NT-proBNP for Pulmonologists: Not Only a Rule-Out Test for Systolic Heart Failure but Also a Global Marker of Heart Disease

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For editorial comment see p. 368

Key Words

Heart disease • Lung disease • Natriuretic peptide • Dyspnea • Sensitivity and specificity

Abstract

Background: Recognizing heart disease is relevant to pulmonologists because many patients suspected to have dyspnea of pulmonary origin harbor heart disease. **Objectives:** To investigate the role of N-terminal pro-brain natriuretic peptide (NT-proBNP) in identifying heart disease and cardiac causes of dyspnea among patients referred for evaluation by a pulmonologist. **Methods:** 697 consecutive outpatients (aged 57.5 ± 16.4 years) with chronic dyspnea prospectively underwent a diagnostic work-up for heart and lung diseases. **Results:** The prevalence of patients with heart disease was 25.3%. The cardiac findings were placed into 6 groups which were associated with an increase in NT-proBNP in the following order: (1) left ventricular hypertrophy [regression coefficient (β) = 0.33, $p = 0.03$]; (2) exercise-induced myocardial ischemia ($\beta = 0.73$, $p = 0.02$); (3) valvular or congenital heart disease or pericardial effusion ($\beta = 0.93$, $p < 0.0001$); (4) pulmonary hypertension ($\beta = 1.14$, $p < 0.0001$); (5) atrial fibrillation or left bundle branch block ($\beta = 1.22$, $p < 0.0001$), and (6) left ventricular systolic dysfunction ($\beta = 1.94$, $p < 0.0001$).

Using predefined cut-off values of 93 pg/ml (men) and 144 pg/ml (women), sensitivity was 0.75 and specificity was 0.79 for identifying heart disease. The negative predictive value was 0.90. If heart disease had to be considered as a cause of the dyspnea, sensitivity and the negative predictive value went up to 0.90 and 0.97, respectively. **Conclusions:** NT-proBNP performs well as a test for ruling out cardiac dyspnea. It is also useful as a rule-in test for heart disease, which enables the pulmonologist to appropriately select candidates for in-depth evaluation by cardiology.

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Introduction

A normal level of N-terminal pro-brain natriuretic peptide (NT-proBNP) effectively rules out left ventricular systolic dysfunction in outpatients presenting with symptoms possibly due to heart failure who are referred from primary care to hospital-based cardiology services [1–4]. Dyspnea is the leading symptom of heart and lung disease. The referring physician's assessment determines whether a patient with dyspnea will be seen by a cardiologist or by a pulmonologist for further evaluation. NT-proBNP may perform differently in pulmonary practice

because the filtering action of the referring physicians results in differences between the 2 patient populations in terms of the prevalence and spectrum of heart disease [5]. Recognizing heart disease is relevant to the pulmonologist for 2 reasons. First, cardiac and pulmonary dyspneas are not always easy to distinguish. A number of patients referred with suspected pulmonary disease have dyspnea of cardiac origin. Second, many patients with known lung disease harbor concomitant heart disease, which may be masked by the lung-related dyspnea. This particularly applies to COPD [6, 7].

The modest specificity of NT-proBNP in identifying systolic heart failure is an everyday experience. The subsequent high rate of false-positive results undermines its diagnostic value in the view of many clinicians. There are, however, several other cardiac disorders, such as atrial fibrillation [8], valvular disease [9–11], left ventricular hypertrophy [12] and pulmonary hypertension [13, 14] that may also cause dyspnea and a rise in NT-proBNP. All these disorders reduce the specificity of NT-proBNP in identifying left ventricular systolic dysfunction, but NT-proBNP would also be valuable to the pulmonologist as an indicator of the entire set of cardiological differential diagnoses. This marker should either reliably exclude a cardiac disorder or make it so probable that consulting a cardiologist would be worthwhile. We examined the value of NT-proBNP in detecting heart disease among patients referred for pulmonologist evaluation of dyspnea.

Patients and Methods

Patients

This prospective monocenter study was conducted on consecutive outpatients referred for evaluation of dyspnea of at least 2 weeks duration to the pulmonology service of an academic teaching hospital from January 2005 to January 2007. Dialysis-dependent renal failure and information about a previous measurement of NT-proBNP were exclusion criteria. The study was approved by the ethics committee of the Baden-Württemberg State Chamber of Physicians. Informed consent was obtained.

