**Study objectives:** In dyspneic patients without left ventricular enlargement, it may be difficult to differentiate between obstructive lung disease and diastolic heart failure. Determination of plasma brain natriuretic peptide (BNP) levels, known to increase with ventricular stretch, may be of clinical relevance in this situation. We compared the discriminant power of BNP blood levels and of echocardiography in patients with either chronic obstructive lung disease or diastolic heart failure.

**Patients:** Twenty-six New York Heart Association class III dyspneic patients with normal left ventricular systolic function were enrolled: 17 patients with chronic obstructive lung disease and 9 patients with unequivocal diastolic heart failure.

**Results:** Echocardiographic data were unable to accurately differentiate between the two groups, whereas BNP levels were significantly and markedly higher in patients with diastolic heart failure when compared to those with obstructive lung disease (224 ± 240 pg/mL vs 14 ± 12 pg/mL, p < 0.0001).

**Conclusions:** These preliminary results warrant a prospective, large-scale evaluation of the value of BNP assay for determining diastolic dysfunction, a common cause of dyspnea in elderly patients, and differentiating it from other diagnoses such as obstructive lung disease.

**Key words:** brain natriuretic peptide; chronic airways obstruction; congestive heart failure; diastolic failure; dyspnea

**Abbreviations:** BNP = brain natriuretic peptide; CHF = congestive heart failure; DT = deceleration time; E/A = peak velocity during passive phase of diastolic filling of left ventricle/late peak of velocity following atrial contraction; LVEF = left ventricular ejection fraction; NS = not significant; sPAP = systolic pulmonary artery pressure

---

The cause of dyspnea is often difficult to determine clinically, especially in elderly patients. The prevalence of both chronic obstructive lung disease and congestive heart failure (CHF) is high, and these two conditions are often present in the same patient. This difficulty may be compounded by the occurrence of bronchospasm in elderly patients with heart failure (cardiac asthma). A chest radiograph demonstrating cardiomegaly and an echocardiogram showing depressed left ventricular function easily allow a definite diagnosis of left ventricular systolic dysfunction. In contrast, isolated diastolic heart failure, a frequent cause of CHF in the elderly, is more difficult to demonstrate because of the absence of cardiomegaly and the poor sensitivity of echocardiographic diastolic dysfunction criteria.

Plasma levels of brain natriuretic peptide (BNP) are significantly increased in patients with left ventricular dysfunction in comparison with control subjects or patients with respiratory disease; preliminary data seem to indicate that BNP levels may be elevated in patients with diastolic dysfunction. The
The purpose of our study was to measure plasma levels of BNP in dyspneic patients with either documented diastolic CHF or chronic airways obstruction in order to test the discriminant power of BNP assay between these two diagnoses.

**Materials and Methods**

**Patients**

We planned to study 30 patients: 20 consecutive patients with chronic airways obstruction and 10 consecutive patients with isolated diastolic dysfunction. Twice as many subjects with chronic airways obstruction were enrolled because poor echogenicity is common in such patients. It was therefore expected that half of the echocardiographic study findings would be considered suboptimal. Sample size was limited to 30 patients because we postulated that BNP assays would be of clinical interest only if marked differences were found between both groups. Thirty patients were considered to be enough to assess such a difference. Patients were all studied in a compensated phase of their illness and were all in New York Heart Association class III for dyspnea.

Of the 20 patients with chronic airways obstruction, 3 patients were subsequently withdrawn because of infectious bronchitis occurring during the study (n = 2) and paroxysmal atrial fibrillation (n = 1). The 17 remaining patients (mean ± SD age, 65 ± 6 years) had severe chronic airways obstruction, with a mean FEV$_1$ of 1.3 ± 0.6 L/s and normal systolic left ventricular function at echocardiography or radionuclide ventriculography (mean left ventricular ejection fraction [LVEF] of 64 ± 5%). All these patients were in sinus rhythm.

Patients included in the diastolic heart failure group had a previous history of recurrent pulmonary edema based on an acute severe breathlessness, interstitial or alveolar edema on chest radiographs, and a rapid response to specific treatment of CHF. These patients were in sinus rhythm, and all had FEV$_1$ values within the normal range. Ten patients were initially included; 1 patient was subsequently excluded because of paroxysmal atrial fibrillation. Nine patients were therefore studied (mean ± SD age, 68 ± 3 years; LVEF, 66 ± 4%; and FEV$_1$, 2.4 ± 0.4 L/s). Patient characteristics are listed on Tables 1–3.

