**Objectives**
This study was designed to determine whether measurement of plasma pro-B-type natriuretic peptide (proBNP) could be used in discriminating between cardiac and pulmonary dyspnea in the general population.

**Background**
Natriuretic peptides are useful markers in ruling out acute cardiac dyspnea in the emergency department, but their diagnostic significance in evaluating chronic dyspnea in the general population is unknown.

**Methods**
Within the Copenhagen City Heart Study, a large, community-based population study, dyspnea was evaluated by spirometry, oxygen saturation, echocardiography, and plasma proBNP.

**Results**
Of 2,929 participants, 959 reported dyspnea. The plasma proBNP concentration was higher in the group with dyspnea (mean 17.8 pmol/l; 95% confidence interval [CI] 16.3 to 19.4 pmol/l) than in the group without (10.6 pmol/l; 95% CI 10.0 to 11.4 pmol/l; p < 0.001). In the group with dyspnea, left ventricular hypertrophy and/or systolic dysfunction was associated with a 2.6-fold increase in plasma proBNP concentration (p < 0.001), whereas pulmonary dysfunction was not associated with increased plasma proBNP (p = 0.66). Using multivariable regression analysis, a model to estimate the expected concentration of plasma proBNP based on age and gender was established for dyspeptic subjects: an actual plasma proBNP concentration below half of the expected value ruled out left ventricular systolic and diastolic dysfunction (sensitivity 100%, 95% CI 100% to 100%; specificity 15%, 95% CI 12% to 17%).

**Conclusions**
In the general population with dyspnea, plasma proBNP concentrations are increased in left ventricular dilatation, hypertrophy, systolic dysfunction, or diastolic dysfunction, but are unaffected by pulmonary dysfunction. (J Am Coll Cardiol 2007;50:1694–701) © 2007 by the American College of Cardiology Foundation

Dyspnea is a common symptom in patients seeking medical care. Cardiac and pulmonary disorders are 2 common causes of dyspnea, and the clinical distinction between the 2 can be very difficult (1,2). These conditions often have an adverse and potentially hazardous treatment, emphasizing the need for a correct diagnosis. In hospital settings, echocardiography is often used when detecting structural cardiac abnormalities, but it is not readily accessible in the general practice. In addition, to refer every patient with dyspnea in the general population to echocardiographic examination demands considerable resources. An assessable biomarker that can discriminate pulmonary from cardiac disorders would therefore be useful.

The recognition of natriuretic peptides secreted from the overloaded heart has been the basis for a key study by Davis et al. (3) and subsequent studies (4–8) that assessed the diagnostic value of measuring natriuretic peptides to differentiate between acute pulmonary and cardiac dyspnea. The concept that measurement of the peptides is useful (3–8) and cost effective (9) in the emergency department is now well documented. However, the data are limited to selected patients and cannot be extrapolated to the general population.
If the natriuretic peptides are true markers of cardiac and not pulmonary disorder, they might have a place not only in the evaluation of the acutely ill but also in ambulatory settings.

We therefore performed a large population-based study evaluating the association between the concentration of plasma pro-B-type natriuretic peptide (proBNP) and dyspnea as characterized by spirometry, oxygen saturation, and echocardiography.

Methods

Study population. This study was performed as a substudy of the Fourth Copenhagen City Heart Study, a longitudinal cohort study of cardiovascular disease and risk factors (10,11). At the first examination in 1976 to 1978, a random sample of 19,329 predominantly white citizens living within a well-defined area of the inner Copenhagen City boundary was drawn from the Central Office of Civil Registration and invited to take part in the study. The sample was stratified by gender and age (5-year age strata from the age of 20 years) so that nearly equal numbers within each stratum were invited. At the fourth examination in 2001 to 2003, a total of 12,600 people were invited in a random order. This study population consisted of participants from the previous examinations (n = 11,600), supplemented by a random sample of people from the younger age strata (n = 1,000). Of the 12,600 people, 6,238 (49.5%) participated, and 2,929 (47.0%) randomly selected men and women (20 to 95 years) underwent both an echocardiographic and a spirometric examination, thus constituting the population included in the present report. Whether or not a participant underwent echocardiography and spirometry was completely independent of his or her health status and other risk factors.

All subjects gave informed consent to participate, and the study was performed in accordance with the Second Helsinki Declaration and approved by the regional ethics committee.

