ± SD or median (range). †Functional class measured by New York University Pediatric Heart Failure Index (NYUPHFI) score (53). ‡After second palliative step. §Fontan, both TCPC and right atriopulmonary connection or right atrioventricular connection. The BNP levels were determined by Triage BNP immunoassay (Biosite Diagnostics), IRMA (Shionoria), or ADVIA Centaur (Siemens). The NT-proBNP was evaluated with ECLIA (Roche Diagnostics).

APC = aortopulmonary connection; AVR = atrioventricular valve regurgitation; BDG = bidirectional Glenn; β = beta coefficient; cath. = catheterization; CHF+ = with congestive heart failure; CHF− = without congestive heart failure; LV = left ventricle; RA = right atrium; SaO₂ = oxygen saturation; SVP = single ventricle patients; TCPC = total cavopulmonary connection; VEDV = ventricular end-diastolic volume; other abbreviations as in Table 1.

tween oxygen saturation and BNP were often not demonstrable in these patients.

Tetralogy of Fallot. Since Lillehei et al. (56) reported the first intracardiac surgical TOF repair in 1954, the outcome of patients after corrective surgery has improved over the years. Despite an increasing post-operative survival, pulmonary valve regurgitation and RV dilation and dysfunction often occur. Plasma BNP correlated with RV dilation and severity of pulmonary regurgitation in the majority of the studies. Together with the observed correlation between BNP and exercise capacity, these findings may have important clinical implications. The BNP measurement could contribute to the timing of pulmonary valve replacement in TOF patients with PR. However, the studies that have been conducted so far cannot be used to resolve this important issue, because most studies present cross-sectional data. Although 3 longitudinal studies found elevated BNP levels before pulmonary valve replacement, which decreased afterwards, results of individual BNP measurements differ widely. Large prospective studies are warranted to elucidate the true prognostic value of BNP in these patients.

Interestingly, Van den Berg et al. (18) failed to observe a correlation between NT-proBNP and RV size, presumably because their results on NT-proBNP, functional reserve, and exercise performance were overall within normal ranges, reflecting the good clinical condition of their study population. Despite these findings the (modest) changes found in NT-proBNP were related to relevant RV loading condition abnormalities, worse functional capacity, and decreased functional reserve, confirming the diagnostic potential of BNP (18).

Systemic RV. A ventricle with right ventricular morphology is not designed to pump as a systemic ventricle, which may lead to late RV dysfunction. The treatment of systemic ventricular dysfunction is challenging, and early detection is crucial. The BNP was positively correlated with RV dysfunction in most studies. One of the 3 studies that failed to demonstrate a correlation between BNP and RV function did find a strong negative correlation between RV ejection fraction and atrial natriuretic peptide (28), which is remarkable because of the very close correlation between atrial natriuretic peptide and BNP that is reported in adult CHD patients (57). Maybe the atria play a pivotal role, whereas Mustard and Senning patients have extensive atrial scars due to surgery. In addition, TR often coexists and tends to worsen progressively. Although Ebstein's anomaly may be present, in most cases, TR is secondary to annular dilation from RV failure, and tricuspid valve replacement is not convincingly helpful. Therefore, early detection of an increase in TR is needed. The BNP could contribute to this detection as a strong correlation was observed between plasma BNP and TR severity in several studies. One study by Kozelj et al. (33) could not confirm these findings, maybe due to their relatively small study population, which might have been underpowered to demonstrate a correlation. In addition BNP was correlated with RV end-diastolic volume in most studies. Only

Koch et al. could not demonstrate a relation between BNP and end-diastolic RV diameter (27). Although, as they say, their retrospective study design has led to echocardiographic assessment of RV dimensions by variable investigators over several years, which might not have been accurate enough to detect a correlation.

Single ventricle. Patients with univentricular hearts and a Fontan circulation comprise a large scala of CHD. Ventricular function is crucial in the long-term prognosis of Fontan patients. Because of the variable and enlarged ventricular anatomy reliable estimates of ventricular function with echocardiography are difficult to obtain and, preferably, CMR imaging should be used. Nevertheless, Robbers-Visser et al. (45) could not demonstrate a correlation between CMR-derived function parameters, primarily because the majority of patients presented with BNP levels within the normal range.

Interestingly, BNP levels in asymptomatic patients after TCPC were comparable to those of healthy controls, unlike BNP levels in asymptomatic Fallot or systemic RV patients. Completion of the Fontan circulation will cause unloading of the ventricle, which could explain lower BNP as BNP relates with ventricular volume load. However, a strong correlation between BNP and severity of heart failure was found in symptomatic patients. Therefore, BNP assessment in patients after TCPC may indeed contribute to early detection of heart failure.

Study limitations. Most studies were performed cross-sectionally and originally not designed to assess BNP. Furthermore, overall investigated patient numbers were small, the used cardiac function parameters varied largely, and limited follow-up data are currently available. Therefore, future research should be done in a large prospective study, preferably with sequential BNP and cardiac function assessment to determine the true prognostic value of BNP for patients with CHD.

Conclusions

This systematic review has demonstrated BNP levels to be elevated in patients after correction for tetralogy of Fallot and in patients with a systemic RV, whereas BNP mainly correlated with end-diastolic RV dimensions and pulmonary regurgitation in Fallot patients and RV function in systemic RV patients. Patients with a univentricular heart had elevated BNP levels before completion of the Fontan circulation or when symptomatic, revealing a clear association between BNP and NYHA class. However, to elucidate the prognostic value of BNP assessment in CHD, a large, well-designed, prospective study is warranted.

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