Diagnostic Procedures

One physician (S.W.) examined the patients at their first visit. Blood samples were drawn for measurement of NT-proBNP (index test) using an ELISA assay, which was supplied free by the manufacturer (Roche Diagnostics, Mannheim, Germany). The company was not involved in the design of the study, the statistical analysis, and the preparation of the manuscript. The examining physicians were blinded to NT-proBNP values. The patients underwent a diagnostic work-up for heart and lung disease (reference test) within 10 days of the index test. The work-up included chest X-ray, pulmonary function tests, resting ECG, exercise ECG, and Doppler echocardiography. Further studies were done

when indicated. One senior cardiologist (E.M.) did 94% of the echocardiograms. Treatment was not changed during the period from the index test to the reference test.

Diagnostic Criteria

Classification of Cardiological Findings

Left ventricular systolic function was graded into normal, and mildly, moderately or severely impaired. Pulmonary hypertension was diagnosed if the peak systolic gradient across the tricuspid valve measured with continuous wave Doppler was ≥ 35 mm Hg. The severity of mitral or aortic regurgitation was graded into mild, moderate, or severe. The severity of aortic stenosis was graded by the mean transvalvular pressure gradient (Δp) into mild (Δp 20–30 mm Hg), moderate (Δp >30–50 mm Hg), or severe (Δp >50 mm Hg). Left ventricular hypertrophy was diagnosed if the end-diastolic septal wall thickness was ≥ 12 mm or if the Sokolow criteria were fulfilled in the presence of arterial hypertension. A diagnosis of heart disease was only made on echocardiographic or ECG evidence and not on clinical or radiological grounds alone.

Relevant cardiological findings were prospectively defined and placed into 6 characteristic groups. Hierarchical categories were created to rank patients who had findings that fell within more than 1 characteristic group unambiguously:

Category 6: Impaired left ventricular systolic function (i.e. group 6).

Category 5: Atrial fibrillation or left bundle branch block (i.e. group 5) and no finding belonging to a higher category.

Category 4: Pulmonary hypertension (i.e. group 4) and no finding belonging to a higher category.

Category 3: At least mild aortic stenosis, at least moderate aortic regurgitation, at least moderate mitral regurgitation, severe tricuspid regurgitation, atrial septal defect, pericardial effusion (i.e. group 3) and no finding belonging to a higher category.

Category 2: Exercise-induced myocardial ischemia due to angiographically proven coronary disease (i.e. group 2) and no finding belonging to a higher category.

Category 1: Left ventricular hypertrophy (i.e. group 1) and no finding belonging to a higher category.

The patients with heart disease were classified as to whether the cardiological finding was thought to be (a) the principal cause of dyspnea, (b) a contributing factor, or (c) not related to the dyspnea. The presence of arterial hypertension or minor echocardiographic findings was also recorded. The latter included mild aortic regurgitation, mild mitral regurgitation and a borderline systolic pressure gradient of 30–34 mm Hg across the tricuspid valve.

Classification of Lung Disease

Existing disease was classified as obstructive lung disease or as other disease. The former was classified as asthma and COPD. The degree of airway obstruction (FEV_1/VC <5th percentile) was stratified into 3 levels of severity based on the FEV_1 : mild to moderate ($FEV_1 \geq 60\%$ of predicted), moderately severe (FEV_1 50–59% of predicted) or severe to very severe (FEV_1 <50% of predicted). The COPD patients were also classified according to the GOLD stages.

Data Analysis

The NT-proBNP values had a skewed distribution and therefore are presented as medians. The influence of all 6 cardiological

Table 1. Cardiological findings and heart disease categories

Characteristic group	n	Number of patients in heart disease category					
		6	5	4	3	2	1
Impaired left ventricular systolic function (6)	30	30					
Mild	13						
Moderate	9						
Severe	8						
Rhythm or conduction disturbances (5)	51	7	43				
Atrial fibrillation	42						
Left bundle branch block	9						
Pulmonary hypertension (4)	61	12	6	43			
Valvular or congenital heart disease or pericardial effusion (3)	26	4	5	3	14		
Aortic regurgitation (moderate, severe)	2 (2, 0)						
Aortic stenosis (mild, moderate, severe)	11 (10, 0, 1)						
Mitral regurgitation (moderate, severe)	7 (6, 1)						
Severe tricuspid regurgitation without pulmonary hypertension	3						
Atrial septal defect	1						
Pericardial effusion	2						
Exercise-induced myocardial ischemia (2)	12	3	1	1	1	6	
Left ventricular hypertrophy (1)	66	5	8	10	3	0	40

n is the number of cardiological findings in each characteristic group. The number of patients in the corresponding heart disease category is given at the top of each column. The numbers of patients with secondary cardiological findings are given lower down in each column. For example, left ventricular hypertrophy was present in 5 out of the 30 patients with impaired left ventricular function, 3 had exercise-induced myocardial ischemia, 4 had valvular or congenital heart disease or pericardial effusion, 12 had pulmonary hypertension and 7 had rhythm or conduction disturbances.

