

This is an author produced version of a paper published in International Journal of Cardiology. This paper has been peer-reviewed but does not include the final publisher proof-corrections or journal pagination.

Citation for the published paper:

Larsson DA, Meurling CJ, Holmqvist F, Waktare JE and Thilen UJ.

"The diagnostic and prognostic value of brain natriuretic peptides in adults with a systemic morphologically right ventricle or Fontan-type circulation."

International Journal of Cardiology, 2006 Jun 12.

[doi:10.1016/j.ijcard.2006.01.023](https://doi.org/10.1016/j.ijcard.2006.01.023)

Access to the published version may require journal subscription.

Published with permission from: Elsevier

**THE DIAGNOSTIC AND PROGNOSTIC VALUE OF BRAIN NATRIURETIC PEPTIDES IN ADULTS WITH A
SYSTEMIC MORPHOLOGICALLY RIGHT VENTRICLE OR FONTAN-TYPE CIRCULATION**

**David A Larsson¹, BM; Carl J Meurling¹, MD, PhD; Fredrik Holmqvist¹, MD; Johan EP
Waktare², MD, Ulf J Thilén¹, MD**

¹Department of Cardiology, University Hospital, Lund, Sweden

²The Cardiothoracic Centre, Liverpool, UK

Correspondence to:

David Larsson

Department of Cardiology, University Hospital

S-221 85 Lund, Sweden

Tel: +46-46-173518

Fax: +46-46-157857

david.larsson@med.lu.se

ABSTRACT

Background: In acquired heart disease, brain natriuretic peptide (BNP) and N-Terminal pro-brain natriuretic peptide (NT-proBNP) are increasingly used as diagnostic and prognostic markers. In adult congenital heart disease, the abnormal anatomy and physiology complicate assessment of cardiac function. We studied the clinical correlates of measurement of natriuretic peptides (NP) in adults with a right ventricle in the systemic position or with Fontan-type physiology.

Methods: A prospective longitudinal study (follow up time 23 ± 13 months, mean \pm SD) was conducted in a specialised centre on 61 patients (age 26 ± 8 years; NYHA class 1.5 ± 0.6) including Senning/Mustard corrected transposition, congenitally corrected transposition and Fontan/total cavopulmonary connection. Plasma NP concentration was compared with NYHA class, exercise capacity and echocardiographically determined systemic systolic ventricular function.

Results:

Neurohormone concentrations were generally elevated (mean = 290% of upper reference limit) and related to NYHA class ($P < 0.001$, NYHA I vs. II – IV). No clinically significant relationship to ventricular function or exercise capacity was found however. An NP measurement could not predict the future course of the disease in terms of functional status or ventricular function.

Conclusion: In contrast to patients with acquired heart disease, measurement of NP seems to have low clinical value in adults with a right ventricle in the systemic position or with Fontan-type physiology.

KEYWORDS: Grown-up congenital heart disease, Adult congenital heart disease, Fontan, transposition, natriuretic peptides, echocardiography.

INTRODUCTION

Earlier diagnosis and improved treatment of children born with heart defects in the past few decades have led to an increased number of patients surviving into adulthood [1]. Many of these need to be followed in the adult clinic, but the relative rarity of individual malformations, the abnormal anatomy and the complex physiology make assessment of cardiac function difficult. A simple investigation such as a blood test which had the capacity to quantitatively or qualitatively evaluate ventricular function or predict those at risk of deterioration would be clinically valuable.

Brain natriuretic peptide (BNP) is a neurohormone released mainly from the ventricles of the heart during pressure overload, the main stimulus being myocardial stretch [2]. Cleavage of the precursor proBNP yields both BNP and N-terminal pro-brain natriuretic peptide (NT-proBNP) [3]. Whereas BNP has diuretic, natriuretic, vasodilatory and sympatho-inhibitory effects, there are no known physiological effects of NT-proBNP [2].

Neurohormonal activation is an integral part of the heart failure syndrome. In congestive heart failure due to acquired heart disease, the degree of activation correlates to symptoms, severity of left ventricular dysfunction and prognosis [4-6]. Therefore, natriuretic peptides (NP) have become increasingly used in the evaluation of patients with acquired heart disease. However, information about neurohormonal activation in congenital heart disease is scant and derived from heterogeneous patient cohorts.

