

Plasma Concentrations of N-Terminal Pro-Brain Natriuretic Peptide in Control Children From the Neonatal to Adolescent Period and in Children With Congestive Heart Failure

Thomas S. Mir, MD*; Sönke Marohn*; Stephanie Läer, MD‡; Michele Eiselt, MD*; Oswin Grollmus, MD*; and Jochen Weil, MD*

ABSTRACT. *Objective.* To determine plasma levels of N-terminal pro-brain natriuretic peptide (N-BNP) in control children to establish a normal age-dependent range from the neonatal period to adulthood. In addition, plasma concentrations of N-BNP were measured in children with congestive heart failure (CHF) and correlated with ejection fraction and clinical symptoms of heart failure.

Methods. For establishing a normal age-dependent range of plasma N-BNP, venous blood samples were taken in 133 control patients from the neonatal period to adulthood (10 days–32 years) and in 31 children with CHF. Plasma N-BNP levels were determined by an enzyme immunoassay. In children (1 month–14 years) with CHF, plasma N-BNP levels were correlated to ejection fraction measured by echocardiography and clinical symptoms of heart failure using the Ross Score.

Results. N-BNP levels in control children, adolescents, and adults did not show a significant age-related difference. In control children, the normal range was established between 150 (10th percentile) and 430 fmol/mL (90th percentile). Mean plasma N-BNP in control children was 311 fmol/mL (range: 74–654 fmol/mL). In 31 children with CHF, the plasma N-BNP levels were significantly higher (mean: 846; range: 219–2718) than in control children. N-BNP levels showed a negative correlation with the ejection fraction ($r = -0.53$) and a positive correlation with the clinical heart failure score ($r = 0.74$).

Conclusions. Plasma N-BNP levels reflect the severity of symptoms of heart failure and the impairment of cardiac function in children with CHF. In the future, determination of plasma N-BNP levels may be used as a helpful adjunct to monitor the effect of various treatments for CHF in children. *Pediatrics* 2002;110(6). URL: <http://www.pediatrics.org/cgi/content/full/110/6/e76>; N-BNP, children, heart failure, natriuretic peptides.

ABBREVIATIONS. BNP, brain natriuretic peptide; N-BNP, N-terminal pro-brain natriuretic peptide; CHF, congestive heart failure; DCM, dilated cardiomyopathy; HLHS, hypoplastic left heart syndrome, FALL, postoperative tetralogy of Fallot; MR, mitral

regurgitation; VSD, ventricular septal defect; AVSD, atrioventricular septal defect.

The cardiac natriuretic hormones play an important role in the regulation of extracellular fluid volume and blood pressure. These peptide hormones induce natriuresis, diuresis, and vasodilation and act specifically to counter the effects of the renin-angiotensin-aldosterone system. The natriuretic peptide system allows the heart to participate in the regulation of vascular tone and extracellular volume status. The brain natriuretic peptide (BNP) is a recently discovered natriuretic hormone of cardiac origin.¹ BNP is secreted from the cardiac ventricular myocytes in response to an increase in ventricular wall tension and is related to left ventricular filling pressures.² BNP mediates in arterial and venous vasodilation. Human pro-BNP consists of 108 amino acids; processing releases the biologically active 32-amino acid peptide and an amino-terminal fragment (N-BNP).^{3–6} It was shown that N-BNP is a sensitive and specific marker of ventricular dysfunction.^{7–10} In addition, N-BNP is stable in whole blood for >24 hours at 20°C and is not significantly influenced by exercise and position of the patient.^{5,11} This makes it a potential additional tool in the assessment of ventricular systolic dysfunction. Normal values for circulating levels of N-BNP in adults have been reported.^{4,6,9} Plasma levels of N-BNP in control children and in children with heart failure have not been reported.

The aim of the study was to establish the normal age-related plasma N-BNP level in children from the neonatal period to the adult period. Furthermore, plasma N-BNP levels were measured in children with congestive heart failure (CHF) and correlated to ejection fraction and clinical symptoms.