characteristic groups on NT-proBNP was assessed by multiple linear regression analysis after the NT-proBNP values had been transformed to their natural logarithm. Next, the groups were ranked according to their standardized regression coefficients, and the 6 heart disease categories were created as described above. A multiple linear regression model was used to investigate the effects of pulmonary disease groups and lung function parameters on NT-proBNP in the entire group and the impact of arterial hypertension and minor echocardiographic findings on NT-proBNP in patients without heart disease. The effects of age, sex, interaction of age and sex, and body mass index (BMI) [15, 16] were simultaneously taken into account as confounding variables in all of the multiple linear regression models. Using previously defined cut-off values of 93 pg/ml for men and 144 pg/ml for women [17], sensitivity, specificity, predictive values and likelihood ratios for identifying heart disease categories 6, 5–6, 4–6, 3–6, 2–6 and 1–6 and for identifying heart disease as a principal or contributory cause of dyspnea were calculated. Receiver operating characteristic (ROC) curves were constructed for both sexes and for different age and weight categories after dichotomizing the entire group by the median values for age and BMI in the group of patients with heart disease [18]. The values for area under the curve (AUC) with 95% CIs were calculated and compared with each other [19]. Given the explorative nature of the study, no adjustment for multiple testing was made. $p < 0.05$ was considered to be significant. Analyses were performed using SAS, version 9.1 with the %roc macro for ROC curve analysis.

Results

A total of 738 patients were enrolled in the study, 41 of whom had to be excluded because of incomplete data (missing NT-proBNP values, 3 patients; failure to turn up to the reference tests, 33 patients; incomplete reference tests, 5 patients), so that 697 patients (365 men and 332 women, mean age 57.5 ± 16.4 years) were eligible for analysis.

The prevalence of patients with sole cardiac disease was 5.9%. Pulmonary disease was present in 78.6% of cases, either alone (59.2%) or in combination with heart disease (19.4%). There were 246 cardiological findings in the 176 patients with heart disease, as shown in table 1. Table 2 shows the baseline characteristics, comorbidities and the NT-proBNP values for each heart disease category. A total of 356 patients had asthma and 124 had COPD with the following distribution by GOLD stage: 5 had stage 1, 49 had stage 2, 36 had stage 3 and 34 had stage 4. Heart disease was found in 43.5% of patients with COPD and left ventricular systolic function was impaired in 8.1% of patients with this condition. Of the 68 patients in the class 'other lung disease', 43 had interstitial lung dis-

Fig. 1. Relative frequency of heart disease among the study population stratified by age. The black portion of each bar represents the frequency of patients with impaired left ventricular systolic function.

Fig. 2. Box-and-whisker plots of NT-proBNP levels among patients with dyspnea stratified by the presence of heart and lung disease. NT-proBNP levels are plotted on a logarithmic scale. The line within the box denotes the median. The box spans the interquartile range (25th–75th percentiles). The ends of the whiskers represent the minimum and maximum values.

ease and 12 had pneumoconiosis. Hypercapnic respiratory failure was present in 20 patients. The frequency of heart disease among the study population stratified by age is shown in figure 1.

Women had higher NT-proBNP than men [regression coefficient (β) = 1.61, 95% CI 1.02–2.19, $p < 0.0001$]. Age

Fig. 3. Box-and-whisker plots of NT-proBNP levels stratified by the degree of airway obstruction in patients with (white box) and without (hatched box) concomitant heart disease. The degree of airway obstruction had no effect on NT-proBNP in either group. NT-proBNP levels are plotted on a logarithmic scale. The line within the box denotes the median. The box spans the interquartile range (25th–75th percentiles). The ends of the whiskers represent the minimum and maximum values.

($\beta = 0.04$, 95% CI 0.03–0.05, $p < 0.0001$) and BMI ($\beta = -0.03$, 95% CI -0.04 to -0.01 , $p < 0.01$) also influenced NT-proBNP.

