How obesity affects the cut-points for B-type natriuretic peptide in the diagnosis of acute heart failure: Results from the Breathing Not Properly Multinational Study

Lori B. Daniels, MD, Pa,b Paul Clopton, MS, Vi,b Vikas Bhalla, MD, Pa,b Padma Krishnaswamy, MD, Pa,b Richard M. Nowak, MD, MBA, Ja,b James McCord, MD, Ja,b Judd E. Hollander, MD, Da,b Philippe Duc, MD, Ha,b Torbjorn Omland, MD, PhD, Fa,b Alan B. Storrow, MD, Da,b William T. Abraham, MD, Da,b Alan H.B. Wu, PhD, Ji Philippe G. Steg, MD, Ha,b Arne Westheim, MD, PhD, MPH, Fa,b Cathrine Wold Knudsen, MD, Fa,b Alberto Perez, MD, Gi Radmila Kazanegra, MD, Pa,b Howard C. Herrmann, MD, Da,b Peter A. McCullough, MD, MPH, Gi and Alan S. Maisel, MD Pa,b San Diego, CA; Detroit, MI; Pennsylvania, PA; Paris, France; Oslo, Norway; Cincinnati and Columbus, OH; Hartford, CT; and Kansas City, KS

Background B-type natriuretic peptide (BNP) is valuable in diagnosing heart failure (HF), but its utility in obese patients is unknown. Studies have suggested a cut-point of BNP ≥100 pg/mL for the diagnosis of HF; however, there is an inverse relation between BNP levels and body mass index. We evaluated differential cut-points for BNP in diagnosing acute HF across body mass index levels to determine whether alternative cut-points can improve diagnosis.

Methods The Breathing Not Properly Multinational Study was a 7-center, prospective study of 1586 patients who presented to the Emergency Department with acute dyspnea. B-type natriuretic peptide was measured on arrival. Height and weight data were available for 1368 participants. The clinical diagnosis of HF was adjudicated by 2 independent cardiologists who were blinded to BNP results.

Results Heart failure was the final diagnosis in 46.1%. Mean BNP levels (pg/mL) in lean, overweight/obese, and severely/morbidly obese patients were 643, 462, and 247 for patients with acute HF, and 52, 35, and 25 in those without HF, respectively (P < .05 for all comparisons except 35 vs 25). B-type natriuretic peptide cut-points to maintain 90% sensitivity for a HF diagnosis were 170 pg/mL for lean subjects, 110 pg/mL for overweight/obese subjects, and 54 pg/mL in severely/morbidly obese patients.

Conclusions Body mass index influences the selection of cut-points for BNP in diagnosing acute HF. A lower cut-point (BNP ≥54 pg/mL) should be used in severely obese patients to preserve sensitivity. A higher cut-point in lean patients (BNP ≥170 pg/mL) could be used to increase specificity. (Am Heart J 2006;151:999-1005.)

Heart failure (HF) is a serious personal and public health problem that affects >5 million Americans, resulting in massive disability and health care costs. Several studies have shown that obesity is a major modifiable risk factor for congestive HF (CHF), impacting both systolic and diastolic ventricular function as well as coronary artery disease. With the growing pandemic of obesity in the United States and elsewhere, the scope of the problem of HF is likely to continue to increase.

B-type natriuretic peptide (BNP) is useful in establishing or excluding the diagnosis of CHF in patients who present to the emergency department (ED) with acute dyspnea. However, recent studies have shown that obese and overweight individuals have considerably lower circulating natriuretic peptide levels compared with individuals with a normal body mass index (BMI). The lower levels of BNP relative to lean patients seem to persist even when obese patients are in HF, despite a similar severity of HF.

Despite that obese patients have lower BNP levels, little is known about how to interpret BNP for diagnosing CHF in this population. For the general...
population, studies have suggested a cut-point of BNP ≥100 pg/mL for the diagnosis of CHF. We sought to determine whether the optimal cut-point for BNP in diagnosing acute CHF changes with BMI and, if so, to develop an algorithm to improve diagnosis.

