N-terminal pro-brain natriuretic peptide for discriminating between cardiac and non-cardiac dyspnoea

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Abstract

Aim: Evaluation of N-terminal pro-brain natriuretic peptide (NT-proBNP) to confirm or disprove heart failure in community patients complaining of dyspnoea. Methods and results: General practitioners referred 345 consecutive patients complaining of dyspnoea to our hospital-based clinic, where a diagnosis was established based on a combined programme for heart and lung diseases including echocardiography. The level of NT-proBNP in plasma was also measured. The mean (S.D.) concentration of NT-proBNP in patients with heart failure was significantly higher, 189 (270) pmol/l in patients with heart failure (n=81), than in patients with non-cardiac dyspnoea (n=264), 17 (38) pmol/l (P<0.001). In patients ≥50 years NT-proBNP <11 pmol/l for men and <17 pmol/l for women excluded heart failure with a negative predictive value of 97% while the positive predictive value was 53%, the sensitivity 95% and the specificity 68%. Areas under receiver operator characteristic curves for men and women were 0.93 and 0.90, respectively. Conclusion: In a relevant setting of primary care patients complaining of dyspnoea, NT-proBNP seems promising for disproval of heart failure, and this test may reduce the need for echocardiographic screening by 50%. However, the discrimination levels of NT-proBNP found in this study may need prospective confirmation, before the test can be generally recommended.

Keywords: NT-proBNP; Brain natriuretic peptide; Heart failure; Dyspnoea

1. Introduction

Heart failure patients usually present with breathlessness but low specificity of dyspnoea often leads to misdiagnoses [1–5]. Given the serious prognosis of heart failure and the yield of medical treatment, improved diagnostics are essential. Echocardiography is a key examination but many patients with suspected heart failure are not referred [6–9].

B-Natriuretic peptide (BNP) is released from the myocardium predominantly in the ventricles in response to myocardial stretch. BNP is produced in a pro-form (proBNP). On release this molecule is split into two parts, the active hormone BNP and the N-terminal 76 amino acid proBNP (NT-proBNP). BNP is closely related to left ventricular dysfunction [10–12] and NT-proBNP has shown a similar or even better correlation [13,14]. In addition, NT-proBNP is more stable and has a longer half-life compared to BNP. NT-proBNP may, therefore, be very appropriate for examination of patients suspected of heart failure, particularly in general practice [15,16].

Previous work has focused on the role of natriuretic peptides as a screening test in unselected community populations [11,17], or in patients with a high pre-test likelihood of heart failure [18–20]. However, the usefulness of a blood sample diagnosis of heart failure in such populations cannot necessarily be extrapolated to general practice where patients may present with more unspecific symptoms. However, one community study indicates that a blood test for BNP can be used to identify patients in whom heart failure is extremely unlikely [21].

In this study we tested the yield of NT-proBNP for
detection and exclusion of heart failure in a patient population seen in general practice because of dyspnoea, the most sensitive clinical indicator of heart failure.

2. Methods

2.1. Patients

We invited all general practitioners \((n=74)\) in our hospital region to refer consecutive patients complaining of dyspnoea of at least 2 weeks duration. On referral the general practitioner indicated whether the cause of dyspnoea was considered to be heart failure, lung disease, a combination of the two or other conditions. All patients were examined within 2 weeks of referral. The inclusion period lasted from October 1998 to October 2000.

2.2. Symptoms

In the clinic patients classified their grade of dyspnoea according to Fletcher’s dyspnoea scale (Table 1) [22].

2.3. Examinations

The final diagnoses were based on a combination of history, physical examination, ECG, chest X-ray examination, lung spirometry, echocardiography and blood tests (blood-haemoglobin, thyroid hormones, creatinin, sodium, potassium and glucose). If indicated these examinations were in individual cases complemented by exercise ECG, lung scintigraphy, CT X-ray of the thorax, coronary arteriography, or other relevant examinations.

2.4. Definitions

2.4.1. Heart failure

We used the criteria for heart failure published by the European Society of Cardiology [23], demanding symptoms of heart failure and objective evidence of cardiac dysfunction at rest. Obviously, the inclusion of patients with dyspnoea secured that all patients were symptomatic, and cardiac dysfunction was diagnosed and classified by means of echocardiography. A diagnosis of systolic dysfunction was made in the presence of an ejection fraction (EF) of less than 45% based upon wall motion index score [24,25] or a fractional shortening below 25% in case of global dysfunction of the left ventricle [26]. Isolated diastolic dysfunction of the left ventricle was diagnosed in the presence of an EF of at least 45% in combination with increased left ventricular mass index and no significant valve disease [27]. Patients were classified as having significant valve disease according to echocardiography, when referred for further evaluation in a tertiary heart centre, unless obvious contraindications for open-heart operation were present. Heart failure caused by arrhythmia was diagnosed in patients with persistent atrial fibrillation and a heart rate above 100 beats/min at rest, or in patients with a conduction abnormality and a heart rate below 40 beats/min.