METHODS

Children Without Heart Disease

N-BNP plasma concentrations were measured in 109 control children and in 24 control adults. These children were admitted for uncomplicated pediatric diseases such as mild upper respiratory tract infections, delayed puberty, obesity, motor and developmental disorders, social and behavioral problems, and neurologic disorders such as migraine. These patients were divided into 4 groups according to international conference on harmonization guidelines¹²: infants (11 days–24 months; $n = 41$), children (2–11 years; $n = 43$), adolescents (12–17 years; $n = 25$), and adults (17–32 years; $n = 24$). Venous blood samples were taken exclusively at

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the occasion of a routine blood analysis. The routine blood analysis was taken to rule out organic lesions or infections. Only patients without cardiac, hepatic, and renal diseases and water and electrolyte disturbances were included in the study. Approval was given by the local Ethics Committee, and informed consent was obtained from all of the children's parents.

Children With CHF

In addition, N-BNP plasma concentrations were measured in 31 children (mean: 13 months; range: 1 month–14 years) with CHF. These 31 children with CHF were divided into 2 groups. The first group (total = 21) consisted of children with CHF caused by dilated cardiomyopathy (DCM; $n = 14$), hypoplastic left heart syndrome (HLHS; $n = 4$), postoperative tetralogy of Fallot (FALL; $n = 2$), and mitral regurgitation (MR; $n = 1$). The second group (total = 10) comprised children with CHF as a result of left to right shunt caused by ventricular septal defect (VSD; $n = 7$) and atrioventricular septal defect (AVSD; $n = 3$). Children with a Ross Score (Table 1) of ≥ 1 point were regarded as symptomatic and were included in the study. Venous blood samples were taken exclusively at the occasion of a routine blood analysis. The routine blood analysis was taken to rule out infections, electrolyte imbalances, or anemia. Correlations between plasma N-BNP levels and clinical score were obtained in all 31 patients. Correlation between plasma N-BNP levels and ejection fraction of the systemic ventricle were obtained in 21 patients with DCM, HLHS, FALL, and MR only. At the time of the serum sampling, 27 of the 31 children with CHF received anticongestive treatment with diuretics (27 of 31 children), digoxin (12 of 31 children), and angiotensin-converting enzyme inhibitors (18 of 31 children). Approval was given by the local Ethics Committee, and informed consent was obtained from all of the children's parents.

BNP Measurement

Blood samples were transferred to chilled plastic tubes that contained aprotinin and ethylenediaminetetraacetic acid and then immediately placed on ice and promptly centrifuged. An aliquot of plasma was frozen immediately at -80°C and thawed only once at the time of assay, which was performed within 4 weeks after the sampling. N-BNP plasma concentrations were determined with a competitive Enzyme Immuno Assay (Biomedica, Vienna, Austria). For each determination, a minimum of 0.15 mL of plasma was needed. The kit incorporates an immunoaffinity-purified sheep antibody specific for N-BNP (amino acids 8–29). The intra- and interassay variation coefficient was 6% and 8%, respectively.

Echocardiography

Two-dimensional echocardiography (Sonotron CFM 800 and Sonotron system V, VingMed, Oslo, Norway) was used for non-invasive measurement of systolic systemic ventricular function.

M-mode measurements of left ventricular function were obtained in a parasternal long axis. The arithmetic average of 3 measurements was obtained.^{13,14} In children with functional single-ventricle, ejection fraction of the systemic ventricle was determined by planimetry from the apical or subcostal 4-chamber view. Echocardiographic measurements were performed on the same day the blood samples were taken. The plasma N-BNP levels of all 31 children with CHF were not known to the investigators in the echo laboratory. Invasive measurements of heart function using heart catheterization were not performed.

