Utility of N-Terminal Pro B-Type Natriuretic Peptide to Differentiate Cardiac Diseases from Noncardiac Diseases in Young Pediatric Patients

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Background: Previous studies comparing children with cardiac disease with children with lung disease or healthy children indicated that natriuretic peptides are promising markers in pediatric patients. The aim of this study was to further clarify the diagnostic usefulness of N-terminal pro-B-type natriuretic peptide (NT-proBNP) measurements in a less preselected population of children younger than 3 years, a population in which clinical symptoms are frequently unspecific.

Methods: NT-proBNP concentrations (Roche Diagnostics) were measured in sera of 142 pediatric patients (age range, 33–1070 days) presenting at the Gynaecologic and Pediatric Hospital (Linz, Austria) between January 2003 and January 2004. ROC curve analysis for the diagnostic performance of NT-proBNP, the Mann–Whitney U-test for group comparison, and linear regression analysis for influencing factors were performed.

Results: NT-proBNP concentrations were significantly increased in infants with cardiac diseases [median (25th–75th percentile), 3681 (1045–13557); n = 23] compared with infants with other diseases [241 (116–542) ng/L; n = 119], and ROC analysis revealed good performance for NT-proBNP in differentiating between infants with and without cardiac diseases [mean area under the curve (AUC) with 95% confidence interval (CI), 0.87 (0.76–0.94)]. A subgroup analysis of exactly age- and sex-matched infants was performed, which revealed results comparable to those for the whole study population [mean (95% CI) AUC, 0.84 (0.68–0.93)].

Conclusion: In a heterogeneous group of pediatric patients <3 years of age, NT-proBNP showed good diagnostic performance to distinguish between cardiac diseases and various noncardiac diseases.

The natriuretic peptides B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) have emerged as useful markers of heart failure in symptomatic adults (1–3). This is of particular relevance when echocardiography is not easily available. In asymptomatic patients with moderate to severe left ventricular systolic and diastolic dysfunction, natriuretic peptides were found to be increased and are of diagnostic value as well. Both markers have comparable diagnostic accuracy (4, 5). Furthermore, patients with heart failure appear to benefit from a disease monitoring based on natriuretic peptide measurements (6), and a pilot study showed advantages of natriuretic peptide–guided treatment compared with traditional therapy in heart failure patients (1). In patients with acute myocardial infarction (7, 8), acute coronary syndromes (9, 10), stable coronary artery disease (11), hypertension (12), or heart failure (13), natriuretic peptides allow risk stratification. However, published data on the usefulness of natriuretic peptide testing in the pediatric population are still limited. Because of the diverse origins of the underlying heart defects, clinical signs and symptoms may lack sensitivity and specificity, are age-dependent, and can be masked by coexisting diseases; in

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Received September 14, 2005; accepted April 18, 2006.
Previously published online at DOI: 10.1373/clinchem.2005.060608

5 Nonstandard abbreviations: BNP, B-type natriuretic peptide; NT-proBNP, N-terminal B-type natriuretic peptide; NYU PHFI, New York University Pediatric Heart Failure Index; CI, confidence interval; and AUC, area under the curve.
addition, symptoms suggesting heart diseases may also be present in other diseases (14, 15). Thus, heart disease may not always be easily detected clinically in children, and a biochemical marker to identify pediatric patients with cardiac diseases would be helpful. Recently, BNP and NT-proBNP were shown to be increased in pediatric patients with congenital heart diseases (16–21). In infants suffering from respiratory distress, NT-proBNP and BNP were significantly higher when the underlying cause was acute or congestive heart failure compared with acute lung disease (22, 23). Therefore, natriuretic peptides seem to be promising markers in pediatric patients as well. The aim of this study was to further clarify the diagnostic usefulness of NT-proBNP measurements in children younger than 3 years, a population in which clinical symptoms are frequently unspecific. In contrast to the above-mentioned studies, which focused on a comparison of patients with heart diseases with healthy controls or patients with lung diseases, we tested the diagnostic performance of NT-proBNP as a marker of cardiac disease in a less preselected population with a broader spectrum of diseases that better reflected the real situation.