In congenital cardiac conditions with a morphological right ventricle serving as the systemic ventricle, there are concerns about its long-term function. In univentricular malformations palliated by a Fontan procedure, the only well developed ventricle serves the systemic circulation, and the pulmonary circulation runs without employing a subpulmonary ventricle. In these conditions, accurate assessment of systemic ventricular function and the degree of heart failure is of major importance in the follow-up. The roles and relevance of NP in this

setting are by and large unknown. The aim of this prospective longitudinal study was to determine whether NP could yield diagnostic or prognostic information in adults with either a morphological right ventricle in systemic position, or with single-ventricle physiology.

METHODS

Patients and study design

Sixty-one adult congenital heart disease patients (mean age 26 ± 8 , range 17–58 years) managed at a tertiary specialised centre for grown-up congenital heart disease were recruited in a consecutive manner. Anatomically, they constituted three groups: transposition of the great arteries with a Senning or Mustard repair (D-TGA), congenitally corrected transposition of the great arteries (L-TGA) and different forms of univentricular hearts palliated by a Fontan or total cavopulmonary connection (Fontan/TCPC). No patient had a single ventricle of right ventricular morphology. Exclusion criteria included severe hypertensive pulmonary vascular disease (systolic pulmonary pressure > 50 mmHg), clinically significant renal dysfunction (plasma creatinine > 150 $\mu\text{mol/L}$) and substantial hypoxaemia ($\text{SaO}_2 < 90\%$) at rest.

The study was approved by the local ethical committee and complied with the declaration of Helsinki.

BNP and NT-proBNP assays

Plasma concentrations of NP were determined from venous blood samples collected in sitting position after at least five minutes of rest.

Due to a change of methods in our clinical biochemistry laboratory, BNP was measured early in the study period, and NT-proBNP in the later part. For BNP, a radioimmunoassay (Shionoria BNP) was used to detect a concentration between 1 and 578

pmol/L; the given reference value was < 6 pmol/L. For NT-proBNP, an electrochemiluminescence immunoassay (Roche Diagnostics) was used to detect a concentration between 50 and 35 000 ng/L; the given reference values were < 88 ng/L for men and < 153 ng/L for women.

Due to the two assays utilised and the different reference ranges for men and women with NT-proBNP, statistical evaluations were repeated for the whole population with the NP expressed as a percentage of the upper reference value, utilising non-parametric methods (see statistics). NP assays were performed at inclusion and at follow-up visits, but serial analysis was only performed where serial data of the same type was available.

Clinical and Echocardiographic Evaluation

Clinical assessment, echocardiography, and bicycle ergometry were performed at baseline and at regular clinical visits between 1999 and 2004. Patients underwent clinical evaluation, including evaluation of NYHA functional class. Exercise capacity was assessed by bicycle ergometry with gradually increasing resistance and monitoring of heart rate and blood pressure. The result was expressed as a percentage of the expected maximum physical work capacity, taking age and gender into account. In accordance with the clinically used cut-off values, exercise capacity $\geq 80\%$ of the predicted value was considered as normal and exercise capacity $< 80\%$ as impaired.

Systemic systolic ventricular function, expressed as ejection fraction (EF), was estimated by transthoracic echocardiography by a single experienced examiner (UT). An EF $\geq 55\%$ was considered to be normal, while impaired function was subclassified as mildly ($45\% \leq$ EF $< 55\%$), moderately ($30\% \leq$ EF $< 45\%$) or severely (EF $< 30\%$) impaired.

The possible clinical value of measurement of neurohormone concentrations was evaluated in three ways: The baseline NP values (BNP or NT-proBNP) were compared with

NYHA class, ejection fraction and exercise capacity; the predictive value of this baseline NP in relation to future changes in EF and NYHA evaluated; and the correlation of changes in EF, NYHA and exercise capacity to changes in NP examined. A change in the neurohormonal concentration from within the normal range to outside it, or vice-versa, or if the value was outside the normal range at baseline, a change of $\geq 20\%$ was arbitrarily considered significant.

Statistics

The Mann-Whitney *U* test was used for continuous data and the Fisher's exact test for categorical data. Spearman Rank Order Correlation was used for correlation analysis. Results were expressed as mean \pm SD or as median (range) for normally and non-normally distributed data, respectively. $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics are outlined in Table 1. All the 61 patients initially included had baseline NP, NYHA class, and EF available, but bicycle ergometry was only performed in 43 patients. Mean follow-up was 23 ± 13 months, during which one patient died (cancer). Nine patients were not included in follow-up analysis due to late inclusion. A further 17 patients did not have two neurohormone measurements of the same type, leaving 34 patients when studying neurohormone changes.

NP and clinical variables

NP levels were above the upper reference limit in 67% of the subjects. Plasma concentrations of NP (calculated as percentages of the respective upper reference limits) were higher in symptomatic patients (NYHA II-IV) than in asymptomatic patients (330 [50–2200] and 100 [17–

820] %, respectively, $P < 0.001$; Fig. 1), although half of the asymptomatic patients ($n = 35$) had raised NP levels. Even mildly symptomatic patients (NYHA II) had higher NP concentrations than asymptomatic patients ($P < 0.01$). The statistical significance of these differences was further confirmed in separate analyses of raw BNP and NT-proBNP data ($n = 35$ and 26 , $P < 0.01$ and $P < 0.05$ for NYHA I vs. NYHA II-IV, respectively).

Patients with moderate to severe ventricular dysfunction ($EF < 45\%$) had higher mean NP concentrations than patients with no or only mild ventricular dysfunction ($EF \geq 45\%$; $P < 0.01$; Fig. 2). The former group also had a higher mean NP concentration than the group with normal ventricular function alone ($P < 0.05$) but there was no significant difference in NP between those with normal and mildly impaired ventricular function. When separate analysis of BNP and NT-proBNP values ($n = 35$ and 26 , respectively) was performed, there was a non-significant trend associating higher NP values with moderate or severe ventricular dysfunction.

Patients with normal neurohormone values were more likely to have normal exercise capacity ($P < 0.005$; Table 2). The sensitivity and specificity of a normal neurohormone value to identify normal exercise capacity were 55% and 90%, respectively, whereas the sensitivity and specificity of the absence of symptoms (NYHA class I) to identify normal effort capacity were 86% and 71%, respectively. Maximum heart rate (MHR) was 168 (82 – 192) beats per minute, which translated to 86 (43 – 97) % of the predicted value (adjusted for age). In 44 and 21% of the patients, the MHR did not reach 85 and 70% of the predicted value, respectively. NP levels did not differ between the subjects with normal MHR and those with chronotropic incompetence, and there was no significant difference in the NYHA classification of subjects with normal vs. impaired chronotropic response (using either 85 or 70% of the predicted MHR as the cut-off). Furthermore, the same findings were replicated in a subgroup analysis of the D-TGA and Fontan patients ($n = 21$ and 11 , respectively). There were no differences in MHR between the

anatomical groups. 38 patients had a normal and 5 patients an attenuated (increase < 30 mmHg) blood pressure response. There was no patient with a fall in blood pressure during exercise.

Reasons for quitting were fatigue ($n = 41$) and shortness of breath ($n = 2$; BNP = 83 and 133 % of the upper reference limit).

Predictive value of NP and correlation of changes in NP to clinical course

There was no significant difference in initial NP concentrations between groups with increased, decreased or unchanged NYHA class at follow-up in the 51 patients eligible for this analysis (Table 3). Of the 17 patients with normal baseline NP, 2 deteriorated in terms of NYHA class, while of the 34 with elevated levels at baseline, 3 deteriorated. Systemic ventricular function improved in 6 of 17 with normal baseline NP and in 10 of 34 with raised baseline NP. Systemic ventricular function worsened in 2 patients with normal baseline NP and in 3 patients with raised baseline NP.

