Aminoterminal brain-type natriuretic peptide levels correlate with heart failure in patients with bidirectional Glenn anastomosis and with morbidity after the Fontan operation

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Objective: The aims of this study were to generate normal values of aminoterminal pro-brain natriuretic peptide in children with a bidirectional Glenn anastomosis without congestive heart failure and to test the hypothesis that plasma levels of aminoterminal pro-brain natriuretic peptide correlate with the clinical severity of congestive heart failure and morbidity after the Fontan operation.

Methods: Aminoterminal pro-brain natriuretic peptide plasma levels of 78 patients after the bidirectional Glenn operation with a median age of 3.2 years and a median follow-up time of 3 years were measured by using an automated enzyme immunoassay. The severity of heart failure was quantified by using the New York University Pediatric Heart Failure Index.

Results: The 97.5th percentile of aminoterminal pro-brain natriuretic peptide level in patients without congestive heart failure was 339 pg/mL. Aminoterminal pro-brain natriuretic peptide levels strongly correlated with the New York University Pediatric Heart Failure Index score ($P < .001$). In patients with congestive heart failure (31/78), the aminoterminal pro-brain natriuretic peptide levels were significantly higher (median, 670 pg/mL) than in patients without congestive heart failure (median, 171 pg/mL). In 41 patients who underwent the Fontan operation, the time to removal of chest tubes and the length of hospital stay positively correlated with the preoperative value of aminoterminal pro-brain natriuretic peptide.

Conclusions: In children with a bidirectional Glenn anastomosis without signs of heart failure, aminoterminal pro-brain natriuretic peptide levels were within the normal range and correlated with the severity of congestive heart failure. Further studies are needed to determine whether aminoterminal pro-brain natriuretic peptide levels can aide clinicians in the early detection of congestive heart failure in this patient group.

Atrial natriuretic peptide and brain natriuretic peptide (BNP) are natriuretic hormones secreted from the atrial and ventricular cardiac myocytes in response to an increase in ventricular wall stretch and filling pressures.¹ Hypoxia also has been shown to be a direct stimulus for secretion of atrial natriuretic peptide and BNP in human cardiac myocytes.² Concentrations of BNP and its biologically inactive aminoterminal fragment, aminoterminal pro-brain natriuretic peptide (NT-pro-BNP), are of high relevance in the diagnosis and treatment of adults with congestive heart failure (CHF).³⁻⁶ Several investigators established age-related reference values for BNP and NT-pro-BNP in healthy children.⁷⁻⁹ Both peptides have been found to be useful markers in a variety of cardiac diseases in children and adolescents.¹⁰⁻¹⁵ Early and minor deteriorations of single-ventricle

function are difficult to assess by means of echocardiographic analysis, and clinical signs usually appear very late. Therefore, it can be speculated that a laboratory parameter like NT-pro-BNP can help to detect CHF in patients with univentricular hearts. Thus far, data on the usefulness of natriuretic peptides in detecting heart failure in children with single-ventricle physiology after bidirectional Glenn (BDG) anastomosis are limited.¹⁶⁻¹⁸

The aims of this prospective study were to generate normal values of NT-pro-BNP in children with BDG but without CHF and to test the hypothesis that preoperative plasma levels of NT-pro-BNP correlate with the severity of CHF, as well as with morbidity after the Fontan operation.

MATERIALS AND METHODS

From September 2004 to December 2007, NT-pro-BNP plasma levels of 78 patients after the BDG operation were measured with an automated enzyme immunoassay (Elecys 2010; Roche Diagnostics, Basel, Switzerland). The study group included 33 patients who had their routine check-up appointment in the outpatient's clinic and 45 hospitalized patients who underwent either elective cardiac catheterization before the Fontan operation (41 patients) or catheter interventions (3 patients required dilatation of aortic coarctation, and 1 patient with hypoplastic left heart syndrome with severe insufficiency of the native aortic valve had placement of a plug into the left ventricular [LV] outflow tract).