Clinical Symptoms

For patients aged <14 years, we used a modified scoring system described first by Ross¹⁵ for infants with left-to-right shunt and modified by Reithmann et al¹⁶ and Laer et al.¹⁷ Two physicians independently graded the following variables: diaphoresis, tachypnea, breathing with abdominal retractions, respiratory rate, heart rate, and hepatomegaly. These symptoms of CHF were graded on a scale of 0, 1, or 2 points according to the severity. The sum of all points was added up to form the clinical score (range: 0–12 points). A higher score corresponds to more severe symptoms of heart failure. Patients with a score of a minimum of 1 point were included in the study (Table 1). The N-BNP levels of all 31 children with CHF were not known to the clinical investigators.

Statistical Analysis

The data were processed using the SPSS for Windows software (SPSS Inc, Chicago, IL). All data were presented as mean with standard deviation. The Wilcoxon test for unpaired observations was used to compare the means of 2 sets of data. Correlation of N-BNP and clinical score were compared using Spearman rank correlation. The null hypothesis was rejected at the 95% confidence interval, considering $P < .05$ as significant. The normal range of plasma N-BNP was determined by using a cumulative incidence tool (90th and 10th percentile of all measurements).

Because we did not measure the N-BNP plasma levels of the patients with a Ross Score below 1 point, an analysis of the specificity of N-BNP plasma levels could not be performed. A calculation of the sensitivity of N-BNP plasma levels was included.

RESULTS

Plasma N-BNP Levels in Control Children

Plasma N-BNP levels in 109 control children ranged between 74 and 654 fmol/mL (mean: 311 fmol/mL) not showing significantly age-related differences (Figs 1 and 2). The N-BNP levels of the 109 infants, children, and adolescents did not differ significantly from those measured in the 24 adults (303;

TABLE 1. Clinical Score*

	Score (Points)		
	0	1	2
History			
Diaphoresis	Head only	Head and body during exercise	Head and body at rest
Tachypnea	Rare	Several times	Frequent
Physical examination			
Breathing	Normal	Retractions	Dyspnea
Respiratory rate (respirations/min)			
0–1 y	<50	50–60	>60
1–6 y	<35	35–45	>45
7–10 y	<25	25–35	>35
11–14 y	<18	18–28	>28
Heart rate (beats/min)			
0–1 y	<160	160–170	>170
1–6 y	<105	105–115	>115
7–10 y	<90	90–100	>100
11–14 y	<80	80–90	>90
Hepatomegaly (liver edge from right costal margin)	<2 cm	2–3 cm	>3 cm