Health examination. Hypertension was defined as systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or use of antihypertensive medication (12). Ischemic heart disease was defined as either a history of hospital admission because of acute coronary artery occlusion, percutaneous coronary intervention, or coronary artery bypass grafting, or major ischemic alterations on the electrocardiogram as defined by the Minnesota codes 1.1-3. Diabetes mellitus was defined as plasma glucose concentration ≥11.1 mmol/l, use of insulin or other antidiabetic medicine, self-reported disease, or hemoglobin A1c level >7.0% (13,14).

A slightly modified Medical Research Council (MRC) dyspnea scale was used for the assessment of dyspnea: category 0, no dyspnea; category 1, troubled by shortness of breath when hurrying on level ground or walking up a low hill; category 2, walks slower than people of the same age on level ground because of breathlessness; category 3, must stop because of breathlessness when walking at own pace on level ground; category 4, breathless when dressing or undressing; and category 5, breathless at rest or when sitting still. Dyspnea of MRC categories 1 and 2 was considered mild and of categories 3, 4, and 5 was considered severe.

Plasma proBNP measurement. The plasma proBNP concentration was quantified using a processing-independent assay (Fig. 1) (15). The analytical validation of this assay has been reported elsewhere (16,17). The processing-independent assay results are fully comparable to the commercially available Modular N-terminal–proBNP assay by Roche (Karlsruhe, Germany) on linear regression analysis ($r^2 = 0.91$; slope 1.37 ± 0.02; p < 0.001) with an average 1.7-fold difference (mean plasma proBNP 222 pmol/l, 95% confidence interval [CI] 201 to 243 pmol/l vs. mean N-terminal–proBNP 386 pmol/l, 95% CI 328 to 442 pmol/l).

Pulmonary function. Forced expiratory volume in 1 sec (FEV1) and forced vital capacity (FVC) were measured with a dry wedge spirometer (Vitalograph, Maidenhead, United Kingdom) which was calibrated daily with a 1-l syringe. At each examination, 3 sets of values were obtained, and as a criterion for correct performance of the procedure at least 2 measurements differing by <5% had to be produced. The highest measurement of FEV1 and FVC was used in the analyses as absolute values and as percentage of predicted values using internally derived reference values based on a sub sample of healthy never-smokers. Resting peripheral oxygen saturation was measured by pulse oxymetry. Subjects were considered as having pulmonary dysfunction if FEV1 or FVC were below 60% of the predicted value, the oxygen saturation was below 92%, or a history of asthma was reported.

Echocardiography. Three experienced echocardiography technicians using a GE Vingmed Ultrasound’s Vivid Five with a 2.5-MHz probe (Horten, Norway) performed all echocardiograms. The collected data were stored on magneto-optical discs and an external FireWire hard drive (LaCie, France), and analyzed off-line by 1 expert with the EchoPAC software version 6.4.3f (GE Medical, Horten, Norway). All subjects were examined with 2-dimensional and M-mode echocardiography in the left lateral decubitus position. All images were recorded in second harmonic imaging at the time of end-expiration. One loop of the apical 4-chamber, 2-chamber, and long-axis projections was recorded, more if atrial fibrillation was present. The 16 standard segments model, as suggested by the American Society of Echocardiography (18), was used for evaluation of regional function. Left ventricular systolic dysfunction was defined as left ventricular ejection fraction <50%.

One loop of the parasternal long axis was recorded and 1 M-mode still frame in the correct 90° angle between the tips

Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>FEV1</td>
<td>forced expiratory volume in 1 s</td>
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<tr>
<td>FVC</td>
<td>forced vital capacity</td>
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<td>MRC</td>
<td>Medical Research Council</td>
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<td>NPV</td>
<td>negative predictive value</td>
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<td>PPV</td>
<td>positive predictive value</td>
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<td>ProBNP</td>
<td>pro-B-type natriuretic peptide</td>
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<tr>
<td>ROC</td>
<td>receiver-operator characteristic</td>
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Discriminating Cardiac From Pulmonary Dyspnea

Mogelvang et al.

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of the mitral leaflets and the tips of the papillary muscles. If the correct angle could not be obtained, 2-dimensional images were used instead to quantify the myocardial thickness and the dimensions of the left ventricle. Left ventricular mass index was calculated as the anatomic mass divided by body surface area (20). Left ventricular hypertrophy was defined as left ventricular mass index /11350 104 g/m² for women and /11350 116 g/m² for men (21). Left ventricular dilatation was considered if the diameter of the left ventricle at end-diastole/height /11350 3 cm/m.