**Methods**

All patients underwent an echocardiographic study with determination of left ventricular systolic function, measurement of

---

**Table 1—Patients With Chronic Airways Obstruction***

<table>
<thead>
<tr>
<th>Group 1, Patient No.</th>
<th>Age, yr</th>
<th>Sex</th>
<th>FEV$_1$, L/s</th>
<th>LVEF, %</th>
<th>sPAP, mm Hg</th>
<th>E/A</th>
<th>DT, ms</th>
<th>BNP, pg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 55 Male 2.10 60 26</td>
<td>0.9</td>
<td>300 11</td>
<td>2</td>
<td>67 Female 0.90 61 NO</td>
<td>0.5</td>
<td>245 18</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3 64 Male 1.00 70 37</td>
<td>1.1</td>
<td>210 11</td>
<td>64</td>
<td>64 Male 0.88 63 46</td>
<td>0.7</td>
<td>190 17</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>7 57 Female 1.75 64 NO</td>
<td>0.9</td>
<td>245 35</td>
<td>57</td>
<td>61 Female 1.45 74 37</td>
<td>1.7</td>
<td>205 5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>8 47 Male 0.77 60 NO</td>
<td>0.9</td>
<td>280 8</td>
<td>67</td>
<td>71 Male 0.91 62 NO</td>
<td>1.2</td>
<td>200 10</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>10 63 Male 0.72 64 35</td>
<td>0.9</td>
<td>240 2</td>
<td>76</td>
<td>76 Male 1.97 70 37</td>
<td>0.8</td>
<td>275 21</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>12 60 Female 1.67 66 NO</td>
<td>0.7</td>
<td>230 47</td>
<td>60</td>
<td>56 Male 1.60 65 NO</td>
<td>1.0</td>
<td>240 5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>14 69 Male 1.10 72 45</td>
<td>0.6</td>
<td>275 10</td>
<td>69</td>
<td>61 Male 0.91 58 40</td>
<td>1.2</td>
<td>205 20</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>16 66 Male 2.80 58 NO</td>
<td>1.0</td>
<td>255 1</td>
<td>76</td>
<td>76 Male 1.80 66 NO</td>
<td>0.5</td>
<td>350 8</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

*NO = not obtained.

---

**Table 2—Patients With Diastolic Heart Failure***

<table>
<thead>
<tr>
<th>Group 2, Patient No.</th>
<th>Age, yr</th>
<th>Sex</th>
<th>FEV$_1$, L/s</th>
<th>LVEF, %</th>
<th>sPAP, mm Hg</th>
<th>E/A</th>
<th>DT, ms</th>
<th>BNP, pg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 73 Female 1.82 63 35</td>
<td>1.5</td>
<td>205 63</td>
<td>69</td>
<td>69 Female 2.05 62 40</td>
<td>1.2</td>
<td>215 720</td>
<td>202</td>
<td></td>
</tr>
<tr>
<td>3 69 Female 2.50 70 45</td>
<td>1.4</td>
<td>130 202</td>
<td>69</td>
<td>67 Female 2.40 72 40</td>
<td>0.6</td>
<td>290 46</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>5 66 Male 2.94 66 37</td>
<td>1.1</td>
<td>285 136</td>
<td>66</td>
<td>65 Male 2.91 60 40</td>
<td>3.6</td>
<td>140 222</td>
<td>222</td>
<td></td>
</tr>
<tr>
<td>7 66 Male 2.60 67 33</td>
<td>0.5</td>
<td>400 24</td>
<td>68</td>
<td>65 Female 2.20 68 NO</td>
<td>0.5</td>
<td>320 85</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>9 70 Female 1.80 70 NO</td>
<td>2.9</td>
<td>160 521</td>
<td>70</td>
<td>70 Female 1.80 70 NO</td>
<td>2.9</td>
<td>160 521</td>
<td>521</td>
<td></td>
</tr>
</tbody>
</table>

*See Table 1 for expansion of abbreviation.
systolic pulmonary artery pressure (sPAP), and study of transmi-
tral flow pattern. An abnormal transmitral flow pattern, “the
restrictive filling pattern,” is known to be associated with high
filling pressures of the left ventricle and diastolic dysfunction.
This pattern is characterized by a high E wave, a low A wave, and
a shortened E-wave deceleration time (DT) (peak velocity during
passive phase of diastolic filling of left ventricle/late peak of
velocity following atrial contraction [E/A] ratio either > 2 or
between 1 and 2 with an E-wave DT of 140 ms).5 We deliberately
did not use more sophisticated Doppler parameters, such as
pulmonary venous curves and mitral inflow during a Valsalva
maneuver, which can provide valuable information concerning
diastolic function.6 These Doppler parameters are difficult to
record and thus are not suitable for simple triage of patients with
dyspnea and normal left ventricular size.7

Cardiac Peptide Measurements

Venous blood samples were collected into ethylenediaminetet-
ra-acetic acid (1.5 mg/mL) and aprotinine (500 kallikrein units/
ml), rapidly centrifuged at 4°C and stored at −20°C. BNP was
assayed in a blinded fashion within 3 months of collection with
the use of two direct specific monoclonal antibodies radioimmu-
noassay kit (Shionoria BNP; Shionoria; Saclay, France). This
assay system uses two monoclonal antibodies against human
BNP, one recognizing a carboxyterminal sequence and the other
the ring structure of human BNP, and measures human BNP by
sandwiching it between the two antibodies without extraction of
plasma. There was no detectable cross-reactivity with other
natriuretic peptides. This assay has an interassay coefficient of
variation near 10% and a recovery of 100% of added peptide. The
upper limit of normal BNP levels is considered, with this assay, to
be 35 pg/mL.