2.4.2. Lung disease

A diagnosis of lung disease was established based upon clinical examination, chest X-ray examination and lung spirometry. Reference values were obtained from a larger Danish study [28].

2.4.3. Measurement of NT-proBNP

All patients had a venous blood sample (EDTA) taken for NT-proBNP after 30 min of rest in supine position. Samples were centrifuged immediately afterwards, and the separated plasma stored at \(-20^\circ\) before transport for extended storage at \(-80^\circ\). In October 2001, when a final diagnosis had been established in all patients the blood samples were analysed for NT-proBNP using a sandwich immunoassay (EIMA) with two antibodies (Roche Diagnostics) [16]. Subsequently the relationship between NT-proBNP and heart failure was analysed. Data for men and women were analysed.
separately, as it were previously shown, that BNP values are higher for women compared to men [29]. Ageing is also known to influence on the BNP level [29], and our data were analysed separately for patients under the age of 50, and 50 years and above.

The local ethical committee approved the study, and all patients gave informed consent.

3. Statistics

Concentrations of NT-proBNP were not normally distributed and were log transformed before analysis. Group comparisons for NT-proBNP values were tested with one-way ANOVA analysis, and when a significant difference was found a t-test for independent samples was performed. The sensitivity, specificity, positive and negative predictive values and likelihood ratios for NT-proBNP for the diagnosis of heart failure were calculated for different cut-off points obtained from receiver operator characteristic curves (ROC curves). ROC curves were drawn individually for men and women, and area under the curves were calculated for the correlation between levels of NT-proBNP and heart failure.

4. Results

A total of 363 consecutive patients were referred for inclusion in the study. However, 18 patients were excluded from analysis either because of a missing blood sample for determination of NT-proBNP (n=9) or because one or more of the diagnostics essential for the final diagnosis were missing (n=9). The remaining 345 patients had a median age of 65 years (range 18–89 years), and 51% were males. In Table 1 the grade of dyspnoea of the patients is listed according to Fletcher’s dyspnoea scale. In 19% of the patients the duration of dyspnoea was less than 3 months, in 24% between 3 and 12 months and in the remaining 57% of patients the duration of dyspnoea exceeded 12 months prior to referral to the programme. An echocardiogram had been performed within 2 years prior to the examination programme in 11 patients and 7 of them were presently diagnosed as having heart failure.

Heart failure was suspected by the general practitioner in 136 of the patients (39%), pulmonary disease in 124 (36%), and in 51 (15%) a combination of heart and pulmonary insufficiency was suspected. In the remaining 34 patients other or no diagnosis was suggested by the general practitioner. The relationship between the diagnostic suggestions of the general practitioners and the final diagnoses in the clinic is shown in Table 2. It appears that only 81 of the 345 patients (24%) suffered from heart failure. These included 47 men and 34 women of whom 51 had isolated heart failure and 30 a combination of heart failure and lung disease. Systolic dysfunction was found in 25 of the 81 patients (31%) and isolated diastolic dysfunction in 32 patients (40%). Significant valve disease was present in 12 patients (15%), 5 had mitral valve insufficiency, 4 aortic valve insufficiency and 3 aortic valve stenosis. Arrhythmia (mainly uncontrolled atrial fibrillation) was diagnosed in 10 (12%). The remaining two patients with heart failure included a patient with a large atrial septal defect and mild pulmonary hypertension and another patient with earlier pulmonary embolism and moderate pulmonary hypertension. These two individuals formed an independent group of patients with heart failure of other reason. Medical treatment for heart failure patients at the time of diagnosis in the clinic is shown in Table 3. Pulmonary disease predominantly chronic obstructive lung disease was diagnosed in 166 patients (48%). Of the 66 patients (19%) with diagnoses other than lung disease or heart failure, 31 had severe overweight, 20 had angina pectoris, 4 anaemia, 2 dyspnoea of neurologic origin and 2 hyperventilation. Two patients had severe hypertension but no left ventricular hypertrophy or left atrial enlargement. In the remaining five patients the background of dyspnoea was considered to be documented paroxysmal tachycardia, intrathoracic goiter, allergy, side effect from medication and malignant disease, respectively. In 62 out of the 345 patients