Methods
Study population
The Breathing Not Properly Multinational Study was an international, 7-site (5 in the United States, 1 in France, and 1 in Norway), prospective study. Study design and main results have been published elsewhere. A total of 1586 patients were enrolled from April 1999 to December 2000. The study was approved by the institutional review boards of participating study centers, and written informed consent was obtained from all participants. To be eligible for the study, patients had to have shortness of breath as their chief complaint. Exclusion criteria included the presence of advanced renal failure, acute myocardial infarction, or overt cause of dyspnea, including chest wall trauma or penetrating lung injury. A total of 80 of 1666 patients that were screened were thus excluded.

Data collection
Elements from the present and past medical history, the physical examination, and objective assessment of clinical signs were gathered by trained research personnel in the ED. Reports of other blood tests, interpretations of chest radiographs and electrocardiograms, and interpretations of other diagnostic tests were recorded in a structured checklist completed by the ED attending physician.

To determine the patient’s actual diagnosis, approximately 30 days after the ED visit, 2 cardiologists independently reviewed all medical records pertaining to the patient including the case report form, electrocardiogram, chest radiograph, echocardiogram, and all other clinical test results, consultations, and chart information. After reviewing all information, the case was categorized as CHF, history of CHF but acute dyspnea due to noncardiac cause, or not CHF. Consensus between the 2 reviewers was 90% (n = 1228), with similar concordance across all BMI subgroups (P = .52). In the 10% of cases with disagreement, the diagnosis was adjudicated locally by the 2 cardiologists, with additional data from the treating physicians and review by the end points committee if disagreement remained.

The diagnosis of CHF (n = 722 for the whole study population) was supported by positive Framingham and NHANES scores in 621 (86%) and 599 (83%) cases, respectively. Among participants diagnosed with CHF who had valid BMI data (n = 631), the adjudicating cardiologists reported that 81% of chest radiographs, 79% of echocardiograms, 19% of cardiac catheterizations, and 16% of nuclear ventriculograms provided support for the diagnosis of CHF. In addition, the cardiologists reported that 86% had an expected response to CHF therapy. Conversely, 537 (46%) of the 757 patients who were not diagnosed with CHF had a positive response to other drugs including nebulizers, steroids, and antibiotics. Information from echocardiogram, nuclear ventriculography, or cardiac catheterization had evidence to suggest that CHF was not the cause of dyspnea in 80%, and chest radiography was normal or revealed an alternative diagnosis in 29%. Pulmonary function tests revealed bronchoconstriction in 47 (6.4%) and pulmonary embolism was diagnosed in 7 (0.9%).

Measurement of BNP
During initial evaluations, a blood sample was collected into tubes containing potassium EDTA. B-type natriuretic peptide was measured using the Triage B-Type Natriuretic Peptide Test (Biosite Inc, San Diego, CA). The Triage BNP Test is a fluorescence immunoassay for the quantitative determination of BNP in whole blood and plasma specimens. Precision, analytic sensitivity, and stability characteristics of the system have been described previously. The measurable range of the BNP assay is 5.0 to 1300.0 pg/mL. B-type natriuretic peptide values were determined on site by use of the point-of-care method with either whole blood or plasma samples. The mean of 3 determinations was taken. The test was run in a concealed fashion, with results kept in separate data binders linked only by a separate study code, thus blinding both ED physicians and adjudicating cardiologists.

Calculation of BMI
Of the 1586 enrolled participants, 1369 had data for body height and weight. Of these, 1 patient who was a double amputee was excluded from this analysis, leaving 1368 participants with valid data. Body height and weight were by self-report and by actual measurement. A previous study, which evaluated the utility of calculating lean BMI using an estimate of lean body weight did not show any difference in correlation with BNP versus using a conventional BMI value. Therefore, BMI was calculated using the conventional formula of weight in kilograms divided by the square of height in meters.