Figure 2 illustrates that NT-proBNP was not affected by the presence of lung disease. A more detailed regression analysis revealed that the presence of asthma, COPD, other lung disease, hypercapnic respiratory failure, and the degree of airway obstruction had no independent effect on NT-proBNP. The relationship between the degree of airway obstruction and NT-proBNP is shown in figure 3.

All 6 cardiological characteristic groups were associated with an elevation of NT-proBNP. The following order was obtained from the standardized regression coefficients: (1) left ventricular hypertrophy ($\beta = 0.33$, 95% CI 0.03–0.62, $p = 0.03$); (2) exercise-induced myocardial ischemia ($\beta = 0.73$, 95% CI 0.11–1.35, $p = 0.02$); (3) at least mild aortic stenosis, at least moderate aortic regurgitation, at least moderate mitral regurgitation, severe tricuspid regurgitation without evidence of pulmonary hypertension, atrial septal defect or pericardial effusion ($\beta = 0.93$, 95% CI 0.50–1.36, $p < 0.0001$); (4) pulmonary hypertension ($\beta = 1.14$, 95% CI 0.84–1.44, $p < 0.0001$); (5) atrial fibrillation or left bundle branch block ($\beta = 1.22$, 95%

Table 2. Clinical data, comorbidities and NT-proBNP levels in patients with and without heart disease

	Heart disease							No heart disease (n = 521)
	all patients (n = 176)	category 6 (n = 30)	category 5 (n = 43)	category 4 (n = 43)	category 3 (n = 14)	category 2 (n = 6)	category 1 (n = 40)	
Male/female	108/68	25/5	25/18	18/25	11/3	6/0	23/17	257/264
Mean BMI	28.8 (19.4–54.5)	28.7 (20.1–54.5)	28.3 (20.1–43.7)	28.6 (19.4–46.9)	27.9 (20.8–34.4)	27.2 (23.3–29.8)	30.2 (23.5–41.0)	27.2 (15.6–55.1)
Mean age, years	69.6 (36.0–87.2)	70.9 (48.4–85.7)	69.9 (49.8–85.4)	70.5 (38.2–86.1)	66.2 (36.0–81.2)	73.3 (68.2–77.1)	67.9 (44.9–87.2)	53.4 (14.0–84.3)
Mean number of cardiological findings	1.4 (1–4)	2.1 (1–4)	1.5 (1–4)	1.3 (1–3)	1.4 (1–2)	1.0 (1–1)	1.0 (1–1)	–
Median NT-proBNP, pg/ml	291 (10–11,584)	2,144 (68–11,584)	548 (20–5,966)	423 (30–5,350)	234 (18–9,242)	586 (60–1,399)	114 (10–1,740)	55 (2.5–1,148)
COPD	54	10	8	19	5	3	9	70
Asthma	64	10	20	10	8	0	16	292
Other lung disease	17	2	6	7	0	0	2	51
Arterial hypertension	126	21	27	25	11	3	39	178

Figures in parentheses are minimum and maximum. See 'Patients and Methods' for explanations of the categories.

Table 3. Test characteristics of NT-proBNP in identifying different categories of heart disease and heart disease as the predominant or contributing cause of dyspnea

Heart disease	Sensitivity/specificity	Positive predictive value/ negative predictive value	Positive likelihood ratio/ negative likelihood ratio
Category 6	0.97/0.68 (1.00/0.68)	0.12/1.00 (0.12/1.00)	3.04/0.05 (3.15/0.00)
Category 5–6	0.86/0.72 (0.97/0.71)	0.26/0.98 (0.24/1.00)	3.03/0.19 (3.35/0.05)
Category 4–6	0.84/0.75 (0.94/0.74)	0.40/0.96 (0.36/0.99)	3.37/0.22 (3.65/0.09)
Category 3–6	0.83/0.77 (0.93/0.75)	0.45/0.95 (0.38/0.99)	3.54/0.22 (3.73/0.09)
Category 2–6	0.83/0.77 (0.92/0.76)	0.47/0.95 (0.40/0.98)	3.64/0.22 (3.80/0.10)
Category 1–6	0.75/0.79 (0.90/0.78)	0.55/0.90 (0.48/0.97)	3.58/0.32 (4.06/0.13)

The numbers in parentheses denote the test characteristics for identifying heart disease as a cause of dyspnea. Predefined NT-proBNP cut-off values were 93 pg/ml and 144 pg/ml for men and women, respectively. See 'Patients and Methods' for definition of heart disease categories.