Materials and Methods
We retrospectively investigated 142 pediatric patients younger than 3 years presenting at the Gynaecologic and Pediatric Hospital (Linz, Austria) between January 2003 and January 2004. Infants younger than 1 month were excluded because high concentrations of natriuretic peptides immediately after delivery with a subsequent rapid decrease have been reported. The study is consistent with the Declaration of Helsinki. Peripheral venous blood was drawn for routine blood analysis. Serum was stored at −20 °C for occasional reassessment of routine tests, and NT-proBNP concentrations were additionally batch measured within 7 months. The population comprised pediatric patients with cardiac diseases [median (minimum–maximum) age, 75 (33–1042) days; n = 23] as assessed by echocardiography, and infants with no history of heart disease and no signs of heart disease on physical examination [median (minimum–maximum) age, 486 (33–1070) days; n = 119]. Patients without complete data were not included. The infants with cardiac diseases were as follows: 2 with valvular heart disease (tricuspid valve stenosis, n = 1; pulmonary valve stenosis, n = 1); 17 with congenital heart diseases (complex congenital heart diseases, n = 11; atrial septal defects, n = 3; ventricular septal defects, n = 3); 2 with dilated cardiomyopathy; 1 with acute pericarditis; and 1 with cardiac shock with papillary muscle rupture. Infants with cardiac diseases mostly presented with combined defects, with a total of 16 infants suffering from right heart volume overload, 9 suffering from left heart volume overload, 8 suffering from right ventricular pressure load, 1 suffering from left ventricular pressure load, 9 suffering from clinical heart failure, and 6 presenting with cyanosis. All infants with cardiac diseases were classified according to the New York University Pediatric Heart Failure Index (NYU PHFI), which is a heart failure score based on signs and symptoms, physiology, and current medications. Healthy children have low NYU PHFI scores (≤2), whereas children with left-to-right shunt lesions have scores of ~11 (24).

Children with noncardiac diseases (controls) presented with kidney diseases, including tumors (n = 7); lung diseases (n = 15); central nervous system disorders (n = 9); infectious diseases (n = 42); liver disorders (n = 4); epilepsy (n = 9); a connective tissue tumor (n = 1); malformation (n = 6); and minor diseases (n = 26) such as gall or kidney stones, reflux, vomiting, noninfectious diarrhea, sleep apnea, and hypertrophy of tonsils.

NT-proBNP (1–76) was measured by a sandwich electrochemiluminescence immunoassay (Élecsys 1010; Roche Diagnostics) with polyclonal antibodies specific against the epitopes NT-proBNP (1–21) and NT-proBNP (39–50) as described previously (25, 26). The intraassay CV was 1.1% at a NT-proBNP concentration of 170 ng/L (n = 20) and 1.4% at a NT-proBNP concentration of 5080 ng/L (n = 20); the interassay CVs at the same NT-proBNP concentrations were 6.0% (n = 20) and 3.6% (n = 20), respectively.

ROC curve analysis (27) was carried out to investigate the diagnostic performance of NT-proBNP for identifying infants with heart diseases. For this reason, the whole study population was used. Because of differences in age, we performed a subanalysis in which children with cardiac diseases were randomly paired with age- and sex-matched children with noncardiac diseases. The Mann–Whitney U-test was used for group comparisons. Linear regression analysis was performed in log(10)-transformed NT-proBNP values as well. Data are given as the median (25th–75th percentiles). P < 0.05 was considered to indicate statistical significance.

Results
There was no significant difference in sex distribution between the 23 infants with cardiac diseases and the 119 infants with other diseases. However, there was a significant difference in age (P = 0.002), which may be explained by the fact that the group with cardiac diseases was smaller and that these infants mostly had severe cardiac diseases, which manifest early in life. Creatinine concentrations were below the upper reference limit in all infants. Median NT-proBNP concentrations were significantly (P < 0.0001) increased in infants with cardiac diseases [3681 (1045–13 557) ng/L] compared with infants with noncardiac diseases [241 (116–542) ng/L; Table 1]. When infants with noncardiac diseases were further divided into subgroups of kidney, lung, central nervous system, and other diseases, NT-proBNP concentrations were significantly higher in the infants with cardiac disease than in the infants of each subgroup (Table 1). The ROC curve analysis (Fig. 1) showed good performance for NT-proBNP to differentiate between infants with cardiac diseases and infants with other diseases, with a mean [95% confidence interval (CI)] area under curve (AUC) of
We also performed a linear regression analysis in the whole study population (n = 142), which revealed a significant influence of the presence of cardiac disease (P < 0.0001) and of age (P < 0.0001) on log(10)-transformed NT-proBNP concentrations. There was no significant influence of sex (P = 0.318).

Because of the significant difference in age in this population, we performed a subanalysis using random age- and sex-matched controls for each infant with cardiac disease, which revealed results similar to those obtained with the whole study population. Two male patients could not be exactly matched with controls and had to be excluded. The final study population of this subanalysis comprised 21 pediatric patients with a mean age difference of 2.9 days (P = 0.772). NT-proBNP concentrations were still significantly higher (P < 0.0001) in infants with cardiac disease [median (25th–75th percentiles), 3530 (244–149) ng/L] than in infants with other diseases [median (25th–75th percentiles), 3681 (1045–13 557) ng/L]. The mean AUCROC (95% CI) was 0.84 (0.68–0.93). At the optimal cutoff of 2000 ng/L, which had the highest diagnostic accuracy based on the ROC curve analysis, the mean (95% CI) sensitivity was 71% (48%–88%), the specificity was 86% (63%–96%), the positive predictive value was 83% (58%–96%), the negative predictive value was 75% (49%–91%), and the accuracy was 79% (63%–89%).

