Impact of Obesity on Plasma Natriuretic Peptide Levels

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Background—The mechanisms linking obesity to hypertension have not been established, but sodium retention and excessive sympathetic tone are key contributors. The natriuretic peptides are important regulators of sodium homeostasis and neurohormonal activation, raising the possibility that obese individuals have an impaired natriuretic peptide response.

Methods and Results—We examined the relations of plasma B-type natriuretic peptide (BNP) and N-terminal proatrial natriuretic peptide (N-ANP) to body mass index in 3389 Framingham Study participants (1803 women) without heart failure. Multivariable regression analyses were performed, adjusting for clinical and echocardiographic covariates. BNP levels below the assay detection limit and N-ANP levels in the lowest sex-specific quartile were categorized as low. Multivariable-adjusted mean plasma BNP levels in lean (<25 kg/m^2), overweight (25 to 29.9 kg/m^2), and obese (≥30 kg/m^2) men were 21.4, 15.5, and 12.7 pg/mL, respectively (trend $P<0.0001$). Corresponding values in women were 21.1, 16.3, and 13.1 pg/mL (trend $P<0.001$). A similar pattern was noted for plasma N-ANP. Obese individuals had higher odds of having low plasma BNP (multivariable-adjusted odds ratios: men, 2.51; 95% CI, 1.71 to 3.68; women, 1.84; 95% CI, 1.32 to 2.58) and low plasma N-ANP (odds ratios: men, 4.81; 95% CI, 2.98 to 7.76; women, 2.85; 95% CI, 2.01 to 4.04) compared with lean individuals. Diabetes also was associated with low plasma natriuretic peptide levels, and the negative effects of obesity and diabetes on natriuretic peptide levels were additive.

Conclusions—Obese individuals have low circulating natriuretic peptide levels, which may contribute to their susceptibility to hypertension and hypertension-related disorders. (***Circulation***. 2004;109:594-600.)

Key Words: natriuretic peptides ■ obesity ■ epidemiology

Obesity is a major risk factor for hypertension[1] and hypertension-related disorders such as left ventricular hypertrophy.[2] The mechanisms linking obesity to the development of hypertension have not been established, although it has been suggested that renal sodium and water retention[3] and increased activation of the sympathetic and renin-angiotensin systems[1,4] may contribute. Because the natriuretic peptide system plays a key role in the regulation of these processes, it has been speculated that obese individuals have an impaired natriuretic peptide response, and the phrase *natriuretic handicap* has been used to describe this phenomenon.[5] The existence of such a handicap has not been proven, although limited experimental data suggest that plasma atrial natriuretic peptide (ANP) levels fail to rise appropriately in obese subjects after a saline load.[6]

Although the demonstration of low plasma natriuretic peptide levels in obese individuals would support the concept of a natriuretic handicap, the frequent coexistence of conditions such as hypertension and diabetes may confound the relations of obesity and natriuretic peptide levels. Hypertension seems to elevate circulating natriuretic peptide levels,[7,8]

whereas the effect of diabetes is less clear.[9,10] The availability of routine plasma natriuretic peptide measurements on more than 3000 individuals in the Framingham Heart Study made it possible to investigate the impact of obesity on natriuretic peptide levels and to distinguish this impact from that of hypertension, diabetes, and other characteristics.

Methods

Study Sample

The Framingham Heart Study offspring cohort was initiated in 1971 with the recruitment of 5124 participants, offspring (and their spouses) of the original Framingham Heart Study participants.[11] From 3532 attendees at the sixth offspring examination (1995 to 1998), we excluded 143 participants for the following reasons: unavailable plasma natriuretic peptide levels (n=80), renal insufficiency (creatinine >2.0 mg/dL; n=21), history of congestive heart failure (n=33), and missing anthropometric data (n=9). After exclusions, 3389 subjects (96% of attendees; 1803 women) remained eligible.

All subjects underwent a routine physical examination, with medical history, laboratory assessment of cardiovascular disease risk factors (including plasma natriuretic peptide levels), electrocardiography, and echocardiography. Body mass index (BMI, kg/m^2) was

calculated as weight in kilograms divided by height in meters squared. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive therapy. Diabetes was defined as fasting plasma glucose ≥126 mg/dL or use of insulin or hypoglycemic medications.

