Prognostic Value of Plasma B-Type Natriuretic Peptide in the Long-Term Follow-up of Patients With Transposition of the Great Arteries With Morphologic Right Systemic Ventricle After Atrial Switch Operation

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Background: B-type natriuretic peptide (BNP) is an established marker for heart failure assessment, but the prognostic quality of BNP after atrial switch operation (ASO) has not yet been elucidated.

Methods and Results: In 89 patients (median age, 24 years; range, 15–35 years) after ASO, BNP was measured. During a 48-months follow-up we focused on critical cardiac events, defined as decompensation, sudden cardiac death or need for heart transplantation. BNP was considerably lower in 81 patients in functional class (FC) I/II (median, 35 pg/ml; range, 3–586 pg/ml) than in 6 patients in FC III/IV (median, 246 pg/ml; range, 14–1,150 pg/ml, $P \leq 0.073$). BNP was significantly higher after Mustard than after Senning procedure ($P \leq 0.030$). There was no significant difference in BNP between simple or complex transposition of the great arteries (TGA) ($P \leq 0.44$). Eleven subjects (13%, 95% CI: 7–22%) had a critical cardiac event within 48 months. On ROC analysis BNP had a high predictive value regarding discrimination of patients with and without critical events (area under the ROC curve, 0.90; 95% CI: 0.76 to >0.99, $P < 0.001$). The cut-off was 85 pg/ml (sensitivity, 88%; specificity, 85%). Additionally, estimated event-free-survival was longer after Senning than after Mustard procedure ($P \leq 0.017$). There was no significant difference in outcome between patients with simple or complex TGA with regard to occurrence of critical events.

Conclusions: BNP is a sensitive and specific prognostic marker for critical cardiac events after ASO. (*Circ J* 2015; 79: 2677–2681)

Key Words: Atrial switch operation; B-type natriuretic peptide; Cardiac event; Congenital heart disease; Transposition of the great arteries

B-type natriuretic peptide (BNP), a cardiac hormone with diuretic, natriuretic, vasodilatory and anti-fibrotic properties,^{1,2} is a widely accepted marker in the assessment of left- and right ventricular function and heart failure.³ BNP is mainly secreted by cardiac myocytes.^{4,5} The main stimuli for secretion are volume expansion or pressure load.

In patients with transposition of the great arteries (TGA) after atrial switch operation (ASO), the function of the morphologic right systemic ventricle is the main focus with regard to mid- and long-term morbidity and mortality.^{6–9}

Recent studies support the hypothesis that natriuretic pep-

tides play an important role in detecting ventricular dysfunction in patients with congenital heart disease (CHD).^{10–13} The role of BNP after ASO performed as Mustard or Senning procedure remains to be elucidated.

The objective of the present study was therefore to investigate the impact of BNP in the classification of heart failure after ASO and to evaluate whether BNP is an appropriate prognostic marker to identify patients at high risk for critical cardiac events, defined as decompensation, need for heart transplantation or sudden cardiac death.

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Table. Subject Clinical Characteristics

Variables	n=89
Age (years)	24 (15–35)
M/F	53 (60)/36 (40)
Surgery: Mustard/Senning operation	45 (51)/44 (49)
Age at surgery (years)	1 (0–17)
Functional class I,II/III,IV	83 (93)/6 (7)

Data given as median (range) or n (%).

Methods

Subjects

Eighty-nine clinically stable patients (36 female, 53 male; median age, 24 years; range, 15–35 years) with TGA after ASO having their routine follow-up at the German Heart Centre Munich, were included in the study.

Venous puncture and assessment of plasma BNP were performed as part of the routine examination.

The medical records were reviewed for patient demographics and diagnosis. Patients were assigned to 4 functional classes (FC) according to the recommendations of Perloff et al;¹⁴ FC I, asymptomatic at all levels of activity; FC II, symptoms not curtailing average everyday activity; FC III, symptoms curtailing most but not all average everyday activity; FC IV, symptoms curtailing almost all average everyday activity and could be present at rest.

All patients received extensive information about the aim of the study. All patients or their legal guardians gave written informed consent. The study was approved by the ethics board of the medical faculty of the Technical University Munich.