Discussion

The novel finding of this study is that in a heterogeneous group of young pediatric patients who came to the hospital because of various signs and symptoms, NT-proBNP was a suitable marker to rule out cardiac disease. Because there are controversial results about the dynamics of normal NT-proBNP concentrations in infants and children (20, 21, 28, 29), we decided to investigate a distinct age group of infants from 1 month to 3 years of age. Although Mir et al. (20) and Nir et al. (21) found high NT-proBNP concentrations only during the first days of life with no significant differences between healthy children 1 month to 18 years of age, two other studies (28, 29) revealed an age dependency of NT-proBNP concentrations. Recently, the authors of a large study reported a significant impact of age on NT-proBNP measured by the Roche assay, which we used in this study, with values decreasing with increasing age (30), as we found in our study. We excluded infants in the first month of life because this group has very high concentrations of NT-proBNP immediately after birth that subsequently decrease rapidly (21, 28, 29).

Most previous studies investigated the active hormone BNP in children with different heart diseases. BNP concentrations have been shown to increase according to the severity of heart failure symptoms in children (31), and higher BNP concentrations than in controls have been found in pediatric patients with congenital heart diseases that lead to ventricular dysfunction (17, 32) or left or right ventricular volume overload (16, 17). However, only a

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Table 1. NT-proBNP concentrations in infants with cardiac or noncardiac diseases.

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. of Infants</th>
<th>NT-proBNP, a ng/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac diseases</td>
<td>23</td>
<td>3681 (1045–13 557)</td>
</tr>
<tr>
<td>Noncardiac diseases</td>
<td>119</td>
<td>241 (1045–13 557)</td>
</tr>
<tr>
<td>Noncardiac disease groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>7</td>
<td>317 (215–379)</td>
</tr>
<tr>
<td>Lung</td>
<td>15</td>
<td>174 (102–1262)</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>9</td>
<td>247 (72–640)</td>
</tr>
<tr>
<td>Other</td>
<td>88</td>
<td>226 (116–439)</td>
</tr>
</tbody>
</table>

a Median (25th–75th percentiles).

Compared with patients with cardiac diseases: P < 0.0001; P = 0.005; P = 0.001.

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Fig. 1. ROC curve for the diagnostic performance of NT-proBNP in identifying pediatric patients with cardiac diseases (n = 142).

The optimal cutoff value with the highest diagnostic accuracy is indicated.
few studies have focused on NT-proBNP in children with cardiac diseases. We found significantly higher NT-proBNP concentrations in young pediatric patients with cardiac diseases compared with controls. In this study, NT-proBNP concentrations (median, 3681 ng/L) in infants with cardiac diseases were not as high as in a recent study involving pediatric patients of the same age (median, 18 452 ng/L) (22). However, the authors of the latter study attempted to differentiate between cardiac and lung diseases in very acutely ill infants with respiratory distress. Thus, the ROC curve analysis revealed unrealistically perfect performance of the marker (AUC = 1.0), which clearly needs confirmation. The cutoff value in that study was higher (2940 ng/L) than our cutoff value (2000 ng/L), which is explained by the different study populations. Similar to our study, however, infants with lung diseases did not show significantly different NT-proBNP concentrations compared with controls (22). In an earlier study comparing children with and without heart diseases (21), NT-proBNP concentrations (1321 ng/L) were not as high as in our study (3681 ng/L), which may be attributable to the older population studied (4 months–15 years), although no obvious age dependency was found in this previously published study (21). Another study (20) investigating congestive heart failure in patients up to 14 years of age also showed significantly higher NT-proBNP concentrations in children with cardiac diseases than in controls. Because a different assay was used (Biomedica), the absolute concentrations in their cardiac patients exceeded the concentrations in our study and are not easily comparable. When we strictly age- and sex-matched our pediatric heart patients with controls, we still found good and comparable diagnostic performance of NT-proBNP similar to that obtained when we included the whole population, with a similar cutoff value of 2000 ng/L. Recently, NT-proBNP was also found to be a marker of persistent cardiac disease in children (2 days to 14 years of age) with a history of dilated cardiomyopathy or myocarditis (33). Patients with evidence of severe left ventricular dysfunction or dilatation had significantly higher mean NT-proBNP concentrations (3154 ng/L with the Roche assay) than children who had recovered from ventricular dysfunction (122 ng/L) or controls (113 ng/L). Thus, the few currently published studies indicate that the optimal diagnostic cutoff values for cardiac diseases in children seem to depend on the severity of disease, with higher cutoff values in acutely ill pediatric patients, and may also be age dependent, with higher cutoff values in younger infants.

From our results, we conclude, that in a heterogeneous group of young pediatric patients, NT-proBNP showed good diagnostic performance to distinguish between cardiac diseases and various noncardiac diseases. Our ROC analysis suggested a cutoff value of 2000 ng/L for the exclusion of cardiac diseases in children 1 month to 3 years of age if NT-proBNP is measured with the Roche assay.

The NT-proBNP Elecsys assays were gifts from Roche (Austria). The assay manufacturer had no influence on study design, data analysis or interpretation, or the content of this manuscript.

References