Impact of Body Mass and Body Composition on Circulating Levels of Natriuretic Peptides
Results From the Dallas Heart Study

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Background—The association between higher body mass index (BMI) and lower B-type natriuretic peptide (BNP) level is thought to be mediated by expression of the natriuretic peptide clearance receptor (NPR-C) in adipose tissue. To explore this association, we tested 2 hypotheses: (1) that N-terminal (NT)-proBNP, which is not believed to bind NPR-C, would not be associated with BMI and (2) that lower BNP would be more closely associated with fat mass than with lean mass.

Methods and Results—Measurements of BNP, NT-proBNP, and body composition by direct dual energy x-ray absorptiometry (DEXA) were performed in 2707 subjects from the Dallas Heart Study. The associations between obesity and low BNP (<4 ng/L) or low NT-proBNP (lowest sex-specific quartile) were evaluated with multivariable logistic regression models stratified by sex and adjusted for age, race/ethnicity, hypertension, left ventricular mass, and end-diastolic volume. Higher BMI was independently associated with lower BNP and NT-proBNP (all P<0.001). When BMI was replaced with both DEXA-derived lean and fat mass, greater lean mass, but not fat mass, was associated with low BNP and NT-proBNP levels.

Conclusions—in a large, population-based cohort, we confirm the previously described association between higher BMI and lower BNP and demonstrate a similar inverse association between BMI and NT-proBNP. Interestingly, both BNP and NT-proBNP are more closely associated with lean mass than with fat mass. These findings do not support the hypothesis that the lower BNP levels seen in obesity are driven by enhanced BNP clearance mediated via NPR-C.

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Key Words: natriuretic peptides ■ obesity ■ hormones ■ physiology

Several recent studies have examined the relationship between plasma B-type natriuretic peptide (BNP) and obesity, demonstrating an inverse relationship between body mass index (BMI) and BNP concentration in subjects with\(^1\) and without\(^2\) heart failure. One mechanism that has been suggested to explain this inverse relationship is increased expression of the natriuretic peptide clearance receptor (NPR-C) by adipose tissue, which results in lower BNP levels in obese individuals.\(^3\) To further elucidate the role of NPR-C in mediating the relationship between obesity and BNP, we examined 2 hypotheses: first, that the concentration of amino-terminal (NT)-proBNP, which is not believed to bind NPR-C,\(^4\) would be unrelated to measures of obesity, and second, that BNP would be inversely related to fat mass but not lean mass.

Methods

Study Population
The Dallas Heart Study (DHS) is a probability-based random sample of Dallas County residents. The present study is based on the 2971 subjects from DHS aged 30 to 65 years who participated in all 3 phases of data collection, including medical history, measurement of anthropometrics, collection of blood samples, MRI for the assessment of cardiac size and function, and dual-energy x-ray absorptiometry (DEXA) for body composition analysis.\(^6,7\) We excluded subjects with unavailable DEXA data (n=84), serum creatinine \(>2.0\) mg/dL (n=16), a history of heart failure by self-report (n=95), unavailable BNP (n=51), and unavailable NT-pro-BNP (n=18). This left a final population of 2707 subjects for analysis. This study was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center and conducted in accordance with institutional guidelines; all participants have provided informed consent. Subjects were enrolled into the study between July 2000 and September 2002, and all study-related procedures were completed by November 2002.

Demographic characteristics were determined by subject self-report at the time of study entry. BMI was calculated based on measured height and weight at the time of cardiac imaging. Cardiac MRI was performed to determine left ventricular (LV) mass and volumes.\(^6,7\) To determine interscan variability, patients were scanned once, taken off the scanner briefly, and then rescanned. Interobserver difference for LV mass was 9.2±5 g (5.8±3.5%, n=15), intraob-
Venous blood was collected in standard blood collection tubes containing EDTA. Samples were maintained at 4°C for ≤4 hours and then centrifuged (1430g for 15 minutes) at 4°C. Plasma was then removed and frozen at −70°C until assays were performed. BNP was measured on a TECAN Genesis RSP 200/8 robotic high-throughput platform (Biosite Inc.) and NT-proBNP was measured on the Elecsys proBNP platform (Roche Diagnostics). The CV for the BNP assay averaged 11.2% at a concentration of 30 ng/L and 6.0% at concentrations >60 ng/L; the CV for the NT-proBNP assay was 3.3% at a concentration of 282 ng/L and 3.0% at a concentration of 6012 ng/L. Natriuretic peptide assays were performed between 8 and 24 hours after blood collection. Serum creatinine was measured on the Elecsys CRP assay platform (Roche Diagnostics) and the CV for serum creatinine was 3.3% at a concentration of 1 mg/L and 1.8% at concentrations >2.0 mg/L.