Assessment of Morbidity and Mortality

Patients or their relatives were asked to fill in a questionnaire regarding physical wellbeing, physical capability and pharmacological treatment at the time of BNP assessment. In addition, information on cardiac decompensation with need for hospitalization, need for heart transplantation or cardiac death were collected.

Sample Collection

Venous samples were collected during routine assessment. All samples were collected into tubes containing potassium ethylenediamine tetra-acetic acid. BNP was measured within 8 h after collection using sandwich immunoassay (Triage BNP assay; Biosite Diagnostics, San Diego, CA, USA). Precision and sensitivity of this assay have been described elsewhere.¹⁵

Statistical Analysis

The study was conducted as a retrospective cohort study (ie, the study planning and data collection were performed after the actual study period), but the gathered data were prospective in nature, therefore conventional prospective methodological approaches such as Kaplan-Meier analysis and Cox proportional hazard regression were applicable. The cohort study design allowed for time-to-event analysis, comparing the event risks of subpopulations with different baseline attributes, in particular different BNP levels. Control for potential confounding factors was facilitated by including established outcome predictors in a multivariate Cox regression model.

The BNP assay is able to detect levels between 0 and 1,300 pg/ml. Any level >1,300 was recorded as 1,300 for statistical evaluation. Due to a considerable lack of normality in distribution of BNP level, Mann-Whitney U-test was used to

compare 2 patient groups with respect to this continuous endpoint, BNP level. Data are given as median, IQR, and range. Bivariate correlations between quantitative parameters and BNP level were evaluated using Spearman's correlation coefficient.

Receiver operating characteristics (ROC) analysis was carried out to investigate the diagnostic performance of BNP and to determine the most reliable cut-off in terms of correct prediction of any critical event (decompensation, heart transplantation or death). For the purpose of clinical significance, derivation of optimal BNP cut-off was restricted to a pre-defined lower level of sensitivity of 80% to be exceeded. The area under the ROC curve (AUC) is reported with 95% CI to assess overall predictive performance of BNP.

Time-dependent event-free survival probabilities were estimated using the Kaplan-Meier method. Group comparisons regarding time to event data were performed using log-rank test and Cox proportional hazard models.

All statistical tests were 2-tailed and $P < 0.05$ was regarded as statistically significant. No multiplicity corrections of P-values or confidence levels were applied in the course of multiple testing. All analyses were conducted using SPSS for Windows Version 17.0 (SPSS, Chicago, IL, USA).

Results

A total of 89 patients with TGA after ASO (Mustard or Senning operation) were enrolled. The clinical characteristics are listed in [Table](#).

All patients were in a stable clinical condition without signs of acute cardiac decompensation. Eighty-three patients were asymptomatic, or minimally symptomatic (FC I or II), and 6 had moderate to severe symptoms (FC III or IV).¹⁴

Patients in FC I or II were 1.5 years younger than patients with moderate to severe symptoms (24 ± 5 years vs. 25.5 ± 5 years, $P < 0.54$).

Plasma BNP in all patients was assessed at clinical evaluation, and the median was 37 pg/ml (range, 3–1,150 pg/ml). A statistically significant positive correlation was seen between age and plasma BNP ($r = 0.29$; $P < 0.032$).

Plasma BNP was higher in female compared with male subjects, but the difference was not statistically significant (median, 50 vs. 26 pg/ml; $P < 0.069$).

Plasma BNP in FC I/II compared with that in the higher FC was not statistically significantly different (35 vs. 246 pg/ml; $P \leq 0.073$; [Figure 1](#)).

In patients with simple or complex TGA no significant difference in BNP was seen at evaluation, but BNP was significantly higher in patients after Mustard (median, 43 pg/ml; IQR, 21–88 pg/ml) than after Senning procedure (median, 27 pg/ml; IQR, 13–54; $P \leq 0.030$).

Patient clinical status was followed during a median of 19 months (range, 3–47 months) after BNP measurement. Eight of the 89 patients had 1 or more critical cardiac events (decompensation, heart transplantation or death) during follow-up: 7 patients developed cardiac decompensation, 3 underwent heart transplantation and 1 patient died (FC III at time of evaluation). ROC analysis for BNP regarding the prediction of at least 1 critical event showed an AUC of 0.90 (95% CI: 0.76 to >0.99; $P < 0.001$; [Figure 2](#)).

