The role of NT-proBNP in the diagnostics of isolated diastolic dysfunction: correlation with echocardiographic and invasive measurements

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Aims Diastolic heart failure is a frequent entity but difficult to diagnose. N-terminal pro-B type natriuretic peptide (NT-proBNP) was therefore investigated as a possible non-invasive parameter to diagnose isolated diastolic dysfunction.

Methods and results Sixty-eight symptomatic patients with isolated diastolic dysfunction and preserved left ventricular ejection fraction (LVEF) (>50%) and 50 patients with regular left ventricular (LV) function were examined by conventional echocardiography, tissue Doppler imaging (TDI), and left and right heart catheterization. Plasma NT-proBNP levels were determined simultaneously. Median NT-proBNP plasma levels were elevated [189.54 pg/mL (86.16–308.27) vs. 51.89 pg/mL (29.94 –69.71); P<0.001] and increased with greater severity of the diastolic dysfunction (R=0.67, P<0.001). According to the receiver operating characteristic analysis, LV end-diastolic pressure [area under the curve (AUC) 0.84] was the most specific parameter, which had a low sensitivity (61%), however. The reliability of NT-proBNP was similar to TDI indices (AUC 0.83 vs. 0.81) and improved when compared with conventional echocardiography (AUC 0.59–0.70). NT-proBNP levels had the best negative predictive value of all methods (94%) and correlated strongly with indices of LV filling pressure, as determined by invasive measurements. Multivariable linear regression analysis confirmed NT-proBNP as an independent predictor of diastolic dysfunction with an Odds ratio of 1.2 (1.1–1.4, CI 95%) for every unit increase of NT-proBNP.

Conclusion NT-proBNP can reliably detect the presence of isolated diastolic dysfunction in symptomatic patients and is an useful tool to rule out patients with reduced exercise tolerance of non-cardiac origin.

KEYWORDS Left ventricular diastolic dysfunction; N-terminal pro-B type natriuretic peptide; Heart failure; Biomarker

Introduction
Heart failure with normal or minimally impaired systolic function is attributed to diastolic dysfunction. More than one-third of patients presenting with symptoms and signs of congestive heart failure (CHF) have isolated diastolic dysfunction, which is associated with a poor prognosis. Clinical examination cannot distinguish between systolic and diastolic heart failure. The diagnosis of diastolic heart failure is rather based on exclusion. Doppler echocardiography is used for a quick bedside assessment of diastolic function, but its sensitivity and specificity in detecting diastolic abnormalities are unsatisfactory due to many factors including heart rate, age, left ventricular (LV) loading conditions, and operators skills. Similar problems may be expected for tissue Doppler imaging (TDI), AV-plane displacement, and magnetic resonance techniques. Invasive investigations via left and right heart catheterization to measure LV filling pressures are more reliable, but also load-dependent and not useful for wide spread clinical implementation. For these reasons, simple and reliable diagnostic criteria for diastolic heart failure are lacking and a rapid non-invasive diagnostic test would be of high clinical value.

Abnormal diastolic filling pressure, the key functional abnormality in diastolic heart failure, leads to a release of cardiac neurohormones including natriuretic peptides. Previous studies have reported that B type natriuretic peptide (BNP) and its biologically inactive fragment N-terminal proBNP (NT-proBNP), both of which are released predominantly by the ventricles in response to stretch, may be used for the diagnosis of systolic heart failure. However, the role of these peptides in patients with diastolic heart failure is still under investigation. Although it has been found that BNP and NT-proBNP correlate with diastolic abnormalities in patients with reduced systolic function and in patients with advanced forms of isolated diastolic dysfunction.
were measured, as well as the velocity (Ar) and duration of the
included also pulmonary vein flow analysis in the right upper para-
these three echocardiographic parameters
were abnormal after age and heart rate relaxation. Confirmation
dysfunction was considered when at least two of these parameters
E was indicated by a reduction of the ratio of
derived from LV outflow tract Doppler signals. Slow early LV filling
to
A-
longation of isovolumic relaxation time (IVRT
mild diastolic failure.11–17 The latter is associated with
studies found them not to be useful for the detection of
plasma concentrations and has a longer half-life when
compared with BNP,18 NT-proBNP could be useful for the
detection of all degrees of diastolic dysfunction. To study this hypothesis, we have investigated the potential of NT-
proBNP to detect isolated diastolic dysfunction, according
to the guidelines of the European Study Group On Diastolic
Heart Failure,19 and its accuracy in comparison to estab-
ished invasive and non-invasive methods including left and
right heart catheterization, transmural Doppler echocardi-
ography, pulmonary venous Doppler, and TDI in a series of
patients with clinically suspected CHF despite preserved LV
systolic contractility and dimensions.