### BNP and NT-proBNP Measurement

Venous blood was collected in standard blood collection tubes containing EDTA. Samples were maintained at 4°C for ≤4 hours and then centrifuged (1430g for 15 minutes) at 4°C. Plasma was then removed and frozen at −70°C until assays were performed. BNP was measured on a TECAN Genesis RSP 200/8 robotic high-throughput platform (Biosite Inc.) and NT-proBNP was measured on the Elecsys proBNP platform (Roche Diagnostics). The CV for the BNP assay averaged 11.2% at a concentration of 30 ng/L and 6.0% at concentrations >60 ng/L; the CV for the NT-proBNP assay was 3.3% at a concentration of 282 ng/L and 3.0% at a concentration of 6012 ng/L. Natriuretic peptide assays were performed between 8 and 24 hours after blood collection. Serum creatinine was measured on the Elecsys CRP assay platform (Roche Diagnostics) and the CV for serum creatinine was 3.3% at a concentration of 1 mg/L and 1.8% at concentrations >2.0 mg/L.

### Statistical Analyses

Data were analyzed with the SAS version 9.1 (SAS Corporation) statistical software package. Descriptive statistics stratified by BMI and by natriuretic peptide levels were determined. Given the marked differences in natriuretic peptide levels and body composition between men and women, subsequent analyses were performed stratified by sex. The relationship between natriuretic peptide levels and BMI was examined, with BMI divided into 3 categories: normal weight (BMI <25 kg/m²), overweight (25≤BMI<30 kg/m²), and obese (BMI ≥30 kg/m²). Sex-specific tests for linear trend were performed with linear regression across categories of BMI. Linear regression of the log-transformed natriuretic peptide levels was performed with Tobit models to more precisely quantify the association between circulating natriuretic peptide levels and body fat (modeled with BMI or direct DEXA measurements). Tobit models were used to include the partial information contained in the observations censored at the detection threshold of the assay without biasing the estimates of the linear regression. In addition to body fat and sex, the following covariates were considered potential confounders, on the basis of prior published work and results of the bivariate analyses: age, race/ethnicity, hypertension, diabetes, hypercholesterolemia, prior myocardial infarction (MI), smoking, ejection fraction, serum creatinine, and LV mass and end-diastolic volume. The models were fit through a stepwise backward-selection algorithm. All candidate variables were entered into the initial saturated model, and then variables with probability values >0.05 in the multivariable model were removed iteratively. The final restricted multivariable model contains all variables that remained significant at the P<0.05 level. Effect modification was tested for by creating a dichotomous age variable at the median (44 years) and then sequentially adding multiplicative interaction terms for age, diabetes, or NT-proBNP in the lowest sex-specific quartile."
used logistic regression to model for natriuretic peptide levels in the highest sex-specific quartiles (BNP: ≥9.1 ng/L for men, ≥16.1 ng/L for women; NT-proBNP: ≥39.2 ng/L for men, ≥75.9 ng/L for women). For intergroup comparisons, Student’s t test, Pearson’s χ², or ANOVA F test were used as appropriate. For all analyses, 2-tailed probability values <0.05 were considered statistically significant.

