N-terminal pro-brain natriuretic peptide in the diagnosis of congestive heart failure in pediatric patients with ventricular septal defect

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Original article

Background: **The plasma concentrations of brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) can reflect cardiac function and therefore can be used for the diagnosis of congestive heart failure (CHF) and the evaluation of cardiac function. However, few studies focused on BNP and NT-proBNP in pediatric patients with congenital heart defects. The aim of this study was to assess the value of NT-proBNP in the diagnosis of patients with ventricular septal defect (VSD) and congestive heart failure.**

Methods: **Fifty-one children with VSD aged from 2 months to 2 years (mean 7.9 months) were enrolled in this study. According to the modified Ross Score, they were divided into 3 groups: 20 patients without CHF (score 0-2), 18 patients with mild CHF (score 3-6), and 13 patients with moderate to severe CHF (score 7-12). A group of 15 age-matched healthy children served as controls. The levels of plasma NT-proBNP were determined with an enzyme immunoassay. All participants were subjected to complete echocardiographic examination for measuring left ventricular end diastolic volume index (LVEDVI), left ventricular end systolic wall stress (LVESWS), heart rate-corrected mean velocity of circumferential fibre shortening (mVcFc), left ventricular ejection fraction (LVEF), left ventricular fractional shortening (LVFS), and contractility index (Con). The correlation of plasma NT-proBNP with the modified Ross Score and functional indices measured echocardiographically was analyzed. The sensitivity, specificity and the receiver operating characteristic (ROC) curve for NT-proBNP as a diagnostic marker of CHF were calculated.**

Results: **The levels of plasma NT-proBNP were positively correlated with the modified Ross Score (r=0.75, P<0.01). The levels were significantly higher in patients with moderate to severe CHF (2061±908 fmol/ml) than in those with mild CHF (810±335 fmol/ml), but in the latter the levels were significantly higher than in patients without CHF (309±68 fmol/ml). In 97% of the patients without CHF and healthy controls, the plasma levels were below 400 fmol/ml. In 83% of the patients with mild CHF, the levels ranged from 400 to 1400 fmol/ml, whereas in 85% of the patients with moderate to severe CHF the levels of plasma NT-proBNP were above 1400 fmol/ml. Plasma NT-proBNP was positively correlated with LVEDVI and LVESWS, but it was not correlated with mVcFc, LVEF, LVFS and Con. When plasma NT-proBNP ⩾400 fmol/ml was used as cut-off point for diagnosing CHF, the sensitivity was 89.3%, the specificity was 91.2%, and the area under the ROC curve was 0.944.**

Conclusion: **Plasma NT-proBNP can be used to evaluate cardiac function and diagnose CHF in pediatric patients with VSD.**

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Key words: **N-terminal pro-BNP; congestive heart failure; ventricular septal defect**

Introduction

The plasma concentrations of brain natriuretic peptide (BNP) and N-terminal pro-natriuretic peptide (NT-proBNP) reflect cardiac function and can be used to evaluate the severity of congestive heart failure (CHF).[1-12] Compared with BNP, NT-proBNP shows a number of properties such as stability, higher molecular weight and measurability in the laboratory. Studies found that NT-proBNP is superior to BNP in evaluating cardiac fanction and diagnosing CHF,[13-17] but most of them focused on adult patients

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with congestive heart failure, myocardial infarction, and hypertensive heart disease. To date, little has been known about plasma BNP and NT-proBNP in children with congenital heart disease.[18] Ventricular septal defect is the most common congenital heart defect and also the most common cause of heart failure in children, especially in infants. We analyzed plasma NT-proBNP in pediatric ventricular septal defect (VSD) patients with CHF in order to assess the diagnostic value of the new marker.

Methods

Between May and October 2003, 51 patients (21 girls and 30 boys) with VSD received treatment at Shanghai Children's Medical Center. The patients were between 2 months and 2 years of age (mean age 7.9 months), and 41 (80.4%) of them were younger than one year. The 51 patients were divided into 3 groups according to the modified Ross Score for the diagnosis of heart failure in pediatric patients, with no heart failure (score 0 to 2), mild heart failure (score 3 to 6), and moderate to severe heart failure (score 7 to 12). A group of 15 healthy children served as control subjects. Individual characteristics of the four groups are shown in Table 1. All patients were subjected to echocardiographic examination and plasma NT-proBNP concentrations were measured before echocardiography. All patients had no evidence of neurological diseases, and their renal function and liver function was within the normal range. For the determination of plasma NT-proBNP, blood samples taken by peripheral venous puncture before echocardiography were collected in tubes containing EDTA and aprotinin. Plasma was immediately centrifuged at 4000 r/min for 10 minutes at -4°C, and stored at -80°C. The concentration of plasma NT-proBNP was determined with ELASA (kit purchased from ADR, USA).

Apart from routine assessment of anatomical malformation, echocardiography was used to measure indices of cardiac function and ventricular load. On apical four-chamber view and two-chamber view, left ventricular end-diastolic volume (LVEDV) was determined with the Simpson method and the left ventricular end-diastolic volume index (LVEDVI) was calculated according to the standardization of the surface area. The results of ECG, parasternal short-axis M-mode echocardiography and blood pressure were recorded at the same time for calculating left ventricular end-systolic wall stress (LVESWS) and the heart rate-corrected mean velocity of circumferential fibre shortening (mVcFc) according to the Colan's method.[7] As a combination of LVESWS and mVcFc, the contractility index (Con) was received.[19] Left ventricular fractional shortening (LVFS) and left ventricular ejection fraction (LVEF) were measured at the same time. All indices were measured 4 times and mean values calculated.

The data of the study were presented as mean ±standard deviation. Statistical analysis was made with the SPSS 10.0 software package including correlation analysis, univariate analysis of variance and the graphical presentation of receiver operating characteristic (ROC) curve.

Results

Plasma NT-proBNP concentration and clinical manifestation of CHF

In the 51 patients with VSD, the concentration of plasma NT-proBNP was positively correlated with the clinical CHF score (r=0.75, P<0.01). The concentration of plasma NT-proBNP increased with the severity of clinical presentation. The mean concentration of plasma NT-proBNP in the moderate to severe CHF group was 2061±908 fmol/ml (range from 953 to 3926 fmol/ml), and in the mild CHF group 810±335 fmol/ml (range from 301 to from 1492 fmol/ml), and in the no CHF group 309±68 fmol/ml (range from 192 to 486 fmol/ml), and in the healthy controls 275±62 fmol/ml (range from 181 to 378 fmol/ml). Univariate analysis of variance confirmed that there was significant difference in the four groups (F=35.74, P<0.01), and comparison between each other demonstrated that the plasma concentration in the group with moderate to severe CHF was higher than that in the group with

Table 1. Characteristics of study participants

Group	Cases	Age (mean±SD)	Clinical score
Control	15	2 mon-2 y (13.5±9.1 mon)	all score 0
No CHF	20	3 mon-2 y (11.3±6.1 mon)	3 cases score 0, 7 cases score 1, 10 cases score 2
Mild CHF	18	2 mon-1 y (5.4±3.2 mon)	5 cases score 3, 3 cases score 4, 6 cases score 5, 4 cases score 6
Moderate to severe CHF	13	2 mon-8 mon (2.7±1.1mon)	4 cases score 7, 5 cases score 8, 2 cases score 9, 1 case score 10, 1 case score 11

Table 2. Plasma NT-proBNP concentrations and echocardiographic indices (mean±SD)

Group	Cases	LVEDVI Ml/m^2	LVESWS (g/cm^2)	LVEF (%)	LVFS (%)	Con (circ/s)	mVcFc	NT-proBNP (fmol/ml)
Control	15	48.6±6.3	40.14±8.41	68.1±5.2	36.8±5.2	0.029±0.008	1.30±0.17	275±62
No CHF	20	43.9±7.2	42.5±12.2	68.8±5.6	36.6±4.4	0.025±0.007	1.30±0.24	309±68
Mild CHF	18	74.1±10.5$^{\Delta}$	76.5±14.2$^{\Delta}$	65.8±9.7	34.9±8.3	0.026±0.009	1.28±0.22	810±335$^{\Delta}$
Moderate to severe CHF	13	116.0±36.1$^{\Delta}$	103.82±18.02$^{\Delta}$	67.3±8.1	35.27±6.5	0.023±0.005	1.27±0.15	2061±908$^{\Delta}$
F value		23.14**	32.62**	2.252	1.875	2.047	2.606	35.74**

*: $P<0.05$, **: $P<0.01$; $^{\Delta}$: compared with the patients in the above group, $P<0.05$.

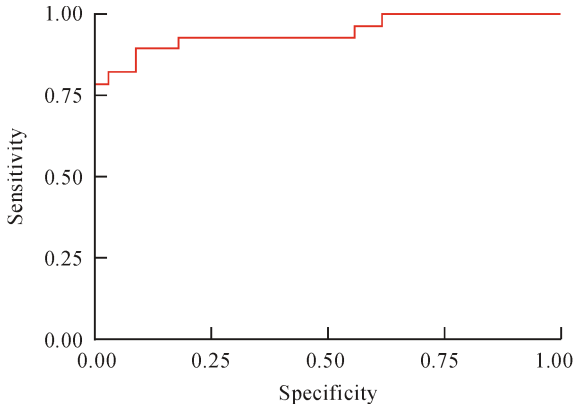

Fig. ROC curve for NT-proBNP as a diagnostic marker of CHF with a cut-off point at 400 fmol/ml.

mild CHF, and that the plasma concentration in the mild group was higher than that in the group with no CHF. No significant difference was found between patients without clinical signs of CHF and healthy controls (Table 2).

In the VSD patients without heart failure and the controls, including 35 children, only one patient had a plasma NT-proBNP concentration above 400 fmol/ml, whereas the remaining 34 (97.1%) had a level below 400 fmol/ml. Fifteen of the 18 patients in the group with mild CHF (83.3%) had a NT-proBNP concentration between 400 and 1400 fmol/ml. In this group, 2 patients had the concentration less than 400 fmol/ml and 1 patient the concentration over 1400 fmol/ml. Finally, 11 (84.6%) of 13 patients in the group with moderate to severe CHF showed a NT-proBNP concentration higher than 1400 fmol/ml, and only 2 patients had the concentration below 1400 fmol/ml.

With a modified Ross Score ⩾3 as a reference standard, the sensitivity of plasma NT-proBNP concentration ⩾400 fmol/ml as a cut-off point for diagnosing CHF was 89.3%, the specificity 91.2%, and the area under the ROC curve 0.944 (Fig.).

Plasma NT-proBNP concentration and echocardiographic indices

Plasma NT-proBNP was shown to be positively correlated with LVESWS (r=0.80, P<0.01) and LVEDVI (r=0.67, P<0.01), whereas it was not correlated with LVEF, LVFS, Con and mVcFc (Table 2). The values of LVESWS and LVEDVI were the highest in patients with moderate to severe CHF, and higher in patients with mild CHF than in those without symptoms of heart failure. No difference was found between the VSD patients without heart failure and controls. LVEF, LVFS, Con and mVcFc did not show any difference between our study groups. However, 2 patients with severe CHF had reduced LVEF and LVFS.

Discussion

Japanese researchers first isolated and purified BNP, a natriuretic polypeptide, in 1988. BNP is secreted by cells of the heart ventricle in response to increased load and wall stress. BNP mRNA triggers the synthesis of proBNP. Upon secretion, proBNP is split into NT-proBNP consisting of 76 amino acids and BNP consisting of 32 amino acids, which is an active hormone. The ratio of NT-proBNP to BNP is 1 in healthy individuals. Impaired cardiac function leads to an increased concentration of both polypeptides, with an higher increase of NT-proBNP than BNP. Thus a higher NT-proBNP/BNP ratio is formed. With a higher molecular weight, NT-proBNP is biologically stable and its blood concentration can be determined more easily. Quantitative analysis has shown that the measured value for NT-proBNP is about 10 times higher than that for BNP.[20] Previous studies showed that NT-proBNP is superior to BNP as a marker of cardiac function.[13-17]

Congestive heart failure is a common clinical syndrome, but clinical symptoms lack specificity, which is particularly true in infants. Clinical scores are used to increase the accuracy in the diagnosis of the disease. The modified Ross Score can be used to grade

the severity of heart failure in children at age of 0 to 14 years in addition to the diagnosis of CHF and the evaluation of cardiac function.[2,21] Since a large VSD is the most common cause of heart failure in infants, we selected VSD patients in our study.

Because of the close correlation between plasma NT-proBNP and modified Ross Score and the high sensitivity and specificity for diagnosing CHF when using a concentration of ⩾400 fmol/ml as the cut-off point, we believe that NT-proBNP can be used as a biochemical marker in the diagnosis and grading of CHF patients.

In VSD patients, the presence of a large left-to-right shunting results in an excessive volume load, and subsequent dilation of the left ventricle which induces the left ventricle afterload overloaded. Increased cardiac volume and afterload are thought to be the main pathophysiological mechanisms leading to heart failure, but not the reduced contractility.[22] Our results show that the plasma concentration of NT-proBNP is correlated with LVEDVI and that both markers are elevated in patients with clinical signs of heart failure, suggesting an association of NT-proBNP concentration and volume load. Plasma NT-proBNP concentration could therefore reflect the degree of volume overload, whereas volume overload, in turn, may be one of the factors leading to increased NT-proBNP levels in CHF patients. LVESWS is a good marker of left-ventricular afterload. Significantly elevated LVESWS in our CHF patients indicated the presence of increased afterload of the left ventricle. The correlation of plasma NT-proBNP with LVESWS also reflects increased afterload. Excessive afterload of the left ventricle may be another factor promoting NT-proBNP secretion. Previous studies demonstrated that myocardial contractility was not reduced in VSD patients with CHF, and the markers reflected heart pump function such as LVEF, LVFS and mVcFc were normal or nearly normal. One of our earlier studies on VSD patients with CHF showed the same results.[23,24] In the present study, only 2 patients with severe CHF had reduced EF, FS and mVcFc, and these markers showed no significant difference between patients with and without CHF. Unlike in previously reported patients with cardiac infarction and dilated cardiomyopathy, no association of NT-proBNP with EF and FS was found in this study. Normal myocardial contractility in VSD patients with CHF may be the leading cause.

In summary, plasma NT-proBNP concentration reflects the severity of clinical symptoms as well as cardiac preload and afterload, which are correlate with the degree of severity of CHF. Thus we concluded that plasma NT-proBNP is a valuable marker for the diagnosis and grading of the severity of children with heart failure, which is identified by other studies on pediatric patients in recent years.[18,25-30] Currently, our clinical work is still influenced by certain undesirable factors including subjective determination of CHF score on the basis of clinical symptoms, technical limitations of cardiac ultrasound examination, and the unfeasibility of invasive data acquisition via heart catheterization. In this situation, NT-proBNP could serve as an objective, simple, non-invasive and economic examination, making follow-up and dynamic observations possible.

One limitation of the present study is the small number of patients with moderate to severe CHF, who are impossible to be differentiated from moderate to severe ones. Moreover, patients with VSD represent one fraction of all children with heart failure. Future studies should clarify whether plasma NT-proBNP can also serve as a diagnostic marker in heart failure caused by other pathological conditions.

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References

1 Mir T, Stephani S, Eiselt M, Grollmus O, Weil J. Plasma concentration of N-terminal pro-brain natriuretic peptide in control children from the neonatal to adolescent period and in children with congestive heart failure. Pediatrics 2002;110: e76-87.
2 Kawai K, Hata K, Takaoka H, Kawai H, Yokoyama M. Plasma brain natriuretic peptide as a noval therapetic indicator in idiopathic dilated cardiomyopathy during β-blocker therapy: a potential of hormone-guided treatment. Am Heart J 2001; 141:925-932.
3 Grzybowski J, Bilinska ZT, Janas J, Michalak E, Ruzyllo W. Plasma concentrations of N-terminal brain natriuretic peptide are raised in asymptomatic relatives of dilated cardiomyopathy patients with left ventricular enlargement. Heart 2002;88:191-192.
4 Talwar S, Downie PF, Squire IB, Davies JE, Barnett DB, Ng LL. Plasma N-terminal proBNP and cardiotrophin-1 are elevated in aortic stenosis. Eur J Heart Fail 2001;3:15-19.
5 Kinnunen P, Vuolteenaho O, Ruskoaho H. Mechanisms of atrial and brain natriuretic peptide release from rat ventricular myocardium: effect of stretching. Endocrinology 1993;132: 1961-1970.
6 Suda K, Matsumura M, Matsumoto M. Clinical implication of plasma natriuretic peptides in children with ventricular septal

defect. Pediatr Int 2003;45:249-254.
7 Spevack DM, Schwartzbard A. B-type natriuretic peptide measurement in heart failure. Clin Cardiol 2004;27:489-494.
8 de Lemos JA, McGuire DK, Drazner MH. B-type natriuretic peptide in cardiovascular disease. Lancet 2003;362:316-322.
9 Maisel AS. The diagnosis of acute congestive heart failure: role of BNP measurements. Heart Fail Rev 2003;8:327-334.
10 Cowie MR, Mendez GF. BNP and congestive heart failure. Prog Cardiovasc Dis 2002;44:293-321.
11 Azzazy HM, Christenson RH. B-type natriuretic peptide: physiologic role and assay characteristics. Heart Fail Rev 2003;8:315-320.
12 Dokainish H, Zoghbi WA, Lakkis NM, Quinones MA, Nagueh SF. Comparative accuracy of B-type natriuretic peptide and tissue Doppler echocardiography in the diagnosis of congestive heart failure. Am J Cardiol 2004;93:1130-1135.
13 Pfister R, Scholz M, Wielckens K, Erdmann E, Schneider CA. Use of NT-proBNP in routine testing and comparison to BNP. Eur J Heart Fail 2004;6:289-293.
14 Mueller T, Gegenhuber A, Poelz W, Haltmayer M. Head-to-head comparison of the diagnostic utility of BNP and NT-proBNP in symptomatic and asymptomatic structural heart disease. Clin Chim Acta 2004;341:41-48.
15 Masson S, Vago T, Baldi G, Salio M, De Angelis N, Nicolis E, et al. Comparative measurement of N-terminal pro-brain natriuretic peptide and brain natriuretic peptide in ambulatory patients with heart failure. Clin Chem Lab Med 2002;40: 761-763.
16 Seino Y, Ogawa A, Yamashita T, Fukushima M, Ogata K, Fukumoto H, et al. Application of NT-proBNP and BNP measurements in cardiac care: a more discerning marker for the detection and evaluation of heart failure. Eur J Heart Fail 2004;6:295-300.
17 Mueller T, Gegenhuber A, Poelz W, Haltmayer M. Biochemical diagnosis of impaired left ventricular ejection fraction—comparison of the diagnostic accuracy of brain natriuretic peptide (BNP) and amino terminal proBNP (NT-proBNP). Clin Chem Lab Med 2004;42:159-163.
18 Law YM, Keller BB, Feingold BM, Boyle GJ. Usefulness of plasma B-type natriuretic peptide to identify ventricular dysfunction in pediatric and adult patients with congenital heart disease. Am J Cardiol 2005;95:474-478.
19 Colan SD, Borow KM, Neumann A. Left ventricular end-systolic wall stress-velocity of fiber shortening relation: a load-independent index of myocardial contractility. J Am Coll Cardiol 1984;4:715-724.
20 Hunt PJ, Richards AM, Nicholls MG, Yandle TG, Doughty RN, Espiner EA. Immunoreactive amino-terminal pro-brain natriuretic peptide (NT-PROBNP): a new marker of cardiac impairment. Clin Endocrinol (Oxf) 1997;47:287-296.
21 Laer S, Mir TS, Behn F, Eiselt M, Scholz H, Venzke A, et al. Carvedilol therapy in pediatric patients with congestive heart failure: a study investigating clinical and pharmacokinetic parameters. Am Heart J 2002;143:916-922.
22 Kimball TR, Daniels SR, Meyer RA, Hannon DW, Khoury P, Schwartz DC. Relation of symptoms to contractility and defect size in infants with ventricular septal defect. Am J Cardiol 1991;67:1097-1102.
23 Yao WQ, Chen SB, Zhou AQ, Wang RF, Sun K, Huang MR, et al. Mechanism of ventricular septum defect with heart failure. Chin J Pediatr 1994;32:139-140.
24 Chen SB, Sun K, Deng XF, Wang RF. Function of the left ventricle in ventricular septal defect combined with heart failure. Chin J Pediatr 1992;30:288-289.
25 Kunii Y, Kamada M, Ohtsuki S, Araki T, Kataoka K, Kageyama M, et al. Plasma brain natriuretic peptide and the evaluation of volume overload in infants and children with congenital heart disease. Acta Med Okayama 2003;57:191-197.
26 Koulouri S, Acherman RJ, Wong PC, Chan LS, Lewis AB. Utility of B-type natriuretic peptide in differentiating congestive heart failure from lung disease in pediatric patients with respiratory distress. Pediatr Cardiol 2004;25:341-346.
27 Westerlind A, Wahlander H, Lindstedt G, Lundberg PA, Holmgren D. Clinical signs of heart failure are associated with increased levels of natriuretic peptide types B and A in children with congenital heart defects or cardiomyopathy. Acta Paediatr 2004;93:340-345.
28 Ohuchi H, Takasugi H, Ohashi H, Okada Y, Yamada O, Ono Y, et al. Stratification of pediatric heart failure on the basis of neurohormonal and cardiac autonomic nervous activities in patients with congenital heart disease. Circulation 2003;108: 2368-2376.
29 Nir A, Bar-Oz B, Perles Z, Brooks R, Korach A, Rein AJ. N-terminal pro-B-type natriuretic peptide: reference plasma levels from birth to adolescence. Elevated levels at birth and in infants and children with heart diseases. Acta Paediatr 2004; 93:603-607.
30 Koch A, Singer H. Normal values of B type natriuretic peptide in infants, children, and adolescents. Heart 2003;89:875-878.

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