B-Type Natriuretic Peptide in Patients with Systemic Right Ventricle

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Key Words

B-type natriuretic peptide • Systemic right ventricle • Atrial switch • Tricuspid regurgitation

Abstract

Objective: To examine the diagnostic value of B-type natriuretic peptide (BNP) in patients with systemic right ventricle. **Methods:** Plasma BNP levels were measured in 48 outpatients with D-transposition of the great arteries after atrial switch procedure or congenitally corrected transposition of the great arteries. **Results:** Plasma BNP was ≤ 20 pg/ml in 52% and < 200 pg/ml in all patients, significantly higher in females compared to males ($p = 0.004$), and positively correlated with age ($r = 0.3$, $p = 0.04$). New York Heart Association class I patients had significantly lower BNP than class II patients ($p = 0.03$). A positive correlation was found between BNP and severity of tricuspid regurgitation ($r = 0.5$, $p < 0.001$). Plasma BNP was weakly, negatively correlated to maximum exercise capability, peak oxygen uptake, maximum heart rate during exercise testing and minimal heart rate in the 24-hour Holter monitoring. Additionally, BNP was negatively correlated with flow velocity across the pulmonary valve in patients with congenitally corrected transposition of the great arteries ($r = -0.81$, $p = 0.03$). **Conclusion:** Plasma BNP is normal in patients with systemic right ventricle, but increases

with deterioration of clinical status and decreasing exercise capability. BNP is positively correlated with severity of tricuspid regurgitation, a prognostic factor for survival.

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Right ventricular morphology and function are of great importance in the rapidly growing field of congenital heart disease [1]. In particular, there is a large cohort of young adults with a right ventricle supporting the systemic circulation. These patients had congenitally corrected transposition of the great arteries (ccTGA) or had undergone the Senning or Mustard procedure more than 20 years ago before the atrial switch procedure was replaced by the arterial switch procedure [2]. The progressive deterioration of right ventricular function and the potential for right ventricular failure are main issues in the long-term follow-up of these patients [1, 2].

B-type natriuretic peptide (BNP) is a hormone with diuretic, natriuretic, vasodilatory and antifibrotic properties secreted mainly by cardiac myocytes in response to volume expansion and pressure load [3, 4]. Plasma levels of both BNP and the N-terminal fragment of its prohormone (NT-proBNP) have emerged as sensitive tests for the diagnosis and prognosis of left heart failure [4, 5]. In addition, there is a growing interest in the use of these

peptides in other conditions such as hypertrophic cardiomyopathy [6], myocardial infarction [7] or congenital heart disease [8–11]. Recent reports suggest a role for natriuretic peptides to detect right ventricular dysfunction, for example in patients with surgically corrected tetralogy of Fallot [12, 13]. The purpose of this study was to assess the diagnostic validity of plasma BNP on patients with systemic right ventricle.

Methods

Study Population

From 2002 to 2006, we measured plasma BNP in all patients with systemic right ventricle who came to our outpatient clinic for follow-up or diagnostic work-up, including venous puncture. These patients were in the supine position during blood sampling, and venipuncture was typically performed between 8:30 and 11:00 a.m. after 10 min of rest.

48 patients (14 females, 34 males; aged 9.6–37.7 years, mean age 19.0, standard deviation ± 5.0 , median age 17.8) were analysed retrospectively (table 1). 41/48 patients had D-transposition of the great arteries after atrial switch procedure (D-TGA); 7/48 patients had ccTGA (3/7 patients after surgical closure of a ventricular septal defect, 4/7 without any surgery).

All 48 patients underwent physical examination, transthoracic echocardiography and standard 12-lead electrocardiogram at the same visit when BNP samples were taken. In addition, 24-hour Holter monitoring and exercise testing on an upright bicycle ergometer were performed in 41/48 and 46/48 patients, respectively. Time interval between BNP measurement and 24-hour Holter monitoring was 0–6 months. Exercise testing was performed at the day of BNP measurement.

All 48 patients were asymptomatic or minimally symptomatic [New York Heart Association (NYHA) classification I (41/48) or II (7/48)].

The study was approved by the local ethics committee.

Sample Collection

Venous samples were collected into tubes containing potassium ethylenediaminetetraacetic acid. BNP was measured immediately by a sandwich immunoassay (Triage BNP assay; Biosite® Diagnostics Inc., San Diego, Calif., USA). The assay uses a murine polyclonal, fluorescent-tagged BNP antibody to label the BNP molecules and immobilized murine monoclonal antibody against the ring structure of BNP to bind the BNP-fluorescent antibody complex. Performance of the assay takes 15 min. The measurable range of the BNP assay is <5.0 to 5,000 pg/ml. Precision and sensitivity of the assay have been described by others [14]. Using this assay, median BNP concentrations and corresponding quartiles for normal subjects are 6 pg/ml (5–13 pg/ml; age <10 years), 7 pg/ml (5–20 pg/ml; age 10–20 years), 7 pg/ml (5–40 pg/ml; age >20–35 years) and 8 pg/ml (5–39 pg/ml; age >35–44 years) [14, 15].