CI 0.90–1.53, $p < 0.0001$), and (6) impaired left ventricular function ($\beta = 1.94$, 95% CI 1.52–2.35, $p < 0.0001$).

In the 521 patients without heart disease, arterial hypertension ($n = 178$) had no effect on NT-proBNP (82 pg/ml vs. 43 pg/ml, $p = 0.07$). None of the minor echocardiographic findings was associated with NT-proBNP. The findings were: mild mitral regurgitation ($n = 46$) 94 vs. 49 pg/ml, $p = 0.08$; mild aortic regurgitation ($n = 34$) 116 vs. 50 pg/ml, $p = 0.07$; borderline systolic pulmonary artery pressure ($n = 10$) 93 vs. 55 pg/ml, $p = 0.83$; overall ($n = 71$) 95 vs. 48 pg/ml, $p = 0.06$. The interaction between arterial hypertension and minor echocardiographic findings had no effect on NT-proBNP ($p = 0.14$). The presence of arterial hypertension or at least 1 minor

echocardiographic finding ($n = 211$) emerged as a predictor of NT-proBNP (83 vs. 41 pg/ml, $\beta = 0.25$, 95% CI 0.04–0.45, $p = 0.02$).

Using cut-off values of 93 pg/ml for men and 144 pg/ml for women [17], a sensitivity of 0.97, a specificity of 0.68 and a positive predictive value of 0.12 were found when impaired left ventricular systolic function was required for the diagnosis of heart disease. Sensitivity went up to 1.00 after the criterion 'heart disease thought to be the principal or a contributory cause of the dyspnea' had been applied to the data. Table 3 shows that the positive predictive value strictly increased from 0.12 to 0.55 with more inclusive definitions of heart disease and from 0.12 to 0.48 if heart disease had to be considered as a cause of

Table 4. Diagnostic value of NT-proBNP in detecting heart disease and identifying a cardiac cause of dyspnea in different age groups and in patients with COPD

	Impaired left ventricular systolic function		Any heart disease		false-positive
	identified	missed	identified	missed	
<i>Age, years</i>					
30–45 (n = 105)	0 (0)	0 (0)	2 (1)	4 (2)	8 (9)
45–60 (n = 185)	6 (6)	1 (0)	15 (13)	10 (2)	23 (25)
60–75 (n = 262)	9 (9)	0 (0)	63 (55)	24 (5)	57 (65)
>75 (n = 90)	14 (14)	0 (0)	52 (46)	6 (4)	20 (26)
COPD (n = 124)	10 (10)	0 (0)	41 (38)	13 (3)	31 (34)

Data are numbers of patients. Given in parentheses are the numbers of patients in whom heart disease was thought to be the principal or a contributory cause of dyspnea. Predefined NT-proBNP cut-off values were 93 pg/ml and 144 pg/ml for men and women, respectively.

Table 5. Clinical assessment – heart disease as the cause of dyspnea

Heart disease category	Heart disease					
	as principal cause		as contributing factor		not related to dyspnea	
	number of patients ³	NT-proBNP	number of patients ³	NT-proBNP	number of patients ³	NT-proBNP
6 (n = 30)	19 (19)	2,830 (145, 11,584) ¹	10 (10)	1,120 (174, 7407) ¹	1 (0)	68 ²
5 (n = 43)	14 (14)	1,334 (211, 5,966) ¹	16 (14)	595 (70, 4,101) ¹	13 (6)	127 (20, 844) ¹
4 (n = 43)	11 (10)	1,871 (69, 5,350) ¹	22 (19)	531 (64, 2,342) ¹	10 (5)	98 (30, 212) ¹
3 (n = 14)	1 (1)	9,242 ²	6 (5)	236 (52, 3,483) ¹	7 (5)	194 (18, 507) ¹
2 (n = 6)	3 (2)	60, 120, 280 ²	3 (3)	891, 1,218, 1,399 ²	0 (0)	
1 (n = 40)	12 (7)	171 (44, 944) ¹	11 (11)	235 (127, 1,740) ¹	17 (1)	66 (10, 129) ¹
Total (n = 176)	60 (53)	953 (44, 11584) ¹	68 (62)	544 (52, 7407) ¹	48 (17)	80 (10, 844) ¹

¹ NT-proBNP values are given as medians (min., max.).

² NT-proBNP values are given as single values.