Statistics

Statistics were done using Statview software (Aldcyd, Meylan,
France). Values for baseline characteristics are expressed as mean
and respective SDs. Cardiac peptide concentrations are given
(graphical presentation with median, 10th, 25th, 75th, and 90th
centiles) and are compared in the two groups of patients using
the nonparametric Mann-Whitney test. Statistical significance
was defined as p < 0.05.

RESULTS

There was no significant difference between the
groups regarding age (68 ± 3 years vs 65 ± 6 years,
not significant [NS]), LVEF (66 ± 4% vs 64 ± 5%,
NS) and sPAP (36 ± 10 mm Hg vs 36 ± 8 mm Hg,
NS; Table 1). However, sPAP was impossible to
determine in 8 of the 18 patients with chronic
airways obstruction and in 2 of the 9 patients with
diastolic CHF. A restrictive filling pattern, as
previously defined, was observed in only three pa-
tients with diastolic CHF (patients 3, 6, and 9) and in
one patient with chronic airways obstruction (patient
5). The median concentration of BNP was signifi-
cantly and markedly higher in patients with diastolic
cardiac dysfunction than in patients with chronic
airways obstruction: 224 ± 240 pg/mL vs 14 ± 12
pg/mL (p < 0.001; Fig 1).

DISCUSSION

The main finding of our study was a major increase
of BNP levels in patients with diastolic heart failure
contrasting with BNP values within normal range in
those with chronic obstructive lung disease. There
was nearly no overlap between the two groups.

BNP is a natriuretic peptide produced within the
heart and released in response to ventricular over-
load and stretch. Several studies1–3 have demon-
strated a marked elevation of BNP plasma levels in
patients with systolic left ventricular failure. Furth-
more, it has been shown8–10 that a restrictive filling
pattern associated with systolic dysfunction was pre-
dictive of even higher BNP levels. A study per-
formed by Nagaya et al11 assessed BNP levels in
patients with right ventricular overload. Increased
BNP levels were noted. However, the study popula-

<table>
<thead>
<tr>
<th>Groups</th>
<th>Age, yr</th>
<th>FEV₁, L/s</th>
<th>LVEF, %</th>
<th>sPAP, mm Hg</th>
<th>E/A</th>
<th>DT, ms</th>
<th>BNP, pg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65 ± 6</td>
<td>1.30 ± 0.60</td>
<td>64 ± 5</td>
<td>36 ± 8</td>
<td>1.0 ± 0.4</td>
<td>247 ± 46</td>
<td>14 ± 12</td>
</tr>
<tr>
<td>2</td>
<td>63 ± 3</td>
<td>2.40 ± 0.40</td>
<td>66 ± 4</td>
<td>36 ± 10</td>
<td>1.5 ± 1.1</td>
<td>238 ± 91</td>
<td>224 ± 240</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD.
hypertension due to large atrial septal defects, primary pulmonary hypertension, or pulmonary hypertension due to thromboembolism. In a more recent article, the same group demonstrated a correlation between BNP levels and the severity and prognosis of primary pulmonary hypertension. In this study, mean sPAP was 84 ± 1 mm Hg. In our population of patients with chronic obstructive lung disease, pulmonary hypertension was obviously less pronounced (mean sPAP, 36 ± 8 mm Hg at Doppler ultrasound); therefore, a significant increase in BNP levels did not occur. In contrast, a marked elevation of BNP levels was noted in patients with diastolic heart failure given the current lack of standardized diagnostic criteria. 

In our preliminary report, we showed that BNP levels increased with worsening severity of heart failure. Moreover, a significant increase in BNP levels did not occur. In contrast, a marked elevation of BNP levels was noted in patients with diastolic heart failure given the current lack of standardized diagnostic criteria. Therefore, a significant increase in BNP levels did not occur. In contrast, a marked elevation of BNP levels was noted in patients with diastolic heart failure given the current lack of standardized diagnostic criteria.

ACKNOWLEDGMENT: We thank Luc Nonnenmacher for technical help.

REFERENCES
6 Nishimura RA, Tajik AJ. Evaluation of diastolic filling of the left ventricle in health and disease: Doppler echocardiography is the clinician’s Rosetta Stone. J Am Coll Cardiol 1997; 30:8–18