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Abbreviations and Acronyms	
BDG	= bidirectional Glenn
BNP	= brain natriuretic peptide
BTS	= Blalock–Taussig shunt
CHF	= congestive heart failure
LV	= left ventricular
NT–pro-BNP	= aminoterminal pro–brain natriuretic peptide
NYUPHFI	= New York University Pediatric Heart Failure Index
RV	= right ventricular

For clinical assessment of CHF, all 78 patients had a chest radiogram, an echocardiogram, and a clinical examination by an experienced pediatric cardiologist. Because there is no special score available for assessment of heart failure in pediatric patients with univentricular hearts, the New York University Pediatric Heart Failure Index (NYUPHFI),¹⁹ a general score for quantifying the severity of heart failure in children, was used. This score is a weighted linear combination of scores based on symptoms, physical signs, and medical regimen (Table 1). Healthy children without heart failure are expected to score low (≤ 2 points). In the NYUPHFI, having a single-ventricle physiology scores with +2 points, and therefore only a NYUPHFI score of 5 or greater was considered to reflect heart failure in patients after the BDG operation.

Age, sex, body weight, cardiac diagnoses, follow-up time after the BDG operation, serum creatinine level, NT–pro-BNP level, morphology of the systemic ventricle, NYUPHFI score, pulse oximetric saturation, and heart/chest ratio on chest radiographic analysis were analyzed in all patients. In the 45 patients who underwent cardiac catheterization, the following hemodynamic parameters were additionally recorded: increase in pressure over time (dp/dt) of the systemic ventricle, mean atrial pressure, and superior vena caval oxygen saturation. Parameters indicating postoperative morbidity (time to removal of chest tubes, length of stay in the intensive care unit, and total length of hospital stay) were analyzed in the 41 patients who underwent the Fontan operation.

The study complies with the Declaration of Helsinki, and informed consent was obtained from the guardian of each subject enrolled in the study.

All patient data were complete; there was no intention to replace missing data. For the subgroup comparison of the nonnormally distributed metric variable NT–pro-BNP (test of normality: Kolmogorov–Smirnov with Lilliefors significance correction) between groups, the nonparametric Mann–Whitney *U* test was used. Spearman’s rank correlation coefficients were calculated. Data are reported as medians with ranges.

RESULTS

The study group included 50 male and 28 female patients with a median age of 3.2 years (range, 0.9–9.8 years) and a median weight of 14.7 kg (range, 5.9–25 kg). The median follow-up time after BDG anastomosis was 3 years (range, 0.6–5.4 years).

Anatomy and Surgical Procedures

Fifty-four patients had a systemic ventricle of right ventricular (RV) morphology, with hypoplastic left heart syndrome as the most common diagnosis (*n* = 45); 20 patients had a systemic ventricle of LV morphology, with tricuspid atresia as the most common anatomy (*n* = 12);

TABLE 1. New York University Pediatric Heart Failure Index

Score	Signs and symptoms
+2	Abnormal ventricular function or valve insufficiency determined by means of echocardiographic analysis
+2	Dependent edema or pleural effusion or ascites
+2	Failure to thrive or cachexia
+1	Marked cardiomegaly determined by means of radiographic analysis or physical examination
+1	Reported physical activity intolerance or prolonged feeding time
+2	Poor perfusion determined by means of physical examination
+1	Pulmonary edema determined by means of radiographic analysis or auscultation
+2	Resting sinus tachycardia
+2	Retractions
	Hepatomegaly
+1	<4 cm below costal margin
+2	>4 cm below costal margin
	Observed tachypnea or dyspnea
+1	Mild to moderate
+2	Moderate to severe
Medications	
+1	Digoxin
	Diuretics
+1	Low-to-moderate dose
+2	High dose or >1 diuretic
+1	ACE inhibitors or other vasodilators or angiotensin receptor blockers
+1	β -Blockers
+2	Anticoagulants not related to prosthetic valves
+2	Antiarrhythmic agents or implantable cardiac defibrillator
Physiology	
+2	Single ventricle

Heart failure severity is determined based on signs and symptoms, medical regimen, and ventricular physiology. Adding scores attributed to each individual criterion derives a total score. Scores can range from 0 (no heart failure) to 30 (severe heart failure). ACE, Angiotensin-converting Enzyme.

and 4 patients had a systemic ventricle of undetermined morphology.