Statistical analysis
Patient characteristics were described with frequency counts and means and compared across BMI groups with x² tests and an analysis of variance. B-type natriuretic peptide values were log-transformed for use with parametric statistical tests. The relationship between BMI and log BNP was evaluated with simple and partial correlation. Log BNP levels were compared

<table>
<thead>
<tr>
<th>Table I. Mean weight and BMI subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>BMI &lt; 25</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>BMI ≥ 25</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
</tbody>
</table>

Data are means ± SD.
for groups based on BMI and final diagnosis using analysis of variance with post hoc Tukey tests. For convenience, the means were expressed as the antilogs of the transformed means. Means are expressed SD. Logistic regression was used to evaluate the relationship of BMI group and log BNP to the final diagnosis of CHF. Separate receiver operating characteristic (ROC) curves were drawn for each BMI group. Decision statistics (sensitivity, specificity, and positive and negative predictive values) were computed for various BNP cut-points.

### Results

The baseline characteristics of the entire Breathing Not Properly Multinational Study cohort have previously been reported. Among the 1368 patients with valid height and weight data, 526 were lean (BMI < 25), 595 were overweight or obese (25 ≤ BMI < 35), and 247 were severely or morbidly obese (BMI ≥ 35). The range in BMI was 12.9 to 74.4, with a mean BMI for the population of 28.7 ± 8.3. The mean weight and BMI for patients within each subgroup is shown in Table I and did not vary among those with or without a final diagnosis of HF.

Table II shows the baseline characteristics in each BMI subgroup. Patients with a higher BMI were more likely to be younger, female, and nonwhite. They were also more likely to have a prior history of CHF or diabetes and were more likely to be classified as New York Heart Association class I or II. Less rales and murmurs were audible in patients with higher BMIs, but more lower-extremity edema was present. Overall, 631 patients had a final diagnosis of acute CHF (46.1%). The likelihood of a final diagnosis of acute CHF in patients presenting with dyspnea did not differ with respect to BMI (P = .76).

The correlation between log BNP and BMI was r = −0.19 (r² = 0.04, P < .001) for all patients. In those with acute CHF, the correlation was r = −0.33 (r² = 0.11,
Body mass index remained a significant predictor of log BNP level even after correcting for the baseline characteristics listed in Table II (partial $r^2 = 0.22$, partial $r^2 = 0.05$, $P < .001$).

Figure 1 depicts mean BNP levels stratified by final diagnosis and by BMI group. Among those with acute CHF, the mean BNP levels were 643, 462, and 247 pg/mL in lean, overweight/obese, and severely/morbidly obese patients, respectively. The corresponding BNP levels in patients without acute CHF were 52, 35, and 25 pg/mL. Post hoc tests indicated that the BNP level for each of these 6 groups was significantly different from each of the other groups ($P < .05$), except that overweight/obese patients without CHF did not differ significantly from severely/morbidly obese patients without CHF.

Logistic regression analysis was used to predict CHF from the 3 BMI groups and log BNP in an additive model. Both BMI group and log BNP were significant predictors ($P < .001$ for each). When the interaction of BMI group and log BNP was added to the model, the interaction effect was not significant ($P = .38$), indicating that the additive model was correct. The prediction functions for the additive model are illustrated in Figure 2.

At a cut-point of BNP $\geq$100 pg/mL, the sensitivity in differentiating between dyspnea due to CHF and dyspnea due to other causes has previously been reported for the entire study population as 90% (95% CI 88%-92%), with a specificity of 79% (95% CI 76%-81%). Using this cut-point in the severely/morbidly obese group, however, yields a sensitivity of only 77%, with a high false-negative rate. Conversely, using this cut-point of BNP $\geq$100 pg/mL in the lean group yields a specificity of only 65%, with significant numbers of false-positive results. Table III shows the sensitivity and specificity of using BNP $\geq$100 pg/mL in each of the 3 BMI groups.

Figure 3, A shows the superimposed ROC curves for a diagnosis of CHF from BNP levels in each of the 3 BMI subgroups. Although the areas under the curves are similar, equivalent BNP values are at considerably different positions on the curves. Separate curves for sensitivity and specificity as a function of BNP cut-points are shown in Figure 3, B. The BNP cut-point values where sensitivity and specificity are equal differ across BMI groups. To achieve 90% sensitivity, the BNP cut-point in the lean patients is BNP $\geq$170 pg/mL.
whereas in the severely/morbidly obese patients, the equivalent cut-point is only 54 pg/mL (Figure 4).