Methods

Patient population
We investigated prospectively 118 patients admitted to our unit who
had preserved LV function and normal LV dimensions as determined
by echocardiography and ventriculography. Sixty-eight patients with
exertional dyspnoea (NYHA class I–III) who met the criteria for iso-
lated diastolic dysfunction were compared with 50 patients with
normal diastolic function. Patients with atrial fibrillation, lung
diseases, renal dysfunction, significant heart valve disease, or
other severe concomitant diseases were excluded. Medications
that can influence haemodynamics (diuretics, beta-blockers,
calcium-blockers, and ACE- and AT1-receptor inhibitors) were all
paused for 48 h before examinations were performed.

All investigated patients gave informed written consent for inva-
sive diagnostic procedures, including echocardiography and right
and left cardiac catheterization, which were performed by using
standard techniques. Our study complies with the Declaration of
Helsinki. The locally appointed Ethics Committee has approved
the research protocol.

Definition and assessment of diastolic dysfunction
Following the guidelines from the European Study Group on Diastolic
Heart Failure,19 the diagnosis of diastolic dysfunction was defined
after the evidence of abnormal LV relaxation, filling, and/or dia-
stolic distensibility in the presence of clinical signs of CHF, with
measurable normal or only mildly impaired systolic function (EF ≥ 50%). During LV angiography, slow isovolumic LV relaxation
was indicated by an increase in dP/dtmin (≥ −1100 mmHg/s) and/or
a prolongation of the time constant of LV pressure decay (Tau
≥ 48 ms) as derived and calculated from digitalized LV pressure
recordings using a modified commercially available software
program (MacLab, Winstech, Germany), and/or during echocardi-
ography (VINGMED System Five operating at 2.5–3.5 MHz) by a pro-
longation of isovolumic relaxation time (IVRT ≥94–100 ms) as
derived from LV outflow tract Doppler signals. Slow early LV filling
was indicated by a reduction of the ratio of E-wave (early filling)
to A-wave (atrial filling) peak velocities (E/A < 1) and/or of the
E-wave deceleration time (DT ≥ 220–260 ms) as derived from LV
Doppler signals. Because the specificity and sensitivity of any one of
these three echocardiographic parameters per se are low, diastolic
dysfunction was considered when at least two of these parameters
were abnormal after age and heart rate relaxation.20 Confirmation
included also pulmonary vein flow analysis in the right upper para-
septal pulmonary vein where systolic (S) and diastolic (D) velocities
were measured, as well as the velocity (Ar) and duration of the
atrial reversal wave. Using TDI, the ratio of early-to-late annular
velocity of lateral mitral leaflets origin (E’/A’) was determined in
the apical four-chamber view. All echocardiography data were
copied to VHS videotape for subsequent playback, analysis, and
measurement. Reduced LV diastolic distensibility was indicated by
an increase in LV end-diastastic pressure (LVEDP ≥ 16 mmHg)
as derived from LV pressure recordings and/or by pulmonary capillary
wedge pressure (PCWP) measured by right heart catheterization
(Swan–Ganz catheter) at rest (≥12 mmHg) or during exercise
(≥20 mmHg) (cycle ergometry). Exercise was performed by
bicycle ergometry in a recumbent position with the use of a contin-
uous protocol, which began with a workload of 25 W that was
increased by 25 W every 2 min. Patients were asked to cycle at a
rate of 50 r.p.m. at each stage, and exercise was terminated when
the patient reached 75% of the calculated maximum heart rate or
because of dyspnoea or of the occurrence of leg/general fatigue.
NT-proBNP plasma levels were determined at rest using the commer-
cially available Elecsys® proBNP sandwich immunoassay on an
Elecsys 2010 (Roche Diagnostics, Germany). All measurements
were obtained without knowledge of NT-proBNP data.