A BNP-cut-off of 85 pg/ml was determined (sensitivity, 88%; specificity, 85%). Due to the low prevalence of critical events in the documented follow-up time this cut-off-level had a positive predictive value of only 37%, but had a high negative predictive value of 99%. Regarding event-free survival, there was a highly significant difference between patients with

BNP below and above 85 pg/ml ($P < 0.001$). None of the patients with BNP below this cut-off had a critical event during follow-up, whereas the event-free survival in the group with BNP > 85 pg/ml was approximately 40% after 2 years (Figure 3).

Comparing patients after ASO for either simple or complex TGA, there was no statistically significant difference in event rates (log-rank test, $P \leq 0.44$), and there was an almost equal distribution of critical events within the first 2.5 years of follow up, but a significantly higher risk for the occurrence of a critical event was observed for Mustard compared with Senning patients (log-rank test, $P \leq 0.017$; HR, 8.48; 95% CI: 1.04–69.2; Figure 4).

Discussion

In patients with TGA after ASO, failure of the morphologic right systemic ventricle is the main determinant of morbidity and mortality.¹⁶

The etiology of this myocardial dysfunction is still hypothetical. Possible reasons include reduced preload in the case of baffle obstruction with inadequate ventricular filling, the atypical spheric shape and the structural morphology of the right ventricle with elevated end systolic and end diastolic volumes and an impairment of myocardial perfusion with reduced coronary flow reserve.¹⁷

In the clinical follow-up of these patients, a clinical parameter for estimating the appearance of cardiovascular complications and for risk stratification of cardiac events is needed.

The value of chest X-ray in detecting ventricular function is still controversial, and it has been suggested that less than half of the patients with ventricular dysfunction have a cardiothoracic ratio $> 55\%$.¹⁸ On comparison with other techniques there is a weak correlation between cardiothoracic ratio and radionuclide-, echocardiographic- and magnetic resonance imaging-derived volumes and ejection fraction.¹⁹ Electrocardiogram (ECG), chest X-ray and Holter-ECG findings were specifically not predictive of sudden cardiac death after

Senning or Mustard repair.²⁰

Heart rate is, according to the Frank-Starling mechanism, directly related to preload. In the case of baffle obstruction (reduced preload), which is not necessarily related to ventricular dysfunction, patients have an elevated heart rate compared with those without obstruction, therefore heart rate is a less favorable marker in detecting myocardial dysfunction.²¹ Additionally, after ASO many adult patients are treated with β -blockers or angiotensin-converting enzyme inhibitors; this medication has a significant influence on heart rate and blood pressure. Accordingly, blood pressure and heart rate vary widely according to the individual, and are not suitable for risk stratification of ventricular dysfunction.

In a previous study we noted a statistically significant negative correlation between BNP and coronary flow reserve, which is significantly attenuated in patients with dysfunction of the morphologic right systemic ventricle.²¹

BNP and N-terminal proBNP (NT-proBNP) are valuable biomarkers for the assessment of myocardial dysfunction.^{22,23} Data on patients with systemic right ventricle, however, particularly adults after ASO for TGA, are scarce.^{22–26} The majority of studies describe these patients as a small subgroup of a heterogeneous collective.

To our knowledge this is one of the biggest studies to analyze BNP after ASO for TGA so far, demonstrating that BNP is, indeed, an important prognostic marker in this particular group of patients.