Pulsed-wave Doppler at the apical position was used to record mitral inflow (between mitral leaflets) and left ventricular outflow. Peak velocities of early (E) and atrial (A) diastolic filling and deceleration time of the E-wave (DT) were measured and the E/A ratio was calculated. Severe diastolic dysfunction was defined as DT /11021 140 ms and E/A /11021 2.5, E/A /11022 2, or E/A /11022 70 years /11022 1.5, respectively. The time interval from mitral valve closing to opening (TST) was determined as the period from the end to the onset of the mitral inflow, left ventricular ejection time (ET) was determined as the period from onset to the end of the left ventricular outflow, and the myocardial performance index was calculated as: (TST /11002 ET)/ET (22). Myocardial performance was considered reduced if the myocardial performance index was /11022 0.40.

Statistical analyses. The plasma proBNP concentrations in the population were positively skewed and therefore logarithmically transformed before further statistical analysis (unless stated otherwise): the mean values presented in the text refer to geometric mean values. Comparisons between groups were performed by the Student t test and Fisher exact test. Linearity between plasma proBNP values and continuous variables was examined visually by scatter plots. According to these, plasma proBNP was linearly correlated to the square of age. The ability of plasma proBNP to detect cardiac dysfunction was assessed using receiver-operating characteristics (ROC). Associations to plasma proBNP were tested by univariate and multivariable regression analyses for the echocardiographic (left ventricular systolic dysfunction, hypertrophy, dilatation, diastolic dysfunction, myocardial performance index) and the non-echocardiographic (age, gender, body mass index, plasma creatinine, diabetes, hypertension, ischemic heart disease, pulmonary dysfunction) parameters. These parameters were chosen because they have been shown to influence the plasma concentrations of natriuretic peptides. To establish a parsimonious model for predicting plasma proBNP concentrations, the most insignificant parameter in the multivariable analysis was removed by backward elimination (retention threshold, p /11021 0.05). Forward selection was undertaken afterward, yielding the same result. Linearity, variance homogeneity, and the assumption of normality were tested with plots of residuals. Interaction was tested among the significant parameters. The diagnostic performances of different ratios of measured (untransformed) to predicted plasma proBNP in detecting left ventricular systolic dysfunction and/or diastolic dysfunction were then evaluated. The 95% CIs for the diagnostic estimates were calculated using bootstrap estimation (10,000 replications) with the 2.5th and 97.5th percentiles as lower and upper limits, respectively. Values of p /11021 5% on 2-sided tests were considered significant. All analyses were performed by SAS software (SAS System for Windows, release 8.02, SAS Institute Inc., Cary, North Carolina).
Results

The characteristics of the study population are listed in Table 1. The 2 groups differed significantly with regard to almost all of the shown characteristics, reflecting a higher sickness profile in the dyspneic group (Table 1). Plasma proBNP is eliminated by the kidneys, but there was no significant difference between the groups regarding plasma creatinine. Almost one-half of the dyspneic subjects had neither an abnormal echocardiogram nor pulmonary dysfunction (Fig. 2). Not only was the mean plasma proBNP concentration higher in the group with dyspnea than in the group without, but also the plasma proBNP concentrations increased according to the severity of dyspnea (Fig. 3), even after adjustment for age and gender.

Plasma proBNP concentration is increased in individuals with left ventricular systolic dysfunction and/or hypertrophy (23). To evaluate the effect of pulmonary and cardiac dysfunction on plasma proBNP, the dyspneic population was divided into 4 strata according to cardiac and pulmonary dysfunction. As shown in Figure 4, the mean plasma proBNP concentration was greatly increased in the groups with cardiac dysfunction (left ventricular systolic dysfunction and/or hypertrophy), whereas it was unaffected by pulmonary status. Overall, the mean plasma proBNP was 2.6-fold higher in subjects with cardiac dysfunction compared with subjects without (38.0 pmol/l, 95% CI 32.0 to 45.2 pmol/l vs. 14.9 pmol/l, 95% CI 13.5 to 16.4 pmol/l, p < 0.001). In contrast, there was no significant difference between the group with pulmonary dysfunction and the group without (18.6 pmol/l, 95% CI 15.2 to 22.7 pmol/l vs. 17.6 pmol/l, 95% CI 16.0 to 19.4 pmol/l, p = 0.66). Notably, these differences persisted after adjusting for age, gender, diabetes, hypertension, and ischemic heart disease, for both cardiac (p < 0.001) and pulmonary dysfunction (p = 0.85). There was no interaction between cardiac and pulmonary dysfunction on plasma proBNP concentrations (p = 0.19).