**Results**

**Baseline Characteristics, BMI and Natriuretic Peptide Levels**

Baseline characteristics for the study population are shown stratified by BMI category in Table 1. Increasing BMI was associated with an increased likelihood of being female or black; an increased likelihood of having hypertension, LV hypertrophy (LVH), or diabetes; and higher LV ejection fraction, LV mass, and LV end-diastolic volume. The distributions of natriuretic peptide levels and of body composition are presented in Table 2; baseline characteristics stratified by BMI category in Table 1. Increasing BMI was associated with an increased likelihood of being female or black; an increased likelihood of having hypertension, LV hypertrophy (LVH), or diabetes; and higher LV ejection fraction, LV mass, and LV end-diastolic volume. The distribution of natriuretic peptide levels and of body composition are presented in Table 2; baseline characteristics stratified by BMI category in Table 1. Increasing BMI was associated with an increased likelihood of being female or black; an increased likelihood of having hypertension, LV hypertrophy (LVH), or diabetes; and higher LV ejection fraction, LV mass, and LV end-diastolic volume. The distribution of natriuretic peptide levels and of body composition are presented in Table 2; baseline characteristics stratified by BMI category in Table 1.

**Association Between Body Composition and Natriuretic Peptide Levels**

The association between natriuretic peptide levels and BMI is illustrated in Figure 1. For both sexes, BNP and NT-proBNP levels decreased in a stepwise fashion across categories of increasing BMI ($P<0.0001$ for trend for all comparisons). In multivariable Tobit linear regression analysis, an inverse association was confirmed between BMI and BNP, as shown in Table 4. Of note, a similar inverse association was observed between BMI and NT-proBNP. To eliminate the

**TABLE 2.** Distribution of Natriuretic Peptides and Body Composition Stratified by Gender (n=2707)

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th></th>
<th>Men</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10%</td>
<td>25%</td>
<td>50%</td>
<td>75%</td>
</tr>
<tr>
<td>BNP, ng/L</td>
<td>0</td>
<td>0</td>
<td>4.9</td>
<td>16.0</td>
</tr>
<tr>
<td>NT-proBNP, ng/L</td>
<td>9.5</td>
<td>20.5</td>
<td>39.0</td>
<td>75.8</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.4</td>
<td>25.7</td>
<td>30.9</td>
<td>36.1</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>22.3</td>
<td>25.0</td>
<td>28.3</td>
<td>31.6</td>
</tr>
<tr>
<td>Lean mass, kg</td>
<td>37.8</td>
<td>41.8</td>
<td>47.0</td>
<td>53.4</td>
</tr>
</tbody>
</table>

Results presented are mean±SD for continuous variables or percentage for categorical variables. Lower BNP is defined as below the assay threshold of 4 ng/L; lower NT-proBNP is defined as the lowest sex-specific quartile (<7.6 ng/L for men, <20.4 ng/L for women). *Statistically significant difference ($P<0.05$) between lower and higher BNP. †Statistically significant difference ($P<0.05$) between lower and higher NT-proBNP.
assumption of a linear relationship between natriuretic peptide levels and BMI, we repeated the multivariable models using BMI as a categorical exposure variable. The results of these models with BMI treated categorically were qualitatively unchanged from those that modeled BMI as a continuous covariate. Model 1 used BMI as a measure of obesity, and model 2 replaced BMI with directly measured fat and lean mass values from DEXA body composition analysis. Both models are shown stratified by gender and adjusted for age, race/ethnicity, hypertension, LV mass, and end-diastolic volume. Other considered covariates (see statistical methods section) were not statistically significant in the final multivariable model. When BMI was replaced in the models by direct measurements of fat and lean mass from DEXA body composition analysis, only lean mass retained the independent inverse association with both BNP and NT-proBNP; fat mass was not associated with either BNP or NT-proBNP, also shown in Table 4.