Plasma BNP levels of the patients were compared to clinical, spiroergometric, echocardiographic and electrocardiographic data.

Table 1. Clinical data

	Males (n = 34)	Females (n = 14)
D-TGA/ccTGA	28/6	13/1
Age, years	19.0 (5.5)	19.2 (3.6)
Height, cm	171.4 (10.1)	165.0 (5.5)
Body weight, kg	61.8 (14.7)	57.8 (7.5)
Body mass index	20.8 (3.8)	21.2 (2.3)
NYHA class I/II	29/5	12/2

Data are presented as means with SD in parentheses.

Statistical Analysis

Plasma BNP levels are expressed as medians with interquartile ranges in parentheses. Statistical differences between the diagnostic groups, NYHA stage and the 2 sexes were evaluated using the rank score test to unpaired data (Wilcoxon rank-sum test). Because the distribution of plasma BNP values was positively skewed, correlation and regression analyses were performed using natural log-transformed BNP values. The associations of ln BNP with age, body height and body mass index were assessed by univariate regression analyses; the associations of ln BNP with echocardiographic indices were assessed by Spearman's correlation coefficient. p values were two-tailed, with a value <0.05 considered to be significant. All data were analysed with SPSS 14.0 for Windows®.

Results

BNP Levels

Plasma BNP concentration was between 5 and 198 pg/ml in all patients [20 (11–31) pg/ml]. 25/48 patients had low BNP levels ≤ 20 pg/ml. In 15/48 patients, BNP concentration was 21–35 pg/ml and 8/48 patients had BNP plasma levels of 50–200 pg/ml (fig. 1).

BNP and Baseline Clinical Data

Plasma BNP was significantly higher in females than males [31 (18–97) vs. 18 (9–26) pg/ml; $p = 0.004$]. There was a positive correlation between plasma BNP and age ($r = 0.3$, $p = 0.038$).

There was no difference in BNP plasma concentration between patients with ccTGA and D-TGA [both sexes together: 27 (9–32) vs. 19 (11–31) pg/ml, $p = 0.75$; males: 21 (9–57) vs. 18 (8–24) pg/ml, $p = 0.44$; females: 29 (29–29) vs. 33 (18–100) pg/ml, $p = 0.90$].

NYHA class I patients had significantly lower plasma BNP levels than NYHA class II patients [19 (9–29) vs. 32 (20–193) pg/ml; $p = 0.028$].

Fig. 1. Plasma BNP concentration according to age in 48 patients with D-TGA after atrial switch procedure (squares) or ccTGA (diamonds). Dark grey symbols represent males, light grey symbols females.

There was no correlation between BNP and body weight, body height or body mass index.

BNP and Echocardiographic Data

There was a positive correlation between plasma BNP and severity of tricuspid regurgitation (TR; scale I–IV according to the colour flow mapping of the regurgitation jet). The following BNP values were observed: no TR: 11 (9–13) pg/ml, TR I: 18 (9–24) pg/ml, TR I–II: 19 (10–28) pg/ml, TR II: 33 (29–86) and TR >II: 115 (32–198) pg/ml ($r = 0.50$, $p < 0.001$; fig. 2).

No association of BNP was found with left ventricular shortening fraction (parasternal short-axis and long-axis view), right ventricular diastolic diameter or ratio of right ventricular diastolic diameter to left ventricular diastolic diameter (apical four-chamber view).

In addition, no association was found between BNP and left ventricular outflow tract obstruction in the total group of patients. However, in the subgroup of patients with ccTGA, BNP was negatively correlated with severity of left ventricular outflow tract obstruction ($r = -0.81$, $p = 0.027$; fig. 3). In patients with flow velocity across the pulmonary valve <2 m/s, BNP was 12 (8–25) pg/ml; in patients with flow velocity 2–4 m/s, BNP was 27 pg/ml; in patients with flow velocity >4 m/s, BNP was 82 (32–131) pg/ml.

BNP and Spiroergometric Data

Mean maximum exercise capability was 2.3 ± 0.5 $W \cdot kg^{-1}$ in male and 1.9 ± 0.3 $W \cdot kg^{-1}$ in female patients. Plasma BNP decreased significantly with increasing maximum exercise capability ($r = -0.39$, $p = 0.008$; fig. 4). In addition, plasma BNP was negatively correlated with

Fig. 2. BNP plasma concentration according to severity of TR. Dark grey symbols represent males, light grey symbols females.