* Modified From Ross,¹⁵ Reithmann et al,¹⁶ and Laer et al.¹⁷

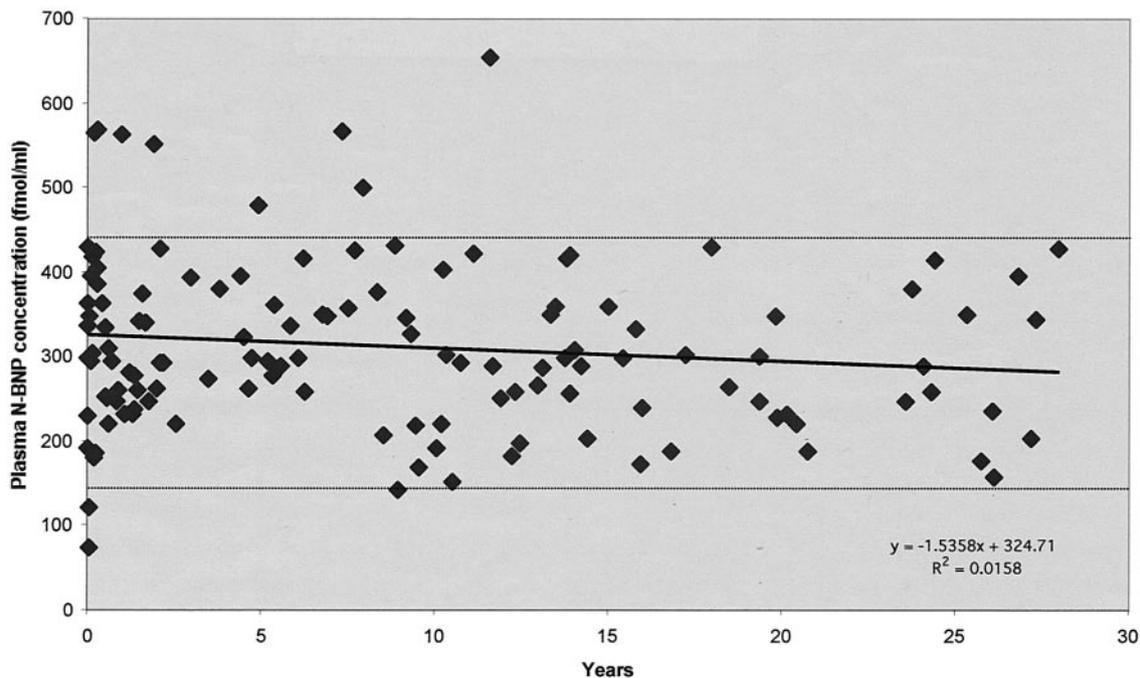


Fig 1. Plasma N-BNP in 133 control children, adolescents, and adults. The normal range of plasma N-BNP (10th and 90th percentiles) for children (10 days–17 years) is 150 to 430 fmol/mL.

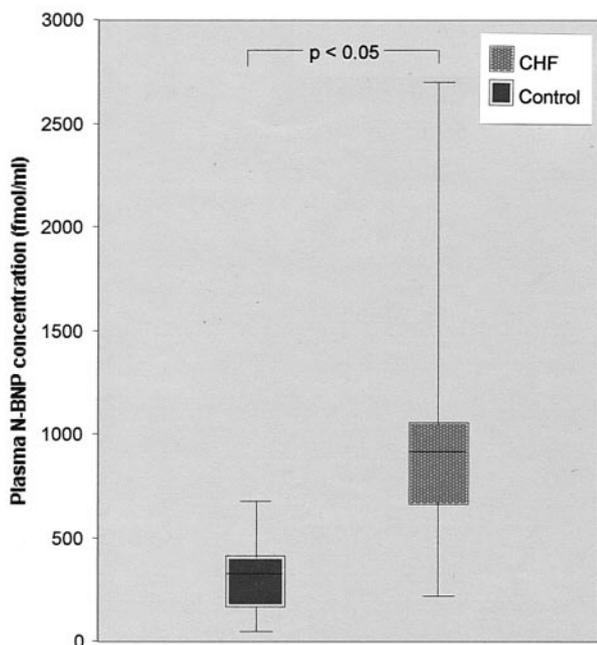


Fig 2. Plasma N-BNP in control children ($n = 133$) and in children with CHF ($n = 31$). Each modified box-plot represents the mean (thick black band) and the 10th and 90th percentiles. The error bars represent the lowest and highest values.

176–626 fmol/mL; not significant). The 10th and the 90th percentiles of N-BNP in control children (11 days–17 years) was 150 and 430 fmol/mL, respectively (Fig 1).

Plasma N-BNP Levels in Children With CHF

In 31 children with CHF, plasma N-BNP levels ranged between 219 and 2718 fmol/mL (mean: 846 fmol/mL) and were significantly higher than in 109 control children ($P < .05$; Fig 2). The 21 children with

CHF caused by DCM, HLHS, MR, and FALL had plasma N-BNP levels between 219 and 2008 fmol/mL (mean: 761 fmol/mL). The 10 children with CHF caused by left-to-right shunt had plasma N-BNP levels between 386 and 2718 fmol/mL (mean: 1022 fmol/mL; not significant).

Four of 31 patients with a Ross Score ≥ 1 point had a plasma N-BNP level within the normal range. The calculated sensitivity of the plasma N-BNP levels in the 31 patients with CHF was 87%.