Logistic regression analyses were also performed in which low BNP or low NT-proBNP were considered as categorical variables; the same covariates were evaluated in these models as in the linear regression models described above. The adjusted ORs for low BNP (≤4 ng/L) and low NT-proBNP (lowest sex-specific quartile: ≤7.6 ng/L for men, ≤20.4 ng/L for women) are shown in Table 5. Again, model 1 used BMI as a measure of obesity, and model 2 replaced BMI with directly measured fat and lean mass values from DEXA body composition analysis. Qualitatively, these results are identical to the linear regression models. Higher BMI was associated with increased odds of low BNP and low NT-proBNP for both men and women. After BMI was replaced with fat and lean mass in the multivariable model, fat mass was not related to the probability of having a low BNP or NT-proBNP for either men or women. However, higher lean mass was associated with an increased probability of low BNP and NT-proBNP for both men and women. Results were similar after exclusion of subjects taking antihypertensive medication, those with LV ejection fraction ≤55%, those with history of MI, and those with symptoms of dyspnea or edema. Results of models for natriuretic peptide levels in the highest sex-specific quartiles (BNP: ≥9.1 ng/L for men, ≥16.1 ng/L as in the linear regression models described above. The adjusted ORs for low BNP (≤4 ng/L) and low NT-proBNP (lowest sex-specific quartile: ≤7.6 ng/L for men, ≤20.4 ng/L for women) are shown in Table 5. Again, model 1 used BMI as a measure of obesity, and model 2 replaced BMI with directly measured fat and lean mass values from DEXA body composition analysis. Qualitatively, these results are identical to the linear regression models. Higher BMI was associated with increased odds of low BNP and low NT-proBNP for both men and women. After BMI was replaced with fat and lean mass in the multivariable model, fat mass was not related to the probability of having a low BNP or NT-proBNP for either men or women. However, higher lean mass was associated with an increased probability of low BNP and NT-proBNP for both men and women. Results were similar after exclusion of subjects taking antihypertensive medication, those with LV ejection fraction ≤55%, those with history of MI, and those with symptoms of dyspnea or edema. Results of models for natriuretic peptide levels in the highest sex-specific quartiles (BNP: ≥9.1 ng/L for men, ≥16.1 ng/L
for women; NT-proBNP: ≥39.2 ng/L for men, ≥75.9 ng/L for women) yielded qualitatively similar results. No significant interactions were observed between natriuretic peptide levels, body composition measurements, and age, hypertension, or diabetes (P > 0.05 for each).

Because fat mass and lean mass were highly correlated, several additional analyses were performed to address issues of collinearity. First, the addition of fat mass to a model that contained lean mass did not qualitatively alter the relationship between lean mass and natriuretic peptide levels; increasing lean mass was associated with decreasing natriuretic peptide levels in models with and without fat mass, yielding very similar point estimates. Furthermore, other analyses performed with different constructs of adiposity (eg, percent body fat) led to the same qualitative result. Finally, we performed stratified analyses comparing subjects with discordant lean mass and fat mass values. BNP and NT-proBNP levels were significantly lower among subjects with below-median fat mass/above-median lean mass than among those with above-median fat mass/below-median lean mass (Figure 2).

**TABLE 4. Tobit Linear Regression Models for BNP and NT-proBNP (n=2707)**

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
</tr>
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<tbody>
<tr>
<td></td>
<td>β±SE</td>
<td>P</td>
<td>β±SE</td>
<td>P</td>
</tr>
<tr>
<td><strong>BNP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>BMI (per 5 kg/m²)</td>
<td>-0.270±0.058</td>
<td>&lt;0.001</td>
<td>-0.099±0.032</td>
<td>0.002</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total body fat mass (per 10 kg)</td>
<td>0.045±0.074</td>
<td>0.54</td>
<td>0.027±0.054</td>
<td>0.62</td>
</tr>
<tr>
<td>Total body lean mass (per 10 kg)</td>
<td>-0.453±0.082</td>
<td>&lt;0.001</td>
<td>-0.334±0.091</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>NT-proBNP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (per 5 kg/m²)</td>
<td>-0.314±0.038</td>
<td>&lt;0.001</td>
<td>-0.109±0.021</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Total body fat mass (per 10 kg)</td>
<td>-0.059±0.051</td>
<td>0.24</td>
<td>0.015±0.036</td>
<td>0.68</td>
</tr>
<tr>
<td>Total body lean mass (per 10 kg)</td>
<td>-0.450±0.055</td>
<td>&lt;0.001</td>
<td>-0.309±0.062</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Multivariable log-transformed Tobit models are stratified by sex and adjusted for age, race/ethnicity, diabetes, hypertension, prior MI, LV, and end-diastolic volume. Results shown are model β-coefficients ±SE.