<table>
<thead>
<tr>
<th>Final diagnosis</th>
<th>Heart failure</th>
<th>Lung disease</th>
<th>Combined lung and heart failure</th>
<th>Other well-defined reason</th>
<th>No diagnosis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>40 (29%)</td>
<td>30 (22%)</td>
<td>6 (5%)</td>
<td>37 (27%)</td>
<td>23 (17%)</td>
<td>136</td>
</tr>
<tr>
<td>Lung disease</td>
<td>2 (1%)</td>
<td>77 (62%)</td>
<td>11 (9%)</td>
<td>12 (10%)</td>
<td>22 (18%)</td>
<td>124</td>
</tr>
<tr>
<td>Combined lung and heart failure</td>
<td>6 (12%)</td>
<td>21 (41%)</td>
<td>13 (25%)</td>
<td>6 (12%)</td>
<td>5 (10%)</td>
<td>51</td>
</tr>
<tr>
<td>Other well defined reason</td>
<td>1 (6%)</td>
<td>5 (31%)</td>
<td>0</td>
<td>7 (44%)</td>
<td>3 (19%)</td>
<td>16</td>
</tr>
<tr>
<td>No diagnosis</td>
<td>2 (11%)</td>
<td>3 (17%)</td>
<td>0</td>
<td>4 (22%)</td>
<td>9 (50%)</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>51 (15%)</td>
<td>136 (39%)</td>
<td>30 (9%)</td>
<td>66 (19%)</td>
<td>62 (18%)</td>
<td>345</td>
</tr>
</tbody>
</table>

Relationship between the diagnostic suggestion made by the general practitioner and the final diagnosis made in the dyspnoea clinic in 345 consecutive patients. Identity marked in bold.
Table 3
Medical treatment for subgroups of heart failure patients at their appearance in our clinic

<table>
<thead>
<tr>
<th>Heart failure diagnosis</th>
<th>Systolic dysfunction</th>
<th>Diastolic dysfunction</th>
<th>Arrhythmia</th>
<th>Other heart failure</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appropriate</td>
<td>4 (16%)</td>
<td>9 (28%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>13 (19%)</td>
</tr>
<tr>
<td>Inadequate</td>
<td>19 (76%)</td>
<td>14 (44%)</td>
<td>5 (50%)</td>
<td>0 (0%)</td>
<td>38 (55%)</td>
</tr>
<tr>
<td>No treatment given</td>
<td>2 (8%)</td>
<td>9 (28%)</td>
<td>5 (50%)</td>
<td>2 (100%)</td>
<td>18 (26%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>25 (100%)</td>
<td>32 (100%)</td>
<td>10 (100%)</td>
<td>2 (100%)</td>
<td>69 (100%)</td>
</tr>
</tbody>
</table>

Inadequate treatment covers patients with, e.g. systolic dysfunction and diuretic therapy only or patients with diastolic dysfunction and high blood pressure despite treatment with one medical drug. The subgroup of 12 patients with primary valve disease are excluded from the table, as only surgical treatment can be considered appropriate in these symptomatic patients. Thus, in 68 out of 81 heart failure patients either no or inadequate treatment was administered at the time of examination.

(18%) no obvious explanation of the dyspnoea was found.

The log transformed mean concentration of NT-proBNP (S.D.) (4.39 (1.31) pmol/l) in patients with isolated heart failure and heart failure in combination with lung disease was significantly higher than in the remaining patients with dyspnoea but no heart failure (2.19 (0.97) pmol/l, P<0.001) (Fig. 1). For raw data the mean concentration of NT-proBNP in heart failure patients was 189 pmol/l vs. 17 pmol/l in no heart failure patients. The lowest mean concentration of NT-proBNP was found in the group of patients with no reliable obvious explanation for dyspnoea. Except for one patient, all had values of NT-proBNP below 29 pmol/l. The patient who did not fulfill this criterion had apparently unimportant aortic valve sclerosis, but his plasma-NT-proBNP was 79.7 pmol/l. For heart failure patients who received adequate treatment, log NT-proBNP was 3.7 (0.8) pmol/l in contrast to the remaining patients with heart failure (4.4 (1.3) pmol/l) (ns).

Subgroup analysis for log NT-proBNP of heart failure patients is shown in Fig. 2.