Overall diastolic stage, determined from the pattern of mitral and
pulmonary venous flow, was defined as impaired relaxation (stage I:
E/A ratio < 1, DT > 220 ms; S/D ratio > 1, Ar < 35 cm/s), pseudonor-
mal (stage II: E/A ratio 1–2, DT > 150–220 ms; S/D ratio < 1,
Ar > 35 cm/s), or restrictive (stage III: E/A ratio > 2, DT < 150 ms;
S/D ratio < 1, Ar < 35 cm/s).21,22 Reduction of the E'/A' ratio (< 1)
in TDI confirmed diastolic dysfunction, including stages I and II. E'
and A' amplitude < 8 cm/s indicated a restrictive flow pattern.
LV mass index was calculated according to Devereux formula3 divided by body surface area. We calculate left atrial volume
index (LAVI) according to the already described formula: LAVI = π/6
(diameter in parasternal long-axis view) × (short-axis in the
apical four-chamber) × (long-axis in the apical four-chamber)24 at
ventricular end-systole divided by body surface area.

Statistical analysis

SPSS Inc. for Windows Standard version 11.0.1 was used for statistical
analysis. Continuous variables are expressed as mean ± SD (range).
Quantitative normally distributed data were compared using the
Student’s t-test. Non-normally distributed variables were
analysed with non-parametric Mann–Whitney U test. To compare
qualitative data, χ2 test was performed. Receiver operating charac-
teristic (ROC) curves were constructed to determine the ability
of NT-proBNP throughout the range of concentrations (cut-off points)
to identify diastolic dysfunction. The diagnostic utility of NT-proBNP
alone was compared with the echocardiographic probability of LV
dysfunction through the estimation of the area under the curve
(AUC) for each parameter separately. Linear regression analysis
was used to determine correlations between continuous variables and
the log-transformed NT-proBNP levels were used, as the values
were not normally distributed. Spearman correlation was used for
correlation assessment of NT-proBNP with the groups of LVDD.
Multivariable logistic regression (backward likelihood ratio model)
was performed to evaluate the ability of NT-proBNP to identify dia-
stolic dysfunction over and above the information provided by other
indicators from Table 1 [age, sex, hypertension, diabetes mellitus,
CAD, LV-hypertrophy, and body mass index (BMI)]. A value of
P < 0.05 was considered statistically significant and α-level adjust-
ment (Bonferroni correction) with factor 3 (P = 0.017) is used to
avoid the experiment-wise Type I error due to multiple testing
between the LV diastolic dysfunction groups.

Results

Study participants
From 180 patients initially planned to enter the study, 11 of
them were excluded because of the low quality of data
The prevalence of diastolic dysfunction was increased in patients with coronary artery disease (CAD) and a higher frequency of diabetes mellitus and suspected myocarditis with abnormal diastolic function (mean age 49 ± 10% and normal LVEDD in the parasternal long axis, which probably reflects systolic relaxation rather than early diastolic filling, did not differ between both groups. Diastolic dysfunction was diagnosed with a high rate of objective measured abnormal diastolic indices. Fifty-one per cent of patients with diastolic dysfunction had three or four abnormal diastolic echocardiographic and/or invasive parameters, 22% had more than five and 15% had more than seven positive indices.