Surgical Procedures in Patients Without CHF

Forty-seven patients had a NYUPHFI score of less than 5 and were considered not to have CHF by the pediatric cardiologist, who was blinded to the NT–pro-BNP levels and the results of cardiac catheterization. Twenty-seven of 47 patients without CHF had a systemic RV morphology (20 cases of hypoplastic left heart syndrome and 7 cases of double-outlet right ventricle with transposition of the great arteries combined with either mitral or pulmonary atresia). As a primary palliative step, 18 of these patients had a Norwood stage I procedure with a right ventricle–pulmonary artery conduit, 5 patients had a Norwood stage I procedure with Blalock–Taussig shunt (BTS), 3 patients had a BTS, and 1 patient needed no operation before the BDG anastomosis. Eighteen of 47 patients had a systemic LV morphology (10 cases of tricuspid atresia, 4 cases of tricuspid atresia

TABLE 2. Patients' characteristics and NT-pro-BNP levels

	All patients	Systemic LV morphology	Systemic RV morphology	Undetermined ventricular morphology
No. of patients	78	20	54	4
Age (y), median (range)	3.2 (0.9–9.8)	3.5 (1.7–7.8)	3 (0.9–9.8)	2.1 (1.7–3.2)
Patients with CHF (n)	31	2	27	2
NT-pro-BNP (pg/mL), median (range)	670 (290–39,763)	366 (316–416)	721 (290–39,763)	597 (561–634)
Patients without CHF (n)	47	18	27	2
NT-pro-BNP (pg/mL), median (range)	171 (32–355)	110 (32–295)	219 (93–355)	76 (33–182)

CHF, Congestive heart failure; NT-pro-BNP, aminoterminal pro-brain natriuretic peptide.

with transposition of the great arteries, 3 cases of pulmonary atresia with intact ventricular septum, and 1 case of double-inlet left ventricle). In this systemic LV morphology group, the following surgical procedures were performed: 10 BTSs, 4 Norwood stage I procedures with a BTS, and 2 Norwood stage I procedures with a right ventricle–pulmonary artery shunt, and 2 patients needed no operation before BDG surgery. In summary, only 6 of 18 patients without CHF with a systemic LV morphology primarily required cardiac surgery compared with 23 of 27 patients with a systemic RV morphology.

Assessment of CHF and NT-Pro-BNP Levels

Thirty-one patients were considered to have clinical signs of CHF with a NYUPHFI score of 5 or greater (median, 6.5; range, 5–19). The following signs of CHF were found in these 31 patients: abnormal ventricular function or relevant valve insufficiency by means of echocardiographic analysis (14 patients), edema (2 patients), failure to thrive (7 patients), cardiomegaly by means of radiographic analysis (27 patients), hepatomegaly (12 patients), sinus tachycardia (15 patients), retractions (2 patients), treatment with digoxin (3 patients), low-dose diuretics (23 patients), high-dose diuretics (8 patients), angiotensin-converting enzyme inhibitors (27 patients), and β -blocker medication (2 patients). In patients with clinical signs of CHF (31/78 patients), the NT-pro-BNP levels were significantly higher (median, 670 pg/mL; range, 290–39,763 pg/mL) than in patients without CHF (median, 171 pg/mL; range, 32–355 pg/mL; Table 2). NT-pro-BNP levels strongly correlated with the NYUPHFI score ($P < .001$; Figure 1 and Table 3), but no correlation was found between the follow-up time and NT-pro-BNP levels (Table 3). Median oxygen saturation measured by means of pulse oximetry of the 47 patients without CHF was 83% (range, 71%–88%) and did not correlate with NT-pro-BNP levels (Table 3).