In patients younger than 50 years the prevalence of heart failure was very low. Among 58 patients under the age of 50, only 2 patients (3%) suffered from heart failure (one male patient with atrial septal defect, normal EF and NT-proBNP = 5.31 pmol/l, and one female patient with hypertension, hypertrophy of the left ventricle and NT-proBNP = 28 pmol/l). Therefore, ROC curves were drawn only for 287 patients aged 50 years or older (Fig. 3). The area under the ROC curve for male patients was 0.93 with 95% confidence limits from 0.89 to 0.97, and for female patients the area was 0.90 with confidence limits from 0.84 to 0.97. Sensitivity, specificity, positive and negative predictive values and likelihood ratios calculated for different cut off points picked from the ROC curve are shown in Table 4. When choosing a predictive value of a negative test (PV<sub>neg</sub>) of 97%, a cut off value at 11 pmol/l for men and 17 pmol/l for women should be applied. This yielded a
sensitivity of 94–96% and a specificity of approximately 70% for both men and women (Table 4). Using these detection limits, four heart failure patients would be overlooked, i.e. 5% of the 79 patients with heart failure aged 50 years and above. Diastolic dysfunction (hypertension with hypertrophy on echocardiography) was found in three of these patients. The remaining patient had third degree atrioventricular block with a ventricular rhythm of 39 beats/min and normal EF.

Table 4
Possible threshold values of NT-proBNP for identification or disproval of heart failure

<table>
<thead>
<tr>
<th></th>
<th>NT-proBNP, Men ($n = 146$)</th>
<th>NT-proBNP, Women ($n = 141$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9 pmol/l</td>
<td>11 pmol/l</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>100%</td>
<td>96%</td>
</tr>
<tr>
<td>Specificity</td>
<td>60%</td>
<td>67%</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>53%</td>
<td>57%</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>100%</td>
<td>97%</td>
</tr>
<tr>
<td>Likelihood ratio of positive result</td>
<td>2.5</td>
<td>2.9</td>
</tr>
<tr>
<td>Likelihood ratio of negative result</td>
<td>0</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Sensitivity, specificity, positive and negative predictive values and likelihood ratios of NT-proBNP for detecting heart failure in patients with dyspnoea at the age of 50 years or older. Values shown for different cut off points obtained from ROC curves.

5. Discussion

Dyspnoea is the most sensitive clinical manifestation of heart failure [30,31] and was, therefore, chosen as the inclusion criterion of this study. However, the specificity is relatively low (50–75%) [30,32] and several papers have documented the difficulties in diagnosing heart failure on a clinical basis alone [1–5]. Using a comprehensive examination programme as reference (not including NT-proBNP) this study confirmed that dyspnoea is non-cardiac in almost 2/3 of patients with a tentative clinical diagnosis of heart failure. Conversely heart failure was demonstrated in more than 10% of patients in whom a non-cardiac origin of dyspnoea was suspected by the general practitioner.

Echocardiography is recommended as the key examination to exclude, reveal and classify heart failure in patients with dyspnoea [23,33]. However, because of tradition and capacity problems in the hospital clinics many such patients do not have an echocardiogram. Instead measurement of natriuretic peptides in the blood has been suggested as a potential screening test for heart failure [23]. Obviously the usefulness of a screening test relies on a high predictive value of a negative test (PV<sub>neg</sub>). Earlier papers on BNP for the diagnosis of heart failure have shown a satisfactory PV<sub>neg</sub> of 97% or even more. However, the corresponding sensitivity in these studies did not exceed 85% [11,34], meaning that at least 15% of patients with heart failure are overlooked and potentially withheld treatment that relieves symptoms and may improve the prognosis. Thus, in a serious condition such as heart failure a high PV<sub>neg</sub> as well as a high sensitivity appear to be mandatory.

In this study, we used the recently discovered and easily measured NT-proBNP. This pro-hormone is more stable and has a longer half-life than BNP but the relationship to heart failure seems to be the same for BNP and NT-proBNP [13,15]. In predominantly in-hospital patients referred to echocardiography, Talwar et al. found a close correlation between NT-proBNP and left ventricular systolic dysfunction in 243 patients [19].
Reduced left ventricular systolic function was predicted with a sensitivity of 94% and a specificity of 55%.

With a combination of several laboratory tests as reference including ECG, echocardiography, chest-X-ray examination, spirometry, etc. the main aim of our study was to examine the value of NT-proBNP as a screening test for heart failure in general practice. Exclusion of heart failure as the reason of dyspnoea by means of a blood test may seem particularly relevant in general practice because the availability of echocardiography is limited.