Correlation Between Plasma N-BNP Levels and Ejection Fraction and Clinical Score in Children With CHF

The children with CHF caused by DCM, HLHS, MR, and FALL ($n = 21$) showed a negative correlation between the plasma N-BNP values and the ejection fraction ($r = -0.53$; $P < .05$; $n = 21$; Fig 3). The ejection fraction of the children with CHF caused by left-to-right shunt (VSD and AVSD; $n = 10$) ranged between 62% and 78% (mean: 68%). Furthermore, a positive correlation was found between the plasma N-BNP levels and the clinical score in the 31 children with CHF ($r = 0.74$; $P < .01$; Fig 4).

DISCUSSION

The novel findings of this study include that children with CHF showed higher plasma N-BNP concentrations than control children and that these N-BNP concentrations correlated with the severity of clinical symptoms. Furthermore, the ejection fraction in children with myocardial heart failure correlated with N-BNP plasma concentrations. These findings open a new additional diagnostic tool that could result in a more precise diagnosis of CHF in children. In addition, the level of this biochemical neurohu-

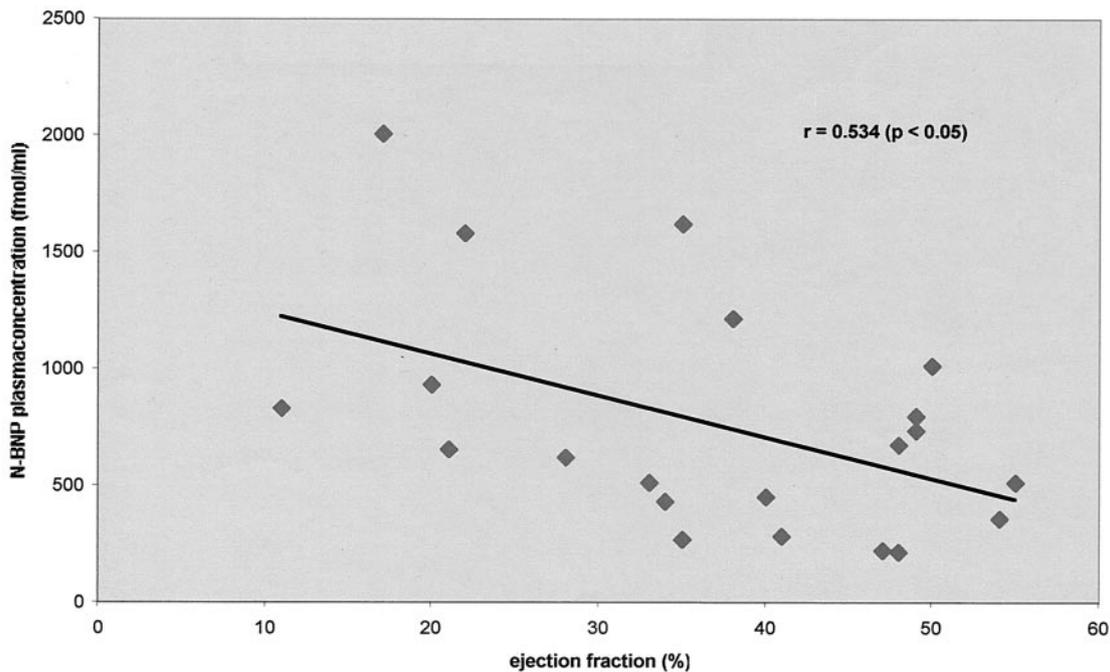


Fig 3. Correlation of plasma N-BNP to clinical heart failure score (Ross Score) in 31 children with CHF. The horizontal line describes the upper normal range for children of 430 fmol/mL.