In patients with two NP measurements of the same type ($n = 34$), the neurohormonal concentration increased significantly (according to definition) in 14 patients (Table 3). However, only a small minority of these deteriorated in NYHA class ($n = 2$) or systemic ventricular function ($n = 1$, $P = NS$). None of the patients exhibiting an improvement in NP levels ($n = 8$) suffered a deterioration in NYHA class or EF. In patients with unchanged NYHA class ($n = 26$) or ventricular function ($n = 21$), the natriuretic peptide concentration could go in any direction, and in those with improved ventricular function ($n = 12$) or functional status ($n = 6$), neurohormone concentrations generally did not diminish. Other arbitrary cut-off values (10, 30 and 40%) were also tested during initial modelling of the data, but this did not improve the discriminatory value of the test. However, higher cut-offs severely reduced the number of patients in whom natriuretic peptide levels changed significantly.

Anatomy, age and gender

The anatomical substrate per se did not seem to influence neurohormone levels. The Fontans had a higher BNP concentration than the patients with transposition; however this was associated with a higher mean NYHA class (Table 1). The distribution of ventricular dysfunction did not differ between the anatomical groups.

NT-proBNP, but not BNP, concentrations correlated weakly with age (NT-proBNP $r^2 = 0.18$, $P < 0.05$).

Gender did not influence BNP or NT-proBNP concentrations, and there were no differences in age, NYHA class, systemic ventricular function or exercise capacity between males and females.

DISCUSSION

The present study demonstrates that neurohormonal activation, indicated by an elevated plasma BNP or NT-proBNP concentration, is a common finding in adult patients with a morphological right ventricle serving the systemic circulation and in patients with a Fontan-type circulation. This is true even when symptoms are absent and the systemic systolic ventricular function is considered to be normal. This is in accordance with three other studies in patients with congenital heart disease [7-9]. However, these previous reports included only 44, 43 and 0% ($n = 21, 23$ and 0) patients with TGA or univentricular malformations, respectively.

No significant differences in NP concentrations between the anatomical groups were found, suggesting that anatomical substrate is not an important determinant of NP secretion in adult complex congenital heart disease. This was also observed in an earlier study by Bolger et al, which examined adults with a more heterogeneous mixture of congenital heart malformations [8].

BNP and NT-proBNP concentrations were clearly related to NYHA class in the present study. The association between impaired NYHA class and increased NP levels is in accordance with studies on acquired heart disease, as well as with a small series of congenital heart disease [8-10].

In 86% of the patients with a normal neurohormone concentration, exercise capacity was normal. However, the ability of an elevated NP value to identify those with impaired exercise capacity was not correspondingly strong. As expected, there was good correlation between high NYHA class (II-IV) and impaired effort capacity. This simple parameter was superior in detecting those with impaired exercise capacity than the presence of an elevated NP level (Specificity 86% vs. 55%, $P = \text{NS}$). Although it is possible that these two tests have different properties, and that a normal NP level could be an indicator of good cardiac status, it seems as if it adds little clinical value over using NYHA class alone. These results are hard to compare with other patient populations, since the pathophysiological background is different from that of subjects with acquired ventricular dysfunction. In heart failure caused by acquired myocardial disease, it is very likely that ventricular performance is the limiting factor. In contrast, in the Fontan state or after a Senning/Mustard correction, additional factors such as impaired ventricular filling due to mechanisms other than diastolic dysfunction or chronotropic insufficiency may be significant or even the sole mechanism of impairment of cardiac output, a concept that is consistent with our finding that D-TGA and Fontan patients with impaired chronotropic response did not show NP levels or NYHA classification significantly different from the rest.

In contrast to the experience from adult acquired and paediatric heart disease [11-13], and therefore somewhat surprising, the association between ejection fraction and peptide concentrations was weak in this study. Although subjects with moderately or severely impaired

ventricular function did have elevated NP concentrations as compared with subjects with normal or only mildly impaired ventricular function, the association was weak and the difference only statistically significant when BNP and NT-proBNP data were combined. It should be noted that our results showed a trend towards higher baseline neurohormonal concentrations with deterioration in ventricular function, and that Bolger and co-workers found a statistically significant stepwise increase in NP levels according to systemic ventricular function [8]. Their patients ($n = 53$) were generally more symptomatic (NYHA 2.0 vs. 1.5 in the present study), which is consistent with our finding that NP appeared to have poor discrimination in evaluating differences between patients with no or mild ventricular impairment. Another important difference between that study and the present was that only seven of their patients had a morphological right ventricle in the systemic position (all TGA), while 16 had univentricular malformations.