³ The numbers included in brackets denote the numbers of patients with NT-proBNP levels above the predefined cut-off values (93 pg/ml for men, 144 pg/ml for women).

dyspnea. The negative predictive values did not fall below 0.90 and 0.97, respectively. The values for sensitivity and the negative predictive values were consistently higher if heart disease had to be considered as a cause of dyspnea. Table 4 illustrates the diagnostic performance of NT-proBNP in various age groups and in the COPD cohort. Table 5 shows that the classification of heart disease as being either the principal cause, a contributing factor or not related to dyspnea is strongly reflected in NT-proBNP levels. Overall, 10.1% of the 128 patients with cardiac dyspnea and 25.0% of the 176 patients with heart disease had NT-proBNP levels below the cut-off. Sex-specific ROC

curves for identifying heart disease and cardiac dyspnea are shown in figure 4. The cut-off values providing the best trade-off between sensitivity and specificity were lower in men than in women. The cut-off values for identifying heart disease were lower than those for identifying cardiac dyspnea in both sexes (men 68 vs. 119 pg/ml, women 127 vs. 140 pg/ml). The AUCs for detecting a cardiac dyspnea were higher than those for detecting heart disease both for men (0.95 vs. 0.88, $p < 0.0001$) and women (0.90 vs. 0.81, $p < 0.0001$). Table 6 shows the effects of sex, age and BMI on NT-proBNP cut-off values and test operating characteristics at a predefined sensitivity of

Fig. 4. a Sex-specific receiver operating characteristic (ROC) curves for the diagnostic performance of NT-proBNP in identifying heart disease (heart disease categories 1–6). AUC is 0.88 (95% CI 0.84–0.92) for men ($n = 365$) and 0.81 (95% CI 0.75–0.87) for women ($n = 332$) (n.s.). The cut-off values for maximal sensitivity and specificity are 68 pg/ml for men (sensitivity 0.88, specificity 0.72) and 127 pg/ml for women (sensitivity 0.78, specificity 0.75). **b** ROC curves for the diagnostic performance of NT-proBNP in identifying heart disease as the principal or contributory cause of dyspnea. AUC is 0.95 (95% CI 0.93–0.97) for men and 0.90 (95% CI 0.85–0.95) for women (n.s.). The cut-off values for maximal sensitivity and specificity are 119 pg/ml for men (sensitivity 0.90%, specificity 0.85%) and 140 pg/ml for women (sensitivity 0.89%, specificity 0.77%).

0.90. The difference between cut-off values for detecting cardiac dyspnea was small between men and women (119 vs. 111 pg/ml) and both age groups (111 vs. 128 pg/ml), whereas the difference between the 2 weight categories was larger (160 vs. 102 pg/ml). Figure 5 shows the estimated density and distribution functions of NT-proBNP for patients with and without heart disease.

Discussion

The use of NT-proBNP has gained a wide acceptance in differentiating heart failure from lung disease in patients presenting with acute dyspnea [20–23]. This is the first study to investigate the role of NT-proBNP in the pulmonologist work-up of patients with chronic dyspnea. As a consequence of the filtering action of the referring physicians, the percentage of patients with sole cardiac disease was only 5.9%. Of note however, about 1 in 4 patients with lung disease had concomitant heart disease.

Our study confirmed that NT-proBNP performs well as a test for ruling out an impaired left ventricular systolic function in a population with a low prevalence of that disorder. The more important finding was that it was not only impaired left ventricular systolic function but all of the cardiological characteristic groups that were associated with an elevated NT-proBNP. The monotonic decrease in sensitivity and the inverse behavior of the values for specificity shown in table 3 mirror the ranking order derived from the standardized regression coefficients. From this it can be concluded that the pulmonologist may use NT-proBNP to identify an array of cardiac disorders. We found no independent effect of lung disease on NT-proBNP, which agrees with a study by Mogelvang et al. [24].

It was common for the patients with heart disease to have more than 1 cardiological finding. The hierarchical disease categories used in this study are not intended as a staging system. They should be regarded as a pragmatic way to make a long list of findings statistically manage-

Fig. 5. a Estimated density functions of NT-proBNP for patients with and without heart disease. **b** Estimated distribution functions of NT-proBNP in patients with and without heart disease. NT-proBNP levels are plotted on a logarithmic scale.