Fig. 3. Correlation of BNP plasma concentration to flow velocity across the pulmonary valve in patients with ccTGA. Dark grey symbols represent males, light grey symbols females.

peak oxygen uptake ($r = -0.35$, $p = 0.020$) during exercise testing.

BNP and Electrocardiogram

There was no difference in BNP levels in patients with ($n = 6$) or without ($n = 42$) pacemaker [17 (11–39) vs. 22 (9–32) pg/ml, $p = 0.69$], nor in patients with ($n = 20$) or without ($n = 28$) sinus node dysfunction [21 (16–47) vs. 17 (8–29) pg/ml, $p = 0.13$]. However, there was a negative correlation between minimal heart rate in the 24-hour Holter monitoring and plasma BNP ($r = -0.35$, $p = 0.025$; fig. 5). Additionally, BNP was also negatively correlated with the maximum heart rate during exercise ($r = -0.29$, $p = 0.049$). No correlation was found between BNP and QRS duration. There was no difference in plasma BNP in patients with ($n = 9$) or without ($n = 32$)

Fig. 4. Correlation of BNP plasma concentration to maximum exercise capability (a) and peak oxygen uptake during exercise testing (b). Dark grey symbols represent males, light grey symbols females.

ventricular arrhythmia documented by Holter monitoring.

Longitudinal BNP Data

Additional BNP measurements at follow-up were available in 14 patients. The time interval between the 2 visits was 0.8–3.2 years [median 1.4 (interquartile range 1.0–1.9) years]. In 10/14 patients, plasma BNP level at follow-up was almost unchanged (difference up to ± 5 pg/ml in 5 patients and ± 11 pg/ml in 5 other patients). There was a mild increase of up to 33 pg/ml in 3 patients (from 8 to 26 pg/ml within 1.6 years, from 48 to 77 pg/ml within 1.5 years and from 22 to 55 pg/ml within 3.2 years); no change in clinical or other findings was identifiable. In 1 patient, BNP had decreased from 40 to 16 pg/ml within 2.5 years; clinical and echocardiographic findings had not changed (NYHA I, TR I), and maximum exercise capability had slightly increased (from 1.8 to 2.1 $\text{W} \cdot \text{kg}^{-1}$).

Additionally, BNP was measured in a patient with atrial flutter and 2:1 atrioventricular block before and 1 day after electric cardioversion. Plasma BNP decreased from 69 pg/ml (atrial rate 250 beats/min, ventricular rate 125 beats/min) to 27 pg/ml (sinus rhythm, heart rate 79 beats/min).

Discussion

BNP and NT-proBNP are useful not only in patients with congestive heart failure, but also in patients with congenital heart disease [8–11]. Some reports have evaluated the role of natriuretic peptides to detect right ven-

Fig. 5. BNP plasma concentration according to minimal heart rate in the 24-hour Holter monitoring. Dark grey symbols represent males, light grey symbols females.

tricular dysfunction in patients with normal connections, for example in patients with surgically corrected tetralogy of Fallot [12, 13]. However, there are only scattered data on BNP in patients with systemic right ventricle, usually assessed in heterogeneous groups of patients with miscellaneous congenital heart disease [8, 9, 12]. We are not aware of any studies focussing on patients with systemic right ventricle. Therefore, we tried to systematically evaluate BNP levels in a relatively homogeneous group of patients with D-TGA after atrial switch procedure or with ccTGA.

Plasma BNP concentration was low in the majority of cases and slightly increased in a few. Indeed, the highest BNP plasma level was less than 200 pg/ml. We found significantly higher BNP levels in female patients and a cor-

relation between plasma BNP and age. A comparable sex-related difference and a comparable moderate increase with increasing age have been reported in healthy adolescents and adults [15–17]. However, even in the third decade of life some patients had low BNP plasma levels. Therefore, our data suggest normal BNP levels in patients with systemic right ventricle without additional problems. Furthermore, these findings correspond well with the clinical experience showing that the right ventricle is capable of performing as the systemic pumping chamber for several decades [2, 17–20].