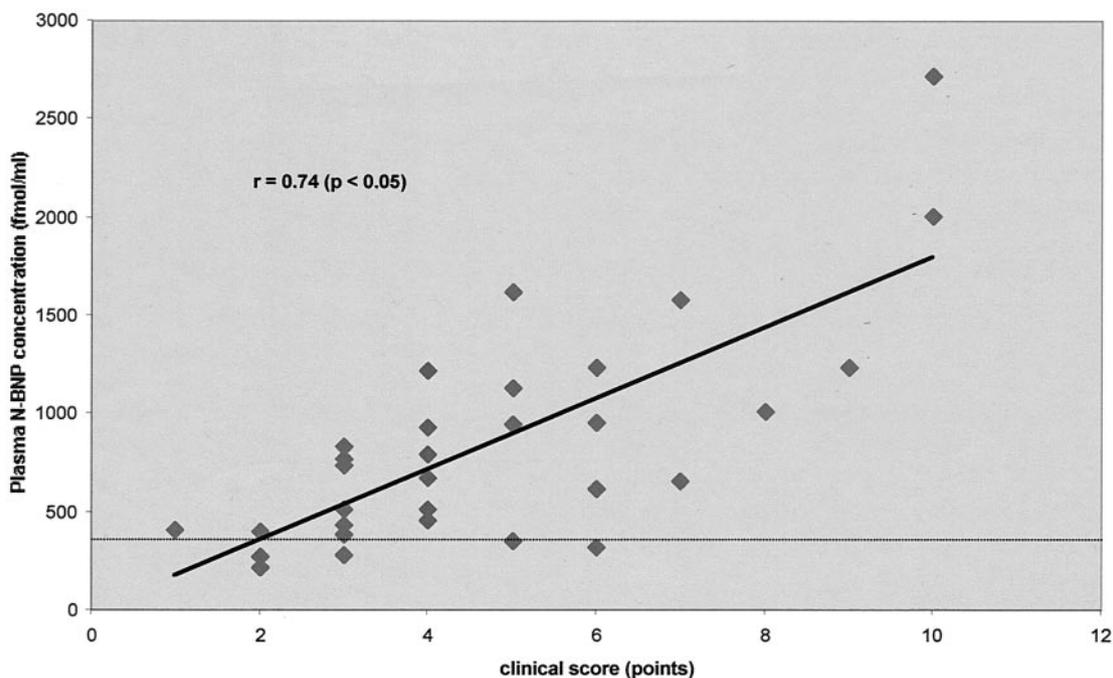


Fig 4. Correlation of plasma N-BNP to ejection fraction in 21 children with CHF caused by DCM, HLHS, FALL, and MR. The horizontal line describes the upper normal range for children of 430 fmol/mL.

moral marker could serve as a cutoff point for either medical (eg, beta-receptor blocker treatment) or surgical interventions in the future as in adults.

As a basis for correlating plasma concentrations of N-BNP with clinical parameters of CHF in children, we established a normal range of the biochemical inactive plasma N-BNP level in children from the neonatal to adolescent period for the first time. In control children (11 days–17 years), plasma N-BNP levels ranged between 150 fmol/mL (10th percentile)

and 430 fmol/mL (90th percentile), showing no significant age-related differences (mean: 311 fmol/mL; 74–654 fmol/mL).

These findings were consistent with previous observations on the biologically active plasma BNP-32 levels in children without heart disease. The plasma BNP-32 levels after the first 5 days of life showed no age dependence until adolescence.^{18–22} Therefore, our results of plasma N-BNP levels in children of different age without heart disease serve as a useful

baseline for comparison of plasma N-BNP levels in children with impaired cardiac function.

The children with CHF showed significantly higher plasma N-BNP levels than control children. A correlation was found between plasma N-BNP levels and the severity of the clinical symptoms of heart failure and between plasma N-BNP levels and the ejection fraction in patients with impaired ventricular function, although correlation between N-BNP plasma levels and ejection fraction was not very strong.