There are several potential, but speculative, physiological and pathological explanations for the disparity in the utility of NP evaluation between acquired and congenital heart disease. First, the release of BNP is mainly stimulated by ventricular myocardial stretch, which would clinically correspond to “preload” or ventricular filling pressure and occurs during diastole. In most reports, including the present, ventricular function is described in terms of systolic function however. Assessment of diastolic function with echo-Doppler cardiography in these patients is very problematic, as the interpretation of “mitral” (systemic atrioventricular valve) flow and tissue Doppler patterns is unclear. In adults with congestive cardiac failure, systolic and diastolic ventricular dysfunction typically coexist, explaining the association between raised BNP levels and systolic ventricular dysfunction. Our finding that neurohormone concentrations often exceeded the upper reference limit even in patients with normal systolic ventricular function could indicate that diastolic ventricular dysfunction is a common feature in

these types of patients. The relationship between systolic and diastolic function in a right ventricle which has supported the systemic circulation since birth or early childhood, is not known. Studies in patients who have suffered pulmonary embolism demonstrate that a stressed and failing right ventricle is associated with increased levels of BNP [14], but this observation was in an acute setting. The stimulus-to-response relationship for a chronically loaded right ventricle might be quite different from the chronically loaded left ventricle. In the Senning/Mustard repair, the atria are relatively stiff and non-compliant conduits, and may be significantly restrictive to flow [15]. Ventricular filling may be impaired due to this, and thus stretch in an impaired (or normal) ventricle would be less of a feature of the pathophysiology, leading to poor correlation between BNP release and severity of overall cardiac dysfunction. In the Fontan state, central venous pressure must exceed the ventricular filling pressure in order to allow forward blood flow, and one would anticipate severe symptoms due to venous congestion if the ventricular filling pressure were markedly increased. Even though our series of Fontan patients contained a number with systolic ventricular dysfunction, none suffered from protein-losing enteropathy, ascites or severe peripheral oedema. It is therefore unlikely that ventricular filling pressures were greatly increased in our series. Despite this, the majority of our patients had abnormal NP levels. This is in accordance with a paediatric series late after cavopulmonary connection, in which BNP was found to be significantly increased without correlation to haemodynamic variables [16].

Our results suggest that evaluation of serum NP is not helpful in predicting clinical course in terms of functional status or systemic systolic ventricular function in medium-term follow-up. This is an important finding, as in acquired heart disease with acute heart failure, a lower as well as a declining BNP concentration is associated with a better outcome [17, 18].

Moreover, there was no clear association between changes over time in neurohormone concentrations and changes in NYHA class or systemic ventricular function. Our definition of a significant change in neurohormone concentration was arbitrarily chosen. Both more liberal and more restrictive definitions have been used by others [19, 20], and there is no clear consensus as to what constitutes the appropriate cut-off for a “significant change”. We did explore other arbitrary cut-offs during initial modelling of the data, but found none that appeared more helpful. We therefore found no evidence that BNP or NT-proBNP assessment was clinically helpful or could replace echocardiography and clinical evaluation in follow-up of these types of patients. However, the follow-up was relatively short, and few patients changed their status, meaning that this study can not properly settle this.

Age and gender have been suggested to influence NP concentrations [21]. In the present study, however, there were no significant gender differences in NP levels. Only a weak trend of increasing NT-proBNP levels with age was seen, however, our population was younger and had a narrower age span than the studies cited above. In normal children, BNP levels do not vary much with age, except that high levels are seen in neonates [22].

An important finding, from a clinical point of view, is the considerable inter-individual variation in neurohormone levels, which would constitute an interpretative problem if BNP or NT-proBNP were to be used for diagnostic purposes. Thus, even if significant differences in NP levels between groups with differing systemic ventricular function were found in larger patient cohorts, this inter-individual variation would likely preclude predicting a given individual’s ventricular function with clinically helpful accuracy. Furthermore, even if a low NP concentration was considered to be a relatively reliable indicator of good cardiac and functional status, it did not yield any clinically important information beyond that obtained by asking about functional status and by echocardiography.