**Table 1. Patients characteristics [variable expressed as mean ± SD (range)]**

<table>
<thead>
<tr>
<th>Demographic variables</th>
<th>Population (n = 118)</th>
<th>Diastolic dysfunction (n = 68)</th>
<th>Regular diastolic function (n = 50)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women/men [n (%)]</td>
<td>53 (45)/59 (55)</td>
<td>31 (46)/37 (54)</td>
<td>22 (44)/28 (56)</td>
<td>0.708</td>
</tr>
<tr>
<td>Age (years)</td>
<td>49 ± 13 (70–26)</td>
<td>51 ± 9 (69–26)</td>
<td>49 ± 10 (70–28)</td>
<td>0.091</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.1 ± 4.1 (32.7–16.3)</td>
<td>26.8 ± 4.0 (31.9–16.5)</td>
<td>25.3 ± 4.0 (32.7–17.9)</td>
<td>0.120</td>
</tr>
<tr>
<td>Vital signs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>91.9 ± 12 (123–61)</td>
<td>93.6 ± 11 (117–73)</td>
<td>90.1 ± 12 (123–61)</td>
<td>0.172</td>
</tr>
<tr>
<td>NYHA II–III [n (%)]</td>
<td>66 (56)</td>
<td>58 (85)</td>
<td>8 (16)</td>
<td>0.001</td>
</tr>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>71 ± 11 (58–90)</td>
<td>70 ± 12 (60–82)</td>
<td>71 ± 11 (58–90)</td>
<td>0.865</td>
</tr>
<tr>
<td>Left heart dimensions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>50 ± 6 (38–59)</td>
<td>51 ± 6 (40–59)</td>
<td>50 ± 4 (38–58)</td>
<td>0.473</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>107 ± 31 (65–198)</td>
<td>114 ± 28 (65–198)</td>
<td>103 ± 26 (72–154)</td>
<td>0.371</td>
</tr>
<tr>
<td>LAVI (mL/m²)</td>
<td>18.8 ± 5.9 (11.3–34.2)</td>
<td>21.0 ± 6.8 (10.4–34.2)</td>
<td>18.1 ± 4.5 (11.3–27.9)</td>
<td>0.303</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>67 ± 10 (84–51)</td>
<td>68 ± 9 (78–51)</td>
<td>65 ± 10 (84–52)</td>
<td>0.093</td>
</tr>
<tr>
<td>Concomitant diseases [n (%)]</td>
<td>49 (41)</td>
<td>30 (44)</td>
<td>19 (37)</td>
<td>0.687</td>
</tr>
<tr>
<td>Hyperlipoproteinemia</td>
<td>33 (28)</td>
<td>21 (31)</td>
<td>12 (24)</td>
<td>0.433</td>
</tr>
<tr>
<td>Arterial Hypertension</td>
<td>44 (37)</td>
<td>29 (43)</td>
<td>15 (30)</td>
<td>0.060</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11 (9)</td>
<td>9 (13)</td>
<td>2 (0.4)</td>
<td>0.011</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>43 (34)</td>
<td>28 (41)</td>
<td>15 (30)</td>
<td>0.086</td>
</tr>
<tr>
<td>Viral/inflammatory myocardiopathy</td>
<td>28 (24)</td>
<td>22 (32)</td>
<td>6 (12)</td>
<td>0.023</td>
</tr>
</tbody>
</table>

*Diastolic dysfunction vs. regular diastolic function.

NT-proBNP levels in patients with isolated diastolic dysfunction

NT-proBNP levels were four-fold elevated in patients with diastolic abnormalities when compared with control patients [189.54 pg/mL (86.16–308.27) vs. 51.89 pg/mL (29.9–69.7); P < 0.001]. There was no significant difference between men and women with diastolic abnormalities [164.3 pg/mL (72.6–260.5) vs. 204.0 pg/mL (108.9–318.9); P = 0.112]. NT-proBNP levels increased significantly according to the severity of overall diastolic dysfunction, ranging from impaired relaxation [151.6 pg/mL (90.6–278.1) vs. controls 51.89 pg/mL (29.9–69.7), P < 0.001] to pseudo-normal filling [308.1 pg/mL (261.7–568.2) vs. 151.6 pg/mL (90.6–278.1), P = 0.003] and restrictive filling [2307.1 pg/mL (1592.0–6440.1) vs. 308.1 pg/mL (261.7–568.2), P < 0.001] and correlated with the Spearman coefficient R = 0.67, P < 0.001 (Figure 1). Even after α-level adjustment, the differences between LVDD groups remained significant (P < 0.017). The proportion of patients with abnormal sex- and age-adjusted NT-proBNP levels among the control, impaired relaxation, pseudonormal, and restrictive subgroup amounted to 8, 74, 94, and 100%, respectively (Figure 2).