Using a PV
\(_{\text{neg}}\) of 97%, a threshold of NT-proBNP for heart failure of 11 pmol/l for men and 17 pmol/l for women was identified in our study for patients aged 50 years or more. The corresponding sensitivity was approximately 95% (96% in men, 94% in women) and the specificity approximately 70% (Table 4). At these threshold values NT-proBNP overlooked four patients considered to have heart failure. However, one of the four patients had an obvious abnormality in the ECG, and the remaining three all had diastolic dysfunction, a condition where no well-established treatment is known to lead to an improved prognosis. Thus, a blood level of NT-proBNP below the thresholds mentioned above was in this study reliable for exclusion of heart failure that can be treated with a prognostic benefit.

Hobbs et al. [20] used the same analytic method for NT-proBNP, but identified a higher threshold value (36 pmol/l) for heart failure than our. However, Hobbs et al. screened an unselected community population and different definitions of heart failure may also have contributed to the differing threshold values. In contrast to Hobbs et al., we considered patients with dyspnoea and enhanced left ventricular mass index as having heart failure and these patients exhibited lower values of NT-proBNP than patients with systolic dysfunction, valve disease or significant arrhythmia. The severity of heart failure has also been shown to have impact on the NT-proBNP level [35] and it should be noted that only 15% of our patients received adequate treatment for heart failure (Table 3). However, log NT-proBNP (S.D.) in these patients (3.7 (0.8) pmol/l) did not differ much from the remaining patients with heart failure (4.4 (1.3) pmol/l, \(P > 0.05\)).

It was surprising that our examination programme gave no final explanation of the dyspnoea in 18% of the patients. However, dyspnoea is also a main symptom in patients suffering from anxiety and other psychiatric conditions. We made no attempt to establish criteria for such conditions but suggest that they might have been responsible in many of our patients with dyspnoea of unclear origin. It is also noteworthy that the level of NT-proBNP in this patient group was low. Only one patient with presumed unimportant sclerosis of the aortic valve had a deviating high value (79.7 pmol/l).

Assuming that an echocardiogram should only be performed in patients with NT-proBNP increased above 11 pmol/l (men) or 17 pmol/l (women), our study showed that echocardiography might be omitted in 145 or 51% of the 287 patients. In addition, our positive predictive values of approximately 50% (Table 4) indicate that only half of the patients with increased blood levels of NT-proBNP would have a normal echocardiogram.

In the recent European guidelines, measurement of natriuretic peptides has been incorporated in the algorithm for diagnosis of heart failure [23]. Accordingly, when a blood test for natriuretic peptides is normal in a patient with presumed cardiac failure, the diagnosis is unlikely, and on the other hand when the test is abnormal, cardiac imaging should be undertaken to validate or disprove the diagnosis. Our results are in line with these recommendations. We discovered, however, that 10% of patients with dyspnoea of presumed non-cardiac origin turned out to suffer from heart failure after all (Table 4). It therefore seems reasonable to expand screening with NT-proBNP to all patients suffering from dyspnoea of unclear origin, instead of limiting the test to those suspected of heart failure.

6. Limitations

Although the general practitioners were asked to refer all patients who consulted them with dyspnoea of at least 2 weeks duration it is uncertain whether this criterion was firmly adhered to. At least according to the grade of dyspnoea many patients had rather severe symptoms (Table 1) and more than half of the patients had chronic dyspnoea lasting for more than a year. However, testing the NT-proBNP thresholds of 11 and 17 pmol/l for male and female patients, respectively, resulted in PV
\(_{\text{neg}}\) of 100% and sensitivity of 100% in the subpopulation of patients with dyspnoea of recent onset (2 weeks–3 months).

A minor fraction (11 patients) had an earlier echocardiogram performed but these were in some cases patients with valve disease and potential progression to a stage where surgical correction is needed. Only 2% of the entire series were characterised by the combination of an earlier echocardiography and a final diagnosis of heart failure.

7. Conclusion

In our population of patients seen in general practice with dyspnoea as the main complaint we confirmed that heart failure cannot be diagnosed or excluded reliably on a clinical basis alone. However, for patients with an age of 50 years or more, heart failure could be ruled out with a high probability if the NT-proBNP level in blood did not exceed 11 pmol/l in men and 17 pmol/l.
in women. In addition, it was possible to select a threshold that combined a high predictive value of a negative test with high sensitivity and reasonable specificity.

According to our data, exclusion of dyspnoea of cardiac origin by means of a low level of NT-proBNP may make echocardiography redundant in half of the patients who consult their general practitioner because of dyspnoea. However, our heart failure thresholds of blood NT-proBNP should be prospectively confirmed before the test can be considered safe for widespread use.

Acknowledgments

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References