The 95th and the 97.5th percentile of NT-pro-BNP levels in patients without CHF were 334 pg/mL and 339 pg/mL, respectively. NT-pro-BNP levels in patients without CHF and a RV morphology of the systemic ventricle were significantly higher compared with those seen in patients with LV morphology of the systemic ventricle (Table 2). Because renal function influences NT-pro-BNP levels, we ensured

that patients had no signs of renal dysfunction and all serum creatinine levels were within the normal range, with a median of 0.31 mg/dL (range, 0.2–0.65 mg/dL).

Hemodynamic Data

Forty-five patients underwent cardiac catheterization. There was a positive correlation found between mean atrial pressure (median, 7 mm Hg; range, 4–15 mm Hg) and NT-pro-BNP levels (Table 3). dp/dt measurement of the systemic ventricle (median, 1005 mm Hg/s; range, 330–1445 mm Hg/s) and superior vena caval saturation (median, 67%; range, 56%–76%) negatively correlated with NT-pro-BNP levels (Table 3).

Outcome

Six patients with severe heart failure (NYUPHFI score, 10–19) had the highest NT-pro-BNP levels (1192–39,763 pg/mL). Four of these 6 patients died from heart failure during the study period, 1 patient underwent successful heart transplantation, and 1 patient remained stable with medical treatment. NT-pro-BNP levels were significantly higher ($P < .001$) in the 5 patients who died of heart failure or required heart transplantation when compared with those seen in the other study patients who did not reach these end points.

FIGURE 1. Scatter plot of aminoterminal pro-brain natriuretic peptide (NT-pro-BNP) levels (x-axis) and New York University Pediatric Heart Failure Index scores (y-axis) in all 78 patients.

TABLE 3. Correlation of NT-pro-BNP levels with CHF and signs of morbidity after the Fontan operation

Analyzed parameters	n	Correlation coefficient	P value
Correlation of NT-pro-BNP level and NYUPHFI score (all patients)	78	0.899	<.001
Correlation of NT-pro-BNP level and F/U time (patients without CHF)	47	0.117	.44
Correlation of NT-pro-BNP level and pulse oximetric saturation (patients without CHF)	47	0.026	.86
Hemodynamic data			
Correlation of NYUPHFI and dp/dt	45	-0.571	<.001
Correlation of NT-pro-BNP level and dp/dt	45	-0.582	<.001
Correlation of NT-pro-BNP level and mean atrial pressure	43	0.375	.013
Correlation of NT-pro-BNP level and SV _O ₂	43	-0.373	.014
Morbidity after the Fontan operation			
Correlation of NT-pro-BNP level and time to removal of chest tubes	41	0.406	<.01
Correlation of NT-pro-BNP level and length of stay in ICU	41	0.307	.051
Correlation of NT-pro-BNP level and total length of hospital stay	41	0.328	.036

NT-pro-BNP, Aminoterminal pro-brain natriuretic peptide; CHF, congestive heart failure; NYUPHFI, New York University Pediatric Heart Failure Index; F/U, follow-up; dp/dt, increase in pressure over time; SV_O₂, superior vena caval saturation; ICU, intensive care unit.

Outcome After the Fontan Operation

Forty-one patients of the study group underwent the Fontan operation. All received fenestrated Fontan tunnels, except 2 patients with significant pulmonary arteriovenous malformations. There were no early or late deaths in this group. Regarding postoperative morbidity, preoperative NT-pro-BNP levels positively correlated with time to removal of chest tubes (median, 9 days; range, 4–42 days)

and length of total stay in the hospital (median, 17 days; range, 10–57 days) after the Fontan operation. The preoperative NT-pro-BNP levels did not correlate with the length of stay in the intensive care unit (median, 6 days; range, 1–34 days) after the Fontan operation.