Similarly, NT-proBNP levels increased significantly according to the NYHA-classification, ranging from NYHA class I [97.5 pg/mL (77.2–120.6) vs. controls 55.7 pg/mL (32.7–86.3), P < 0.040] to NYHA class II [177.3 pg/mL (74.1–293.3) vs. 97.5 pg/mL (77.2–120.6), P = 0.008] and NYHA class III [334.7 pg/mL (180.2–976.8) vs. 177.3 pg/mL...
Better than the NT-proBNP was almost as good as the L VEDP and TDI and logistic regression analysis, NT-proBNP was an independent predictor of isolated diastolic dysfunction with an Odds ratio of 1.2 (1.1–1.4, CI 95%), for every unit increase in the NT-proBNP level (Table 5).

Correlation of the NT-proBNP plasma levels with Doppler echocardiographic indices, TDI, and invasive measured diastolic indices

Linear regression analysis revealed significant correlations between NT-proBNP and various echocardiographic parameters (Table 6). Thereby, a moderate relation to early diastolic velocity (E) (R = -0.41, P < 0.001), early-to-late diastolic velocity ratio (E/A) (R = -0.36, P < 0.001) of mitral lateral annular movement, and a weak relation to A-Ar duration (R = -0.31, P = 0.037) were found. NT-proBNP and E/A analysis by TDI correlated significantly with all invasive LV diastolic parameters as measured directly by left and right heart catheterization. The best correlation was found with LVEDP, PCWP at rest, and at maximal exercise with R-values of 0.45, 0.42, 0.49 (P < 0.001), respectively. NT-proBNP did not correlate significantly with LVEDD, LVMi, DT, early and late mitral flow,
mitral E/A ratio, PV systolic and diastolic, PV systolic to diastolic ratio (S/D), and reversal atrial flow.

Discussion

To investigate the role of NT-proBNP in the detection of isolated diastolic dysfunction, we formed a comparative study of NT-proBNP, invasive haemodynamics, and comprehensive echocardiography. Our study showed that NT-proBNP plasma levels were increased in patients with diastolic dysfunction and preserved systolic function and correlated with the severity of the disease. NT-proBNP had the best negative predictive value of all methods investigated. The best correlation was found between the NT-proBNP levels and the invasive parameters of LV filling pressure. NT-proBNP levels had similar diagnostic accuracy for diastolic heart failure as TDI and were superior to conventional echocardiography.

The role of NT-proBNP in the detection of diastolic dysfunction

Instant measurement of plasma natriuretic peptides that are normally increased as part of the neurohormonal activation in both diastolic and systolic heart failure is a powerful biochemical test. There are several reports on the efficacy of BNP or NT-proBNP in diagnosing chronic heart failure due to LV systolic dysfunction. A particular advantage of that test is its high negative predictive value, allowing to rule out systolic heart failure. The usefulness of BNPs in detecting diastolic heart failure is still under investigation. Few studies have examined the value of BNPs in diagnosing diastolic dysfunction in comparison with conventional echocardiography. Significantly higher BNP and NT-proBNP levels were found in patients with advanced diastolic dysfunction (restrictive and pseudonormal) and our study supports these findings. Although these peptides were found to correlate with severe diastolic dysfunction, however, their role in the detection of mild diastolic heart failure is uncertain.