A correlation between plasma N-BNP concentrations and clinical parameters was shown in adults with heart disease. Furthermore, it was shown that plasma N-BNP concentrations serve as a prognostic parameter for CHF. Richards et al⁶ reported that plasma N-BNP levels measured 2 to 4 days after acute myocardial infarction predicted impairment of left ventricular function and 2-year survival (sensitivity: 85%; negative predictive value: 91%). Important in this study was that N-BNP measurement was superior to the biologically active BNP-32 for predicting mortality and heart failure during 2 years after myocardial infarction. In another study, it was recently shown that N-BNP levels above a certain threshold predicted left ventricular dysfunction with a sensitivity of 94%, a specificity of 55%, and a negative predictive value of 93%.²³

Concerns had been expressed that angiotensin-converting enzyme inhibitors, diuretics, beta-receptor blockers, and digoxin might modify plasma concentrations of natriuretic peptides and weaken their potential as markers for left ventricular dysfunction. However, the value of the N-BNP assay was demonstrated in patients with renal dysfunction and/or in patients who were treated with angiotensin-converting enzyme inhibitors, diuretics, or beta-receptor blockers.^{3,24}

In adults and children, CHF is characterized by complicated cardiorenal, hemodynamic, and neurohormonal alterations. Although patients who are admitted to the hospital with decompensated heart failure often have improvement in symptoms with the various treatment modalities available, there has been no satisfying way to quantify the short- and/or long-term effects of the treatment.²⁵ The conventional tests for cardiac function, such as echocardiography, clinical scores, or exercise, do not correlate exactly with symptomatic changes in the patient's condition. An additional simple and reliable method to assess therapeutic efficacy in pediatric patients who are being treated for CHF would be a great advantage.²⁶

In contrast to pediatric patients, clinical decision limits for N-BNP in adult patients have been reported. In the outstanding study of Troughton et al,² treatment was monitored by titrating N-BNP levels below 200 fmol/mL ($n = 70$). Troughton compared 2 groups of 35 adult patients who experienced heart failure. One group was offered conventional management, and the other also had the N-BNP levels in their blood monitored. These levels were then used as a precise guide for medication. Those who had their treatment adjusted according to plasma N-BNP

levels did significantly better overall. After 9 months, 25% of these patients were admitted to the hospital needing follow-up care, and 1 died. Among those who were treated in the conventional way, 50% were admitted to the hospital and 6 died. With this investigation, it was shown that by measuring the levels of plasma N-BNP, we could adjust the levels of medication needed to alleviate heart failure more exactly.

That increased levels of vasoconstrictor neurohumoral factors such as norepinephrine, renin, and endothelin-1 have been found to be significant prognosis predictors in CHF suggests an important role of these vasoconstrictors in the pathogenesis of CHF.^{25,27-29} The use of these markers as monitors of therapy is impractical because of difficult assay characteristics, general instability of markers, and wide-ranging, often overlapping, values. The natriuretic peptide family, in particular the aminoterminal-pro BNP, may be a better candidate for neurohumoral profiling in CHF.¹⁸ The measurement of the plasma concentration of natriuretic peptides, especially BNP, can be a valuable tool in the diagnosis, prognosis, and follow-up of all patients with cardiac dysfunction^{7,9,20-22,30} and pulmonary hypertension.¹⁰ It is known that the N-terminal form of BNP is the most discerning neurohumoral marker of early cardiac dysfunction.⁹ As recent studies show, N-BNP seems to be the most stable natriuretic peptide and it is highly valuable for clinical practice in adult patients.^{2,7,8} In addition, the plasma concentration of N-BNP is 10 times higher compared with BNP, which potentially makes it easier to devise a stix test for bedside testing in the future.

Limitations of the Study

A special investigation for the early neonatal period of the first 10 days of life was not included. Because of the circulatory changes after birth, this patient group needs its own study design. We started an extensive investigation on N-BNP levels in this patient group already.

CONCLUSION

Our findings suggest that the determination of N-BNP improves the diagnostic accuracy in the assessment of CHF in a pediatric patient population with suspected or known heart failure. In the future, the determination of plasma N-BNP concentrations in addition to hemodynamic and clinical parameters could be a helpful adjunct to monitor the effect of various treatments for CHF in children and for assessing a patient's prognosis. Ultimately, large-scale randomized, clinical trials in children with CHF will have to be performed to assess definitively the benefit of N-BNP for guiding therapy in children with CHF.

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