Our results of only slightly increased BNP plasma levels are in agreement with recent studies indicating a slightly higher increase in natriuretic peptides in patients with congenital heart disease compared to adults with acquired left ventricular dysfunction [9, 11, 12, 21]. Recent reports have described a good correlation between NYHA class and BNP also in patients with surgically treated congenital heart disease [8, 21]. Although there were no BNP levels of class III or IV patients available, our data suggest a positive correlation between BNP and NYHA classification in patients with systemic right ventricle comparable to patients with normal connections. Almost all patients were asymptomatic, but maximum exercise capability was reduced compared to healthy subjects. We found a significant correlation between increasing BNP plasma level and both decreasing exercise capability and decreasing peak oxygen uptake during exercise testing. Similar inverse correlation of BNP and NT-proBNP with peak oxygen uptake was recently reported in patients after surgical repair of Fallot's tetralogy [22, 23]. In addition, we found negative correlation between BNP and maximum heart rate during exercise. In adults with miscellaneous congenital heart disease, Kambiz et al. [24] found lower maximal heart rate during exercise associated with heart failure, defined as increased NT-proBNP level and decreased peak oxygen uptake.

Interestingly, BNP was also negatively correlated with minimal heart rate in the 24-hour Holter monitoring. This finding might indicate an association of BNP with the frequent loss of regular sinus rhythm in patients with D-TGA after atrial switch procedure [19]. Actually, this correlation was more pronounced in the latter patient group. Elevated plasma BNP during atrial flutter and normal BNP concentration during sinus rhythm in the same patient after cardioversion are compatible findings to this result. However, patients with sinus node dysfunction had discreet, but non-significant higher BNP levels compared to patients without sinus node dys-

function. A correlation between gadolinium uptake suggestive for myocardial fibrosis and documented arrhythmia has been reported in patients with systemic right ventricle [25]. We found no association between BNP and documented ventricular arrhythmia. Additionally, QRS prolongation over time has been described in patients with systemic right ventricle and correlated with right ventricular diastolic volume [20, 25, 26]. However, we found no association between BNP and QRS duration. This discrepancy might be based on the good clinical status of our patients. Prospective longitudinal data on BNP together with individual change in QRS duration might provide additional information. We could not find a correlation between BNP and right ventricular dimension measured by transthoracic echocardiography. Possibly, the assessment of right ventricular dimension in the four-chamber view by variable investigators over several years was not accurate enough to detect a correlation.

The strongest positive correlation was found between plasma BNP and severity of TR. A positive correlation between NT-proBNP and severity of pulmonary regurgitation has been described in patients with repaired tetralogy of Fallot [27]. Consistently, right ventricular volume overload is described to induce an increase in BNP. This has been shown in the blood of patients with congenital heart disease [13, 27, 28], but also directly in animal experiments by quantification of myocardial mRNA [29]. Some authors also found increased brain natriuretic peptides in patients with chronic right ventricular pressure load [12, 30]. However, others did not [13]. These data are less conflicting when additional results are taken into account. Together with increased pulmonary artery pressure and resistance, increased right ventricular pressure load is strongly associated with increased BNP [11, 31, 32], but isolated pressure load of the right ventricle due to pulmonary banding, pulmonary valve stenosis or uncorrected tetralogy of Fallot did not cause an increase in BNP [11, 29]. Therefore, additional factors may contribute to increased plasma BNP in right ventricular pressure load, for example additional volume load or the impaired myocardial architecture after surgery including incision of the right ventricle.

In patients with ccTGA, obstruction of left ventricular outflow tract is found in 30–50% of cases [33]. In this subgroup, BNP was negatively correlated with severity of left ventricular outflow tract obstruction. The finding of low BNP plasma concentration in patients with moderate to severe pulmonary valve stenosis is in line with the clinical feature. Architecture of the heart in patients

with systemic right ventricle profits from a greater pressure in the left ventricle by minimizing the paradoxical bulging of the interventricular septum. Correspondingly, banding of the pulmonary artery has been shown to improve the functional class in such patients [34, 35]. Without obstruction, the shift of the ventricular septum towards the morphologically left ventricle produces distortion of the subvalvular apparatus of the tricuspid valve, and promotes regurgitation across the systemic valve in concert with progressive dysfunction of the right ventricle [36].

In conclusion, determination of plasma BNP may be useful in the long-term management of patients with systemic right ventricle. In general, BNP values are normal in patients without additional problems. BNP is negatively correlated with clinical status, exercise capability and peak oxygen uptake. Additionally, BNP plasma level is

positively correlated with severity of TR, one of the most important prognostic factors for survival of these patients [20, 37].

Limitations

The homogeneity of our study population increases the reliability of correlations partly based on small numbers of patients. On the other hand, the lack of patients with NYHA III–IV limits the study. In addition, there were no patients with severe TR. Therefore, the data reported here cannot necessarily be extrapolated to sicker patients, although it can be speculated that the correlations would be strengthened by including NYHA III–IV patients and patients with severe TR.

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