**TABLE 5. Logistic Regression Models for Low BNP and NT-proBNP (n=2707)**

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds of low BNP</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>BMI (per 5 kg/m²)</td>
<td>1.34 (1.16–1.55)</td>
<td>1.11 (1.02–1.21)</td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>Total body fat mass (per 10 kg)</td>
<td>0.94 (0.79–1.14)</td>
<td>0.97 (0.84–1.12)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total body lean mass (per 10 kg)</td>
<td>1.62 (1.32–2.00)</td>
<td>1.44 (1.12–1.84)</td>
<td></td>
</tr>
<tr>
<td>Odds of low NT-proBNP</td>
<td>Model 1</td>
<td>BMI (per 5 kg/m²)</td>
<td>1.42 (1.20–1.68)</td>
<td>1.19 (1.08–1.31)</td>
</tr>
<tr>
<td></td>
<td>Model 2</td>
<td>Total body fat mass (per 10 kg)</td>
<td>1.05 (0.85–1.32)</td>
<td>0.94 (0.79–1.11)</td>
</tr>
<tr>
<td></td>
<td>Total body lean mass (per 10 kg)</td>
<td>1.55 (1.21–1.99)</td>
<td>1.63 (1.20–2.20)</td>
<td></td>
</tr>
</tbody>
</table>

Multivariable logistic regression models are stratified by sex and adjusted for age, race/ethnicity, diabetes, hypertension, prior MI, LV mass, and end-diastolic volume. Low BNP is defined as <4 ng/L; low NT-proBNP is defined as in the lowest sex-specific quartile (<7.6 ng/L for men, <20.4 ng/L for women).

**Discussion**

In a large, population-based cohort, we confirm the previously described association between higher BMI and lower BNP.1,2 We also make 2 novel observations that provide insight into the mechanism of reduced natriuretic peptide levels in subjects with higher BMI values. First, we demonstrate for the first time a similar inverse relationship between higher BMI and lower NT-proBNP levels. Second, using validated DEXA-derived measurements of body composition, we show that the association between BMI and BNP and NT-proBNP is mediated by lean mass rather than fat mass.

A recent article by Wang and colleagues from the Framingham Heart Study2 showed that higher BMI was associated with lower BNP levels. They postulated that this inverse relationship may be due to increased expression of NPR-C by adipose tissue resulting in increased clearance of BNP in obese subjects and suggested that this may contribute to hypertension in obese subjects. In the present study, the association between higher BMI and lower NT-proBNP suggests that nonclearance mechanisms are likely to be important, because NT-proBNP is structurally distinct from BNP and thus unlikely to be cleared via NPR-C. Of interest, in the Framingham study, NT-proANP levels were also lower in subjects with higher BMI, a finding that also suggests that decreased release of natriuretic peptides from the heart, rather than increased clearance, may be responsible for the association between higher BMI and lower natriuretic peptide levels.16

Previous studies evaluating the association between adiposity and natriuretic peptide levels used BMI as a measure of obesity. Here, when we divided body mass into its fat and lean mass components using DEXA, we found that lean mass and not fat mass was responsible for the association between
higher BMI and lower natriuretic peptide levels. Because the association was similar for BNP and NT-proBNP, we postulate that a substance produced in the lean mass suppresses either synthesis or release of natriuretic peptides from cardiomyocytes. It is also possible that this effect could be mediated by sex steroid hormones that coordinately influence natriuretic peptide synthesis as well as body composition. For example, androgens, which promote the development of lean mass, may suppress natriuretic peptide release, whereas estrogens, which are associated with lower lean mass, increase natriuretic peptide levels. Less likely hypotheses to explain our observations include the possibility that lean mass contributes directly to BNP and NT-proBNP degradation, or that lean mass contributes directly to BNP and NT-proBNP clearance. Further studies will be needed to confirm these findings and to explore the associated mechanisms. Fully elucidating the link between obesity and low natriuretic peptide levels may prove an important step toward understanding the association between obesity and cardiovascular disease.

Acknowledgments
This article was supported in part by the Donald W. Reynolds Foundation, by USPHS GCRC grant #M01-RR00633 from NIH/NCRR-CR, and by Roche Diagnostics, Indianapolis, Ind. Reagents for NT-proBNP were provided by Roche Diagnostics and reagents for BNP by Biosite, Inc, San Diego, Calif.

Disclosure
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References
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