Lubien et al. found that BNP levels were increased in patients with exertional dyspnoea and impaired LV relaxation (202 pg/mL). Although Mottram et al. also found BNP levels increased in patients with hypertension-caused impaired LV relaxation compared with controls, however, in up to 75%, BNP levels were in the normal range (89 pg/mL) in patients with impaired relaxation in this study. Wei et al. reported low but significantly increased BNP levels in hypertension-caused diastolic dysfunction, which showed a moderate sensitivity but an excellent specificity in detecting ventricular diastolic dysfunction in hypertensive
was assay-dependent with a clear benefit for the Elecsys NT-proBNP and BNP for the diagnosis of diastolic dysfunction et al. Lercher life of NT-proBNP when compared BNP is advantageous exertional dyspnoea. It appears that the prolonged half-
even includes the subgroup of clinically stable patients levels correlate with the severity of diastolic disease. This 
graphic measurements. We found that increased NT-proBNP by a combination of invasive and comprehensive echocardio-
problem, we have defined abnormal diastolic performance limited as also observed in our study. To overcome this key 
ations investigated, the impact of a variety of clinical features, and differences in study design and emphasize the 
features in this field of research. Most previous studies used conventional echocardiographic parameters as the 
sole diagnostic criteria to identify isolated diastolic dysfunction. Obviously, the accuracy of transmural flow analysis is 
limited as also observed in our study. To overcome this key problem, we have defined abnormal diastolic performance by a combination of invasive and comprehensive echocardiographic measurements. We found that increased NT-proBNP levels correlate with the severity of diastolic disease. This even includes the subgroup of clinically stable patients with near normal LVEDP at rest, impaired relaxation, and 
exertional dyspnoea. It appears that the prolonged half-life of NT-proBNP when compared BNP is advantageous under these circumstances and enables NT-proBNP to identify mild isolated diastolic dysfunction already. Hammerer-
Lercher et al. recently reported that the performance of NT-proBNP and BNP for the diagnosis of diastolic dysfunction was assay-dependent with a clear benefit for the Elecsys NT-proBNP and Triage BNP assays, but further comparative evaluations are warranted.

<p>| Table 6 Correlation of NT-proBNP levels with invasive and non-invasive diastolic indices according to univariate linear regression analysis |
|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>R-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.33</td>
</tr>
<tr>
<td>Systolic RR</td>
<td>0.28</td>
</tr>
<tr>
<td>Diastolic RR</td>
<td>0.06</td>
</tr>
<tr>
<td>MAP</td>
<td>0.19</td>
</tr>
<tr>
<td>Heart rate</td>
<td>0.27</td>
</tr>
<tr>
<td>LVEDD</td>
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</tr>
<tr>
<td>LVMI</td>
<td>0.08</td>
</tr>
<tr>
<td>Mitral flow</td>
<td></td>
</tr>
<tr>
<td>$E$</td>
<td>0.08</td>
</tr>
<tr>
<td>$A$</td>
<td>0.02</td>
</tr>
<tr>
<td>$E/A$</td>
<td>−0.07</td>
</tr>
<tr>
<td>IVRT</td>
<td>0.30</td>
</tr>
<tr>
<td>DT</td>
<td>0.01</td>
</tr>
<tr>
<td>PV flow</td>
<td></td>
</tr>
<tr>
<td>$S$</td>
<td>−0.15</td>
</tr>
<tr>
<td>$D$</td>
<td>−0.18</td>
</tr>
<tr>
<td>$S/D$</td>
<td>0.04</td>
</tr>
<tr>
<td>$Ar$</td>
<td>−0.20</td>
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<tr>
<td>$A-Ar$ duration</td>
<td>−0.31</td>
</tr>
<tr>
<td>Tissue Doppler</td>
<td></td>
</tr>
<tr>
<td>$E$</td>
<td>−0.41</td>
</tr>
<tr>
<td>$A'$</td>
<td>0.11</td>
</tr>
<tr>
<td>$E/A'$</td>
<td>−0.36</td>
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<tr>
<td>Catheterization</td>
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<tr>
<td>LVEDP</td>
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</tr>
<tr>
<td>$dP/dt_{min}$</td>
<td>0.21</td>
</tr>
<tr>
<td>Tau</td>
<td>0.22</td>
</tr>
<tr>
<td>PCWP, rest</td>
<td>0.42</td>
</tr>
<tr>
<td>PCWP, exercise</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Impaired LV relaxation was detected with a specificity of 90% and a negative predictive value of 94% by a NT-proBNP of 120 pg/mL in 75% of symptomatic patients. This value is similar to the recently recommended official NT-proBNP cut-off value of 120 pg/mL. However, this cut-off value is an average value from several community studies focusing more on LV systolic function and not based on the complicated diagnostic, which is necessary to analyse also sufficient isolated diastolic dysfunction. Our study shows that even lower NT-proBNP levels (90–110 pg/mL) reached the negative predictive value of 94% accompanied with only a slight reduction in specificity (Table 3). Therefore, NT-proBNP is an useful tool to rule out patients with reduced exercise tolerance of non-cardiac origin. From the clinical point of view, the negative predictive value of ≥94% appears most useful, because in patients with exercise-induced dyspnoea at NT-proBNP <90 pg/mL, a cardiac origin of symptoms is highly unlikely, whereas at NT-proBNP >110 pg/mL, diastolic dysfunction is the prominent differential diagnosis. But as advanced forms of diastolic dysfunction may reach NT-proBNP levels similar to those in patients with severe systolic heart failure, NT-proBNP cannot differentiate between diastolic and systolic heart failure and is not a surrogate for echocardiography.