DISCUSSION

In the present study NT-pro-BNP levels in patients later than 6 months after BDG anastomosis without signs of CHF were comparable with those reported in healthy children, with the same enzyme immunoassay test kit used (Table 4). As previously reported by Holmgren and colleagues,¹⁷ we found significantly higher NT-pro-BNP levels in patients with systemic RV morphology compared with those seen in patients with systemic LV morphology. This finding might reflect the fact that despite apparently normal ventricular function, the morphologic right ventricle might be more stressed as a systemic ventricle than the morphologic left ventricle. A further explanation for this finding might be that patients with systemic LV morphology experienced less neonatal cardiac surgeries and less placement of a right ventricle-pulmonary artery conduit compared with patients with systemic RV morphology.

NT-pro-BNP levels strongly correlated with the severity of CHF assessed with the NYUPHFI, as well as with hemodynamic signs of CHF invasively assessed by means of dp/dt measurement. This was not surprising and is in accordance with previous studies on the usefulness of BNP and NT-pro-BNP levels in detecting heart failure and volume overload in patients with congenital heart disease.¹⁰⁻¹⁵ Especially in patients with univentricular hearts, quantitative assessment of ventricular function and early detection of dysfunction is of greatest importance but is still an unsolved problem. With regular measurements of NT-pro-BNP levels in the individual follow-up of patients after the BDG operation, clinicians might have an additional useful tool for early detection of CHF. However, NT-pro-BNP levels do not allow quantitative assessment of ventricular function. In this study the 97.5th percentile of NT-pro-BNP level in patients without CHF was found to be 339 pg/mL (295 pg/mL in patients with RV morphology and 345 pg/mL in patients with LV morphology). In the routine follow-up of patients later than 6 months after the BDG operation, higher levels should lead to a careful work-up involving all available diagnostic modalities and to consideration of initiation

TABLE 4. NT-pro-BNP levels in healthy children compared with those seen in patients after the BDG operation

Study	No. of patients	Age range (y)	NT-pro-BNP (pg/mL), median	NT-pro-BNP (pg/mL), range	NT-pro-BNP upper limits (pg/mL)	Remarks
Present study	47	0.9–9.8	171	32–355	334 (95th percentile)	Patients after Glenn operation without CHF
Nir and coworkers ²⁰	58	0.3–15	90	5–391	348.6 (95th percentile)	Healthy children
Koch and coworkers ²¹	46	0.4–17.5	35.5	10–298	Not available	Healthy children

NT-pro-BNP, Aminoterminal pro-brain natriuretic peptide; BDG, bidirectional Glenn; CHF, congestive heart failure.

or modification of a medical regimen. Because there was no correlation found between pulse oximetric saturation and NT-pro-BNP levels of patients without CHF, this study could not confirm the finding of Hopkins and associates² that hypoxia stimulates secretion of BNP. The finding that superior vena caval saturations measured during cardiac catheterization negatively correlate with NT-pro-BNP levels is not caused by increased NT-pro-BNP levels secondary to hypoxia; it more likely reflects low cardiac output in patients with CHF.

The preoperatively analyzed NT-pro-BNP levels correlated with the duration of excessive pleural fluid drainage after the Fontan operation, indicating that the presence of heart failure prolongs the adaption to the special hemodynamic conditions of any Fontan operation. We speculate that achieving normal preoperative NT-pro-BNP levels by optimizing medical treatment might result in less postoperative morbidity, especially in patients with clinically undetected heart failure. This hypothesis remains to be proved in future studies.

CONCLUSIONS

NT-pro-BNP levels of patients later than 6 months after BDG anastomosis without CHF should not exceed those of healthy children. Plasma NT-pro-BNP concentrations strongly correlate with the severity of heart failure after BDG anastomosis. Further studies are needed to determine whether NT-pro-BNP levels can aide clinicians in the early detection of CHF in this patient group. Patients with failure of normalization or an increase of NT-pro-BNP levels later than 6 months after surgical intervention should be carefully assessed for signs of heart failure and hemodynamic problems. Preoperative optimization of ventricular function might positively influence the postoperative morbidity of patients undergoing the Fontan operation.

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