Study limitations

Echocardiographic assessment of ventricular systolic function in these patients is difficult (which precisely underlines the attractiveness of investigating possible surrogates such as BNP or NT-proBNP), but to minimise the impact of this issue, all examinations were performed by a single very experienced echocardiographer. Furthermore, on 10 occasions clinically indicated radionuclide angiography was performed contemporaneously to the echocardiographic examination; in nine cases the same classification of ventricular function was achieved. There are other ways to assess ventricular function. Magnetic resonance imaging (MRI) is often considered a superior modality. However, at the time of this study, the availability of MRI in our hospital was limited. The myocardial performance index (Tei index) is a nongeometric measure of ventricular function less dependent on pre- and afterload [23]. Its use in congenital heart disease has been suggested, however, the experience in the present setting is limited and the interpretation therefore difficult, though it was recently shown that the Tei index can be used in TGA patients in order to satisfactorily estimate an ejection fraction [24].

Secondly, the dates of the follow-up visits were clinically driven, hence the intervals between visits varied.

Thirdly, the sample size is relatively small, and the numbers in each subgroup even smaller, which makes it hard to reach statistical significance in group comparisons.

Finally, the use of both BNP and NT-proBNP complicates the analysis. The transition from BNP to NT-proBNP was due to a change of methods in the hospital's laboratory. NT-proBNP has a longer half-life compared to that of BNP [25], and this might indicate that it better reflects long-term cardiac status and thus might correlate better with the clinical variables. However, we could not see any such pattern, and we found the inter-individual variation to be

comparable for the peptides. Furthermore, whereas active clearance mechanisms exist for BNP [26], NT-proBNP is likely only passively cleared, making its concentration dependent on the glomerular filtration rate, the measurement of which would have constituted a more secure means than plasma creatinine to limit the influence of renal function on the analyses.

CONCLUSIONS

In summary, BNP and NT-proBNP concentrations are often elevated in congenital heart disease characterised by a right ventricle in the systemic position or by Fontan physiology. The degree of neurohormonal activation is related to the degree of symptoms, but not significantly to systemic systolic ventricular function, nor to exercise capacity in an important way.

REFERENCES

- [1] Brickner ME, Hillis LD, Lange RA. Congenital heart disease in adults. First of two parts. *N Engl J Med* 2000;342(4):256-63.
- [2] Levin ER, Gardner DG, Samson WK. Natriuretic peptides. *N Engl J Med* 1998;339(5):321-8.
- [3] Hall C. Essential biochemistry and physiology of (NT-pro)BNP. *Eur J Heart Fail* 2004;6(3):257-60.
- [4] Sigurdsson A, Amtorp O, Gundersen T, Nilsson B, Remes J, Swedberg K. Neurohormonal activation in patients with mild or moderately severe congestive heart failure and effects of ramipril. The Ramipril Trial Study Group. *Br Heart J* 1994;72(5):422-7.
- [5] Groenning BA, Nilsson JC, Sondergaard L, et al. Detection of left ventricular enlargement and impaired systolic function with plasma N-terminal pro brain natriuretic peptide concentrations. *Am Heart J* 2002;143(5):923-9.
- [6] Kirk V, Bay M, Parner J, et al. N-terminal proBNP and mortality in hospitalised patients with heart failure and preserved vs. reduced systolic function: data from the prospective Copenhagen Hospital Heart Failure Study (CHHF). *Eur J Heart Fail* 2004;6(3):335-41.
- [7] Neffke JG, Tulevski, II, van der Wall EE, et al. ECG determinants in adult patients with chronic right ventricular pressure overload caused by congenital heart disease: relation with plasma neurohormones and MRI parameters. *Heart* 2002;88(3):266-70.
- [8] Bolger AP, Sharma R, Li W, et al. Neurohormonal activation and the chronic heart failure syndrome in adults with congenital heart disease. *Circulation* 2002;106(1):92-9.
- [9] 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(3):340-5.