Discussion
Heart failure is a difficult diagnosis to make in the ED or urgent care setting. Classic signs and symptoms are not always present. This is especially true in obese patients, whose body habitus may mask signs of edema and may muffle the heart and lung sounds during auscultation. For example, in our study, patients with higher BMIs were less likely to have documented murmurs or rales and were not as likely to have visible elevation of jugular venous pressure. History also can be less reliable because obese patients frequently have comorbid conditions that can mimic CHF, including dyspnea caused by deconditioning and orthopnea due to abdominal size. Furthermore, obesity tends to reduce image quality of echocardiograms and chest radiographs.

With all of these pitfalls, BNP is potentially even more valuable to aid in the timely diagnosis of CHF for obese patients. However, prior studies have shown that BNP levels tend to run lower in obese patients, even with similar severities of CHF. Our results confirm this finding. We have shown that there is an inverse correlation between log BNP and BMI, which is stronger in those with acute CHF. Differences in BNP among those without CHF are small; therefore, the BMI masking of BNP elevations is less pronounced in this non-CHF group.

Because BNP values are lower in obese patients, lower cut-points are needed for obese patients if sensitivity is to be preserved. Prior studies have established the utility of BNP in improving the accuracy of a diagnosis of CHF in patients with acute dyspnea. A cut-point of ≥100 pg/mL has been recommended for high sensitivity to limit the number of missed diagnoses. This study shows that for patients with the highest BMIs, a lower cut-point of BMI ≥54 pg/mL should be used to maintain the equivalent level of sensitivity. Otherwise, the diagnosis of CHF in this subgroup may be missed in >1 in 5 patients who present with acute dyspnea and have a BNP level <100 pg/mL.

Conversely, lean patients may have higher BNP levels relative to the general population. As such, if increased specificity is desired, a higher cut-point of BNP ≥170 pg/mL can be used while maintaining 90% sensitivity. The mechanism responsible for lower BNP levels in obese patients has not been fully elucidated and is likely multifactorial, but maybe in part related to increased
metabolism in adipose tissue either via peptide degradation or regulation of clearance receptors. Support for this hypothesis comes from recent data showing that after infusion of exogenous BNP, levels in obese patients fall more rapidly back toward baseline than in lean patients (personal communication with Dr Robert L. Fitzgerald, unpublished data.) Evidence also suggests that natriuretic peptides play an important role in lipid metabolism and may affect the pathophysiology of obesity.26-28

This study has several limitations. First, because HF is a clinical diagnosis, an ideal gold standard does not exist. Here, 2 cardiologists reviewed all of the relevant data and were responsible for classifying patients, but misdiagnoses remain possible, especially in obese patients where signs and symptoms of HF may be confusing. Second, because a combination of patients’ self-reported weights and measured values were used, there may be some inherent inaccuracy in the calculated BMIs. Patients may have over- or underestimated their weights. Furthermore, weights can fluctuate with severity and treatment of CHF. Third, it is possible that when considerable detail is known regarding the state of left ventricular remodeling and the severity of CHF, some of the relationship between BMI and BNP may be explained by cardiac cachexia in those with severe CHF.21 However, cardiac cachexia is unlikely to account for the entire effect, and we therefore feel that the broad implications of BNP and its related cut-points for BMI level are justified. Finally, this was a post hoc analysis of data obtained in a prospective trial; it would be interesting to see whether the observed relationship persists in future prospective studies.

In conclusion, BMI influences the selection of cut-points for BNP in diagnosing acute CHF. In severely and morbidly obese patients, a lower cut-point (BNP ≥54 pg/mL) should be used to preserve 90% sensitivity. Conversely, a higher cut-point may be used in lean patients (BNP ≥170 pg/mL) to increase specificity.

References