Table 6. Cut-off values of NT-proBNP, specificity, and predictive values as determined from the ROC curves for identifying heart disease and cardiac dyspnea in different sex, age and weight categories. Sensitivity was held constant at 0.90

	Sex		Age		BMI	
	male (n = 365)	female (n = 332)	≤71.7 years (n = 544)	>71.7 years (n = 153)	≤28.4 (n = 421)	>28.4 (n = 276)
NT-proBNP cut-off value, pg/ml	59 (119)	63 (111)	38 (111)	78 (128)	72 (160)	50 (102)
Specificity	0.67 (0.85)	0.42 (0.67)	0.43 (0.81)	0.21 (0.50)	0.62 (0.84)	0.51 (0.73)
Positive predictive value	0.53 (0.63)	0.29 (0.31)	0.23 (0.35)	0.61 (0.62)	0.38 (0.53)	0.46 (0.48)
Negative predictive value	0.94 (0.97)	0.94 (0.98)	0.96 (0.99)	0.61 (0.85)	0.96 (0.98)	0.91 (0.96)

The NT-proBNP cut-off values and the test operating characteristics referring to the identification of cardiac dyspnea are shown in parentheses.

able. This approach fits with the suggested role of NT-proBNP in the work-up of dyspnea by the pulmonologist who is not concerned with issues such as identifying specific heart diseases and assessing their severity. Recommending a laboratory test as a diagnostic tool for detecting atrial fibrillation or left bundle branch block may seem quite contentious to cardiologists and chest physicians, but a pulmonologist work-up of dyspnea usually

does not include electrocardiography [25]. Accordingly, this study was not designed to assess the extent to which NT-proBNP added value beyond electrocardiography but to evaluate its role as a diagnostic tool in its own right.

We attempted to avoid making diagnoses of doubtful significance by excluding mild aortic and mild mitral regurgitation from the characteristic groups and by setting the threshold for the peak systolic pressure gradient

across the tricuspid valve at 35 mm Hg. A gradient of 30 mm Hg is considered as the upper limit of normal [26]. Identifying left ventricular hypertrophy in patients with normal systolic function is clearly relevant, because this condition is associated with an increased risk of cardiac death [12]. After systolic dysfunction, the group 'rhythm and conduction disturbances', which mainly consisted of patients with atrial fibrillation, had the greatest impact on NT-proBNP. Wang et al. [8] also observed a strong association between atrial fibrillation and NT-proBNP. As to the effect of myocardial ischemia, our findings are difficult to compare with other studies, because dyspnea rather than angina or a positive exercise test was the criterion for entry [27]. The response of NT-proBNP secretion to ischemic episodes causing dyspnea may differ from the response to ischemia presenting as angina pectoris [28]. A number of participants without heart disease had an elevated NT-proBNP. Arterial hypertension and minor echocardiographic findings might partly account for this observation, because the presence of arterial hypertension or at least 1 minor echocardiographic finding had an effect on NT-proBNP. Left ventricular diastolic dysfunction may be another factor. Many of our patients with normal systolic function and left ventricular hypertrophy, atrial fibrillation, left bundle branch block or pulmonary hypertension probably had diastolic dysfunction. It is to be assumed, however, that not all the patients with this condition were included in the characteristic groups.

The prerequisite for entering this study was dyspnea so that all the patients had at least 1 appropriate symptom of heart disease. Detecting a cardiac abnormality does not imply, however, that it is a cause of dyspnea, so patients were clinically classified as to whether the cardiological finding was thought to be a cause of dyspnea. The AUCs presented in figure 4 show that NT-proBNP has a powerful discriminatory ability to identify cardiac dyspnea. The AUCs and the data given in tables 3–5 indicate that NT-proBNP performs better as a test for identifying cardiac dyspnea than for detecting cardiac abnormalities. This was expected, because heart disease causing dyspnea is more likely to be associated with increases in myocardial wall stress or stiffness, which are thought to be the principal triggers of proBNP release [29].

The predefined goal of this study was to prospectively evaluate the gender-specific cut-off values proposed by Nielsen et al. [17] for a pulmonologist's work-up of chronic dyspnea, which are lower than those recommended in the setting of acute dyspnea [29]. The patients of the Nielsen et al. study were recruited from primary care