![Figure 2](image)

**Flow Diagram of the Study Population**

- **Study population** (n=2,929)
- **Dyspnea** (n=959)
- **Pulmonary dysfunction** (n=123)
- **Abnormal echocardiogram** (n=286)
- **Both pulmonary dysfunction and abnormal echocardiogram** (n=68)
- **Neither pulmonary dysfunction nor abnormal echocardiogram** (n=462)

![Figure 3](image)

**Mean Plasma proBNP Concentrations According to Severity of Dyspnea**

Dyspnea was classified according to a slightly modified Medical Research Council (MRC) dyspnea scale. No dyspnea refers to MRC category 0, mild dyspnea to MRC category 1 to 2, and severe dyspnea to MRC category 3 to 5. proBNP = pro-B-type natriuretic peptide.
The area under the ROC curve was 0.73 (95% CI 0.70 to 0.76) for detecting cardiac dysfunction, whereas it was 0.72 (95% CI 0.68 to 0.76) and 0.75 (95% CI 0.68 to 0.82) for detecting left ventricular hypertrophy and systolic dysfunction, respectively.

To assess whether parameters other than left ventricular systolic dysfunction and hypertrophy were associated with plasma proBNP in subjects with dyspnea, univariate and multivariable regression analyses were performed for several parameters; the results are shown in Table 2, displaying the multivariable regression analyses were performed for several plasma proBNP in subjects with dyspnea, univariate and systolic dysfunction and hypertrophy were associated with plasma proBNP concentrations with changes in relation to age and gender, respectively.

The 95% confidence intervals are given in parentheses. *The benchmark is a 20-yr-old dyspneic woman. ** If the measured plasma proBNP is 20.6 pmol/l (6.1 pmol/l) times the expected concentration in relation to age and gender, then the diagnostic performance in detecting left ventricular systolic and/or diastolic dysfunction in dyspneic subjects is: sensitivity 61% (95% CI 44% to 76%), specificity 78% (95% CI 75% to 81%), NPV 98% (95% CI 97% to 99%), PPV 11% (95% CI 7% to 16%), and accuracy 77% (95% CI 74% to 80%). Conversely, if a person’s measured plasma proBNP level is below one-half of the expected concentration, then left ventricular systolic or diastolic dysfunction can be ruled out (sensitivity 100%, 95% CI 100% to 100%; specificity 15%, 95% CI 12% to 17%; PPV 6% and gender alone (Table 2). If the measured plasma proBNP is higher than expected from age and gender alone, the diagnostic performance in detecting left ventricular systolic and/or diastolic dysfunction in dyspneic subjects is: sensitivity 92% (95% CI 82% to 100%), specificity 33% (95% CI 30% to 36%), negative predictive value (NPV) 99% (95% CI 98% to 100%), positive predictive value (PPV) 6% (95% CI 4% to 8%), and accuracy 36% (95% CI 33% to 39%). If the measured plasma proBNP is more than 2.5 times the expected concentration in relation to age and gender, then the diagnostic performance in detecting left ventricular systolic and/or diastolic dysfunction in dyspneic subjects is: sensitivity 61% (95% CI 44% to 76%), specificity 78% (95% CI 75% to 81%), NPV 98% (95% CI 97% to 99%), PPV 11% (95% CI 7% to 16%), and accuracy 77% (95% CI 74% to 80%). Conversely, if a person’s measured plasma proBNP level is below one-half of the expected concentration, then left ventricular systolic or diastolic dysfunction can be ruled out (sensitivity 100%, 95% CI 100% to 100%; specificity 15%, 95% CI 12% to 17%; NPV 100%, 95% CI 100% to 100%; PPV 5%, 95% CI 4% to 7%; and accuracy 18%, 95% CI 16% to 21%) (Fig. 5).

![Figure 4 Mean Plasma proBNP According to Pulmonary and Cardiac Dysfunction in Dyspneic Subjects (n = 959)](image)

Bar indicate standard errors. proBNP = pro-B-type natriuretic peptide.
Discussion

We examined the diagnostic utility of plasma proBNP measurement for cardiac and pulmonary dyspnea in a large, population-based study. Dyspnea was evaluated by spirometry, oxygen saturation, echocardiography, and plasma proBNP. We found that pulmonary function, in contrast to cardiac function, has no influence on plasma proBNP concentrations. Furthermore, left ventricular dilatation, hypertrophy, systolic dysfunction, and diastolic dysfunction have a considerable impact on plasma proBNP concentrations. We therefore established a model predicting plasma proBNP concentrations from age, gender, and the echocardiographic parameters. Finally, we determined the diagnostic performance of plasma proBNP as a rule-out and rule-in marker of left ventricular systolic or diastolic dysfunction in a general population with dyspnea.