Although the sensitivity of NT-proBNP to detect isolated diastolic dysfunction was moderate (69%) and therefore not accurate for a screening test as also already shown by Redfield et al., NT-proBNP had one of the best sensitivity of the tested methods in our study.

In conclusion, NT-proBNP reliably detects diastolic dysfunction in patients with filling abnormalities and preserved LV systolic function, however, in line with the recent European guidelines incorporating BNP in the algorithm for the diagnosis of heart failure.

**NT-proBNP vs. invasive and echocardiographic measurements**

This study is the first to compare NT-proBNP for the diagnosis of isolated diastolic dysfunction in symptomatic patients with a broad panel of established methods including left and right heart catheterization, transmural, PV Doppler, and TDI. Gold standard for the assessment of diastolic function is invasive measurement with a conductance catheter providing pressure-volume relationships. In the clinical practice, the more easily available measurement of LV pressures during routine left and right heart catheterization also enables direct analysis of the early ($dP/dt_{min}$, Tau) and late period (LVEDP and PCWP) of diastole. However, these values are volume- and heart rate-dependent, which is reflected by our finding of a high specificity (89–95%) but low sensitivity (<61%) of LVEDP and PCWP, respectively, to detect diastolic dysfunction (Table 4). The differences between PCWP at rest and exercise were not as high as expected, because several patients with diastolic dysfunction did not really reach high exercise levels (mean maximal outcome: 83 W; mean exercise duration time 7.3 min) due to dyspnoea, fatigue, or leg pain, which shows the limitation of this method in the clinical routine. Nevertheless, LVEDP and PCWP, both reflecting LV filling pressure, correlated stronger with NT-proBNP levels. PCWP at exercise, used to investigate symptomatic patients with near normal filling pressures at rest, correlated best with NT-proBNP, as we had also shown.
It is also in agreement with our finding that none of the conventional echocardiographic parameters reached sufficient sensitivity and specificity (33–79%) for reliable detection of isolated diastolic function and may explain why the NT-proBNP levels of our study population did not correlate with DT and most of the indices determined by PV Doppler. Although IVRT correlated significantly the diastolic function in patients with concomitant systolic heart failure, Mottram et al. could not verify IVRT as an important diagnostic marker in patients with isolated diastolic dysfunction. Similarly, although a short DT indicates an increase in LA mean pressure in patients with systolic or restrictive diastolic heart failure, our data do not support a diagnostic relevance of DT, reflecting early diastolic filling, as 24% of our patients with diastolic failure had prolonged DTs. This confirms Dahlström and co-workers, who also found no significant relationship between DT and BNP or NT-proBNP in a study population with mild diastolic abnormalities. In summary, owing to many limitations, Doppler echocardiography cannot provide unequivocal evidence of diastolic dysfunction.

TDI is a more recent technique that measures myocardial velocities directly. The early diastolic mitral annular velocity (E/A) has been shown to be a relatively load-independent measure of myocardial relaxation. It correlated significantly better with the NT-proBNP levels in our study population than the E/A ratio determined by conventional echocardiography, consistent with studies of diastolic function comparing TDI or the ratio of mitral velocity to early diastolic velocity of the mitral anulus (E/E) derived from TDI and BNP levels in intensive care patients or patients with systolic or diastolic heart failure. Thus, NT-proBNP levels have similar diagnostic accuracy for diastolic heart failure as TDI and are superior to conventional echocardiography.

In conclusion, according to its ROC, NT-proBNP stands in the line with invasive parameters of LV filling pressure and is characterized by a high negative predictive value. Therefore, NT-proBNP can reliably detect the presence of isolated diastolic dysfunction in symptomatic patients and is a useful tool to rule out patients with reduced exercise tolerance of non-cardiac origin.

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