physicians who were asked to refer patients with dyspnea for a diagnostic work-up for both heart and lung disease. Those authors found a sensitivity of 0.95 and a specificity of 0.68 in a study population with a prevalence of heart failure of 23%. These values agree well with the test characteristics found in our study, when impaired left ventricular systolic function was required for the diagnosis of heart disease. Mogelvang et al. [24] established age- and sex-specific limits to discriminate between cardiac and pulmonary causes of dyspnea in the general population. Rutten et al. [30] recommended a gender-independent optimal cut-off value of 125 pg/ml for identifying heart failure among elderly patients with COPD. Gustafsson et al. [2] found no improvement in diagnostic performance when age-differentiated cut-off values were used in patients who had been referred from primary care with suspected heart failure. Age, sex and BMI are predictors of NT-proBNP, but the application of sex-, age- and BMI-specific cut-off values to the individual patient would make the clinical use of NT-proBNP rather unwieldy. Fundamental to the value of a screening test for cardiac dyspnea is a high sensitivity, which translates into a low risk of overlooking a patient with this condition. The data presented in table 6 suggest that a cut-off value of 100 pg/ml entails sensitivity values above 90% for men and women as well as for both age and weight categories. The negative predictive value of 0.85 found in the older age category should be considered in the context of the low specificity in this cohort. Of note is that no patient with symptomatic left ventricular systolic dysfunction was misclassified when this cut-off value was used, as shown in table 5. Although medical decision-making often revolves around cut-off values, it is important to recognize that NT-proBNP is a continuous variable. The frequency of heart disease increases with rising levels of NT-proBNP, so that NT-proBNP may serve as a rule-in test of heart disease. Our findings support this concept [31, 32]. Figure 5 may provide guidance for selecting operating points for particular clinical situations.

Pulmonologists should not dismiss the use of NT-proBNP as diagnostic sidetracking because heart disease often contributes to the presenting complaint, even in patients with a known pulmonary cause of dyspnea. In this study, more than 2 out of 5 patients with COPD had a relevant cardiological finding. Further, heart disease is a major cause of death among patients with lung disease [33] and NT-proBNP provides prognostic information [8, 34]. The importance of dyspnea as an indicator of risk was emphasized by Abidov et al. [35] in a study on elderly patients referred for cardiac stress testing. Patients with

no known history of coronary disease who reported dyspnea and no chest pain had more than twice the risk of cardiac death compared to patients with typical angina. One conclusion to be drawn from this study is that the cause of dyspnea should be pursued vigorously. Our findings suggest that measurement of NT-proBNP is useful to the pulmonologist as a first step in achieving this goal. The pulmonologist should proceed with an in-depth evaluation by cardiology irrespective of the pulmonary status in elderly patients with an elevated NT-proBNP and whose cardiac status has not yet been determined. At the other end of the scale, cardiac disorders are so uncommon in patients under 45 years of age that the measurement of NT-proBNP will hardly ever be useful for this group.

The following limitations deserve comment. First, placing disparate cardiological findings into a set of 6 groups is somewhat arbitrary. This particularly applies to group 3, because pericardial effusion, atrial septal defect and different types of valvular heart disease have little in common. As shown in table 1, the numbers of patients with these conditions were too low for any attempts to analyze different types of disease separately. Pericardial effusion may cause a low NT-proBNP state, because the myocardial wall is not abnormally stressed despite symptoms of heart failure [31]. On the other hand, none of these disorders can be ignored in a study like this. Second, echocardiography is observer-dependent and imprecise. In everyday practice, however, echocardiography is the gold standard to which the performance of NT-

proBNP must be compared. Third, ergometry was used to detect myocardial ischemia. It is to be assumed that some patients with this condition had to stop the exercise test due to lung-related dyspnea. This further reduces its limited sensitivity so that the prevalence of ischemia was underestimated. Finally, left ventricular diastolic function was not analyzed. Assessment of transmitral flow velocity curves by Doppler echocardiography has many limitations and is unable to provide unequivocal evidence of diastolic dysfunction [36]. Tissue Doppler imaging is superior to conventional Doppler echocardiography, but this technique was not available to us [37].

In conclusion, this study shows that NT-proBNP has a powerful diagnostic ability to identify those with cardiac dyspnea among patients with chronic dyspnea referred to a pulmonologist for evaluation, if cut-off values of 93 pg/ml for men and 144 pg/ml for women are used. A gender-independent cut-off value of 100 pg/ml might be a useful alternative. The potential of NT-proBNP is not exhausted if the diagnostic target is narrowed to ruling out left ventricular systolic dysfunction. Rather, NT-proBNP should be considered as a global indicator of heart disease. Elevated NT-proBNP levels help the pulmonologist to rule in heart disease so that candidates for in-depth evaluation by cardiology can be appropriately selected. Given the high prevalence of heart disease among elderly patients referred for pulmonologist evaluation of dyspnea, NT-proBNP should be added to the diagnostic work-up of patients whose cardiac status has not yet been determined.

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