Not surprisingly, pulmonary and cardiac dysfunctions were more common among subjects with dyspnea than among those without. Hence, a greater prevalence of ischemic heart disease and risk factors (hypertension, diabetes, obesity, age) was observed in the dyspneic group (Table 1).

Subjects with dyspnea had higher plasma proBNP concentrations than those without dyspnea. In addition to this, plasma proBNP increased as a function of MRC classes. This correlation between natriuretic peptides in circulation and the severity of dyspnea in the general population compares well with the original finding by Maisel et al. (5) for patients with acute dyspnea at emergency care facilities.

Myocardial performance index correlated positively with plasma proBNP concentrations in the univariate analysis, but the effect was abolished in the multivariable analysis, including left ventricular systolic dysfunction, diastolic dysfunction, and/or hypertrophy. This confirms that myocardial performance index reflects a combination of systolic and diastolic function (22).

In keeping with the vast documentation (24–26), our findings sustain that the natriuretic peptides are dependent on age and gender. Notably, we found that plasma proBNP concentrations increase exponentially with age. For example, a 20-year-old dyspneic man has an expected plasma proBNP level of 4 pmol/l, compared with 34 pmol/l in an 80-year-old dyspneic woman (Table 2). Hence, age and gender must be taken into account when establishing reference intervals for plasma proBNP (Fig. 5).

Distinguishing between cardiac and noncardiac causes of dyspnea is difficult without echocardiography. However, it is not feasible to refer every single person with dyspnea in the general population for an echocardiographic examination. Using plasma proBNP measurement as guidance for further examination would ease the diagnostic evaluation of dyspnea in this setting. Several studies have shown that the use of natriuretic peptides in screening of different populations can be cost effective (9,27–29). We present a new model to calculate the expected concentration of plasma proBNP for a given person with dyspnea adjusting for age and gender. A person with dyspnea and a plasma proBNP concentration above the blue area in Figure 5 should be referred to echocardiography, whereas a person with a plasma proBNP below the blue area should be examined for noncardiac causes of dyspnea, e.g., spirometry. If the plasma proBNP is in the blue area, there exists only a small risk of left ventricular systolic and/or diastolic dysfunction, and referral to echocardiography should, in addition to the plasma proBNP level, depend on the physical examination, anamnesis, electrocardiography, and perhaps chest radiograph.

Of 959 participants complaining of dyspnea, 462 (48%) had a normal echocardiogram and normal pulmonary function test. Most of these people (83%) were only complaining of mild dyspnea. Compared with their nondyspneic counterparts, they were characterized by higher age, higher body...
mass index, higher frequency of ischemic heart disease and smoking, and lower level of physical activity.

Conventional echocardiography does not provide much information about longitudinal myocardial contractility, which is impaired initially in ischemic heart disease. Further research with more advanced modalities, e.g., tissue Doppler imaging, is needed to determine the myocardial function of dyspneic persons with normal conventional echocardiograms.

**Study limitations.** Certain limitations of the present study must be taken into account: 1) the dichotomization of pulmonary function is a simplification that may lead to loss of information because it tends to equalize severe and mild cases of pulmonary dysfunction. In addition, the chosen threshold can be an object for discussion. To compensate for this, we separately analyzed the influence on plasma proBNP of FEV1 and FVC as continuous variables (percent of predicted). Both parameters were insignificant in the univariate analysis and in the multivariable regression analyses leading to the final model (Table 2). 2) Although not evaluating right ventricular function, the proportion of pulmonary hypertension among subjects with pulmonary dysfunction could not be determined. 3) The lack of information made it impossible to stratify according to the duration of dyspnea. This implies that participants with short-lived or prolonged periods of dyspnea were treated similarly in the analyses. On the other hand, when adjusting for the severity of dyspnea, our results were unchanged. 4) Identification of cardiac dysfunction using echocardiography is different from identifying that cardiac disease is the origin of dyspnea. The latter additionally requires detailed patient history, physical examination, and, at times, additional tests (e.g., D-dimers and computed tomography scans). 5) The presented model has not been confirmed by a validation sample; although validated statistically using bootstrapping, future studies are required to confirm the model.

**Conclusions**

The present findings sustain the connotation that the concentration of plasma proBNP is increased in the presence of left ventricular dilatation, hypertrophy, systolic dysfunction, and/or diastolic dysfunction. The crucial point, however, is that plasma proBNP is unaffected by pulmonary function. Thus, if pulmonary dysfunction is suspected, then pulmonary status should be pursued, regardless of plasma proBNP level. In contrast, if plasma proBNP is higher than expected in relation to age and gender, then cardiac dysfunction is likely and cardiac status should be evaluated regardless of the pulmonary status.

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