In the current study 89 patients after ASO were included. We chose to utilize BNP as marker substance because it might have a better correlation with a chronic clinical condition compared with NT-proBNP, which might be advantageous as a marker for more acute changes during the course of the disease.^{27,28} Few studies have directly compared the prognostic value of BNP and NT-proBNP in patients with heart disease. Some have concluded that these 2 markers are substantially equivalent, others have observed differences, particularly in acute settings: for instance in response to short-term exercise.²⁸

In the current study the 83 patients in FC I/II had a clearly lower plasma BNP level than the 6 patients in FC III or IV. In addition, there was a direct, but not significant, association between functional status and BNP. A similar association was described previously in adults with congestive heart failure from acquired heart disease,^{29,30} as well as in a general group of adults with CHD²² and, most recently, in patients with TGA.^{31,32} Moreover, the present data are also in agreement with the results from a smaller group of younger patients after ASO or with congenitally corrected TGA. In that study, asymptomatic patients had normal BNP, while BNP increased after deterioration of clinical status or with decreasing exercise capacity.³³ In contrast, other groups did not find a relationship between BNP and exercise capacity after atrial redirection.³⁴

Even more important than the association between BNP level and functional status is the relationship between plasma BNP and prognosis. The present data confirm the prognostic value of BNP after ASO. BNP has a high predictive value regarding critical cardiac events, defined as cardiac decompensation, need for heart transplantation or death, during follow-up. These data confirm the Koch et al results.³³ Koch et al found a positive correlation between BNP and a regurgitant systemic atrioventricular valve, that is, the tricuspid valve in TGA after ASO, as well as a negative correlation with the exercise capacity and maximum $\dot{V}O_2$ in these patients. Increasing atrioventricular valve regurgitation is of particular importance in this patient group because it is often combined

with deterioration of systemic ventricular function. Additionally, others have found a positive correlation between BNP and quod vitam prognosis in pediatric heart failure.^{35–37}

Interestingly there is no difference in outcome between patients with simple or complex TGA, but a significantly higher risk for a critical event was observed for Mustard compared with Senning patients.

In the present study group, at least 9% (n=8) had a critical cardiac event within 48 months. Seven patients developed cardiac decompensation, 3 had heart transplantation, and 1 had cardiac death. On ROC analysis, BNP had a high predictive value for discrimination of patients with and without critical events (AUC, 0.90; 95% CI: 0.76 to >0.99, $P<0.001$). The BNP cut-off was 85 pg/ml (sensitivity, 88%; specificity, 85%). Interestingly, the event-free survival after Senning procedure was longer than after Mustard procedure ($P=0.017$), matching the fact that BNP was significantly higher after Mustard procedure, but there were no differences between simple vs. complex TGA with regard to critical events.

This findings are in agreement with a study performed by Deanfield et al, which showed that late outcomes after the Senning procedure are superior to those after Mustard repair, largely because of the lower need for reoperation for venous pathway obstruction.³⁸

The incidence of rhythm disturbances (atrial flutter) was lower in the group of patients after Senning repair, and diastolic function was impaired in the majority of patients after Mustard repair, because abnormal ventricular filling may be due, in part, to flow limitation by the atrial baffle.^{39,40}

In the present study the female patients had higher BNP, but the difference was not statistically significant. The data extend previous knowledge that BNP is significantly higher in women. These findings were not explained by age- or gender-related changes in blood pressure, renal function or cardiac structure. The association of female gender and BNP appears, in part, to be related to estrogen status, because BNP was higher in women using hormone replacement therapy.^{41,42}

In conclusion, neurohormonal activation in adolescents and adults after ASO is an important indicator for the assessment of cardiac function. Moreover, BNP enables identification of patients at risk for critical cardiac events.

This is of critical importance because – in contrast to patients with acquired heart disease – patients with CHD often do not notice clinical deterioration in a timely manner.

Determination of BNP level allows the treating physician to assess the clinical situation, independently from subjective patient information. Moreover, the appearance of cardiovascular complications may be anticipated and treatment can be adjusted accordingly.

Study Limitations

The study was retrospective and the study group was relatively small, which limited the statistical power. There was a wide variety of patients with a different medical history; nevertheless, all patients had TGA after ASO (Senning/Mustard) with a morphologic right systemic ventricle; despite the different pre- and postoperative backgrounds, the function of this ventricle is the main determinant of long-term prognosis in these patients.

The present study was performed at a tertiary care center for adults with CHD. Thus, the present sample of patients does not represent the typical population of CHD seen by a general practitioner or cardiologist. The prevalence of more complex and severe cases in these institutions is likely to be higher than in community-based hospitals and departments for cardiology.

Disclosures

None.

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