- [10] Emdin M, Passino C, Prontera C, et al. Cardiac natriuretic hormones, neuro-hormones, thyroid hormones and cytokines in normal subjects and patients with heart failure. *Clin Chem Lab Med* 2004;42(6):627-36.
- [11] Hobbs FD, Davis RC, Roalfe AK, Hare R, Davies MK. Reliability of N-terminal proBNP assay in diagnosis of left ventricular systolic dysfunction within representative and high risk populations. *Heart* 2004;90(8):866-70.
- [12] Maisel AS, Koon J, Krishnaswamy P, et al. Utility of B-natriuretic peptide as a rapid, point-of-care test for screening patients undergoing echocardiography to determine left ventricular dysfunction. *Am Heart J* 2001;141(3):367-74.
- [13] Mir TS, Marohn S, Laer S, Eiselt M, Grollmus O, Weil J. 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. *Pediatrics* 2002;110(6):e76.
- [14] Kruger S, Graf J, Merx MW, et al. Brain natriuretic peptide predicts right heart failure in patients with acute pulmonary embolism. *Am Heart J* 2004;147(1):60-5.
- [15] Derrick GP, Narang I, White PA, et al. Failure of stroke volume augmentation during exercise and dobutamine stress is unrelated to load-independent indexes of right ventricular performance after the Mustard operation. *Circulation* 2000;102(19 Suppl 3):III154-9.
- [16] Hjortdal VE, Stenbog EV, Ravn HB, et al. Neurohormonal activation late after cavopulmonary connection. *Heart* 2000;83(4):439-43.
- [17] Fisher C, Berry C, Blue L, Morton JJ, McMurray J. N-terminal pro B type natriuretic peptide, but not the new putative cardiac hormone relaxin, predicts prognosis in patients with chronic heart failure. *Heart* 2003;89(8):879-81.

- [18] Cheng V, Kazanagra R, Garcia A, et al. A rapid bedside test for B-type peptide predicts treatment outcomes in patients admitted for decompensated heart failure: a pilot study. *J Am Coll Cardiol* 2001;37(2):386-91.
- [19] Wu AH, Smith A, Wieczorek S, et al. Biological variation for N-terminal pro- and B-type natriuretic peptides and implications for therapeutic monitoring of patients with congestive heart failure. *Am J Cardiol* 2003;92(5):628-31.
- [20] Gackowski A, Isnard R, Golmard JL, et al. Comparison of echocardiography and plasma B-type natriuretic peptide for monitoring the response to treatment in acute heart failure. *Eur Heart J* 2004;25(20):1788-96.
- [21] Wang TJ, Larson MG, Levy D, et al. Impact of age and sex on plasma natriuretic peptide levels in healthy adults. *Am J Cardiol* 2002;90(3):254-8.
- [22] Kunii Y, Kamada M, Ohtsuki S, 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(4):191-7.
- [23] Eidem BW, O'Leary PW, Tei C, Seward JB. Usefulness of the myocardial performance index for assessing right ventricular function in congenital heart disease. *Am J Cardiol* 2000;86(6):654-8.
- [24] Salehian O, Schwerzmann M, Merchant N, Webb GD, Siu SC, Therrien J. Assessment of systemic right ventricular function in patients with transposition of the great arteries using the myocardial performance index: comparison with cardiac magnetic resonance imaging. *Circulation* 2004;110(20):3229-33.
- [25] Pemberton CJ, Johnson ML, Yandle TG, Espiner EA. Deconvolution analysis of cardiac natriuretic peptides during acute volume overload. *Hypertension* 2000;36(3):355-9.

[26] Charles CJ, Espiner EA, Nicholls MG, et al. Clearance receptors and endopeptidase 24.11: equal role in natriuretic peptide metabolism in conscious sheep. *Am J Physiol* 1996;271(2 Pt 2):R373-80.

FIGURE LEGENDS

Figure 1. Neurohormone concentrations (expressed as percentages of the corresponding upper reference limits) compared with NYHA class. Boxes show the median and quartiles, whiskers show the range (ends) and the 10th and 90th percentiles (crosses). $*P < 0.001$ vs. NYHA class I (Mann-Whitney U test).

Figure 2. Neurohormone concentrations (expressed as percentages of the respective reference limits) related to systemic ventricular function. Boxes show the median and quartiles, whiskers show the range (ends) and the 10th and 90th percentiles (crosses). EF = ejection fraction. $*P < 0.01$ moderately to severely impaired function vs. normal to mildly impaired function; $*P < 0.05$ moderately to severely impaired function vs. normal function (Mann-Whitney U test).

TEXT TABLES

Table 1. Patient characteristics.

	All patients	D-TGA	L-TGA	Fontan/TCPC
<i>n</i> (women)	61 (19)	27 (8)	16 (5)	18 (6)
Age \pm SD	26 \pm 8	22 \pm 3	32 \pm 10*	27 \pm 9
NYHA class	1.5 \pm 0.6	1.3 \pm 0.6	1.4 \pm 0.7	1.8 \pm 0.5#
Systemic ventricular function				
<i>EF</i> \geq 55%	23	7	6	10
45% < <i>EF</i> < 55%	12	6	3	3
<i>EF</i> \leq 45%	26	14	7	5
BNP median (range), pmol/L	13 (1–52)	11 (3–43)	12 (1–49)	32 (20–52)§
<i>n</i>	35	19	13	3
NT-proBNP median (range), ng/L	340 (49–1959)	221 (59–609)	462 (49–1262)	397 (68–1959)
<i>n</i>	26	8	3	15
Treatment				
β -blockers	9			
ACE inhibitors	9			
Digoxin	5			
Diuretics	3			

D-TGA = Senning/Mustard corrected transposition of the great arteries. L-TGA = congenitally corrected transposition of the great arteries. Fontan/TCPC = univentricular heart palliated by a

Fontan or total cavopulmonary connection procedure. * $P < 0.05$ L-TGA vs. D-TGA and L-TGA vs Fontan/TCPC (Mann-Whitney U test). # $P < 0.05$ Fontan vs. D-TGA. § $P < 0.05$ Fontan/TCPC vs. D-TGA and L-TGA.

Table 2. Exercise capacity related to natriuretic peptide concentrations and NYHA class.

		Exercise capacity	
		Normal	Impaired
NP	Normal	12	2
	Elevated	10	19
NYHA class	I	19	6
	II-IV	3	15

Impaired exercise capacity was defined as a result < 80% of the expected and an elevated natriuretic peptide level as being higher than the given reference limit. NP = BNP or NT-proBNP. $P = 0.003$ and 0.0002 for exercise capacity vs. NP levels and NYHA class, respectively (Fisher's exact test).

Table 3. Prediction of symptoms and systemic ventricular function and correlation of changes in natriuretic peptide levels to clinical course.

A.

NP	NYHA class			Systemic ventricular function		
	Improved	Unchanged	Deteriorated	Improved	Unchanged	Deteriorated
Initial value						
Normal	1	14	2	6	9	2
Elevated	6	25	3	10	21	3

B.

NP	NYHA class			Systemic ventricular function		
	Improved	Unchanged	Deteriorated	Improved	Unchanged	Deteriorated
Follow-up						
Decreased	1	7	0	3	5	0
Unchanged	3	9	0	4	8	0
Increased	2	10	2	5	8	1

Changes of NYHA class and systemic ventricular function between two visits were compared with initial neurohormone concentrations (above the upper reference limit or not, **A**) and changes in neurohormone concentrations (**B**). A change of $\geq 20\%$ in the natriuretic peptide (NP) concentration, or a change from normal to pathological or vice versa, was considered significant.

Fisher's exact test did not show any significant results. For the statistical analysis, the "improved" and "unchanged" groups were combined (NYHA class and ventricular function), as were the "decreased" and "unchanged" groups (NP). For patients with both BNP and NT-proBNP data, NT-proBNP data was used.

FIGURES

Figure 1.

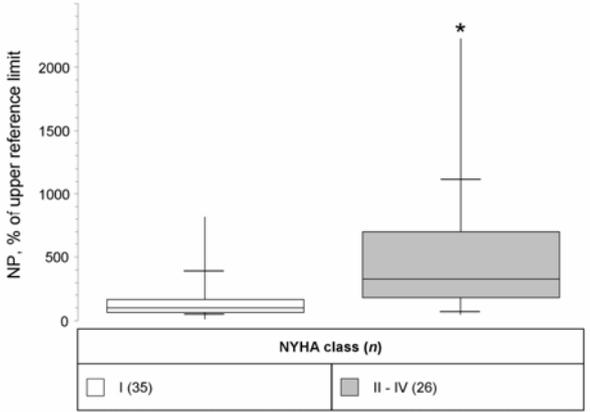


Figure 2.