Subjects underwent a standardized 2D echocardiographic examination. Left ventricular mass was calculated using the American Society of Echocardiography formula.[12] Left ventricular systolic dysfunction was defined as a fractional shortening <0.29 or visually estimated ejection fraction <0.50.

Plasma Natriuretic Peptide Measurements

Fasting subjects underwent phlebotomy in a supine position, typically between 8:00 and 9:00 AM. Samples were drawn in tubes containing EDTA, placed on ice, and centrifuged within 30 minutes. The plasma was frozen at −70°C until assay. Plasma levels of B-type natriuretic peptide (BNP) and the N-terminal component of pro-ANP (N-ANP) were measured using sensitive noncompetitive immunoradiometric assays (Shionogi).[13] Lower detection limits were 4 pg/mL for BNP and 94 pmol/L for N-ANP. Average interassay coefficients of variation were 12.2% for BNP and 12.7% for N-ANP.

Statistical Analyses

We examined the relations of plasma natriuretic peptide levels to BMI using multivariable analyses. Peptide levels were considered as continuous and as dichotomous variables. Low peptide levels were defined a priori as plasma BNP levels at or below the assay detection limit (4 pg/mL, observed in 25% of women and 38% of men) or N-ANP levels in the bottom sex-specific quartile (cut points 195 pmol/L in men and 251 pmol/L in women). Separate criteria were used for BNP and N-ANP because of different degrees of censoring by the lower detection thresholds of the respective assays. Similarly, BMI was treated as a continuous and as a categorical variable using the World Health Organization/National Institutes of Health classification scheme (normal <25 kg/m², overweight 25.0 to 29.9 kg/m², obese ≥30 kg/m²).[14]

For analyses examining continuous natriuretic peptide levels, we performed multivariable linear regressions with natural log-transformed BNP and N-ANP as the dependent variables. Tobit models, implemented using the SAS LIFEREG procedure, were estimated to account for left censoring of the peptide distributions.[15] Sex-specific regressions included BMI plus age, myocardial infarction, atrial fibrillation, diabetes mellitus, smoking, blood pressure stage (systolic blood pressure <140 and diastolic blood pressure <90 mm Hg; systolic blood pressure 140 to 159 or diastolic blood pressure 90 to 99 mm Hg; systolic blood pressure ≥160 or diastolic blood pressure ≥100 mm Hg, or use of antihypertensive therapy),[16] serum creatinine, left atrial size, left ventricular mass, and left ventricular systolic dysfunction. Adjustment for echocardiographic variables was performed because BMI is associated with left ventricular mass[2] and left atrial size,[17] which may directly affect natriuretic peptide levels. Because models used log-transformed dependent variables, we exponentiated the β coefficient for BMI to characterize its multiplicative effect on absolute plasma natriuretic peptide levels. To accommodate missing data for LV mass, we used an indicator variable (measured LV mass, no/yes) and assigned the mean value in place of missing values. In additional models, we replaced the continuous BMI variable with BMI categories (normal, overweight, or obese). The results of the multivariable analyses were also used to examine the relations of BMI category to plasma natriuretic peptide levels according to hypertension status and diabetes status.

We used multivariable logistic regression analyses to analyze correlates of low plasma natriuretic levels.[18] We estimated odds ratios for having low natriuretic peptide levels according to BMI category, with normal BMI individuals as the referent group. Odds ratios were adjusted for the same covariates used in the linear models.

Secondary Analyses

We evaluated the relations of waist circumference, a measure of central adiposity, with plasma natriuretic peptide levels. We tested for the influence of age, sex, diabetes, and systolic blood pressure on the relations of BMI with natriuretic peptide levels by incorporating interaction terms, one at a time, in multivariable models with adjustment for multiple testing. Finally, we repeated all analyses after excluding participants taking ACE inhibitors, β-blockers, or diuretics. A 2-sided P value <0.05 was considered statistically significant.

Results

Characteristics of the study sample (mean age, 59 years; 53% women) are shown in Table 1. Overall, 1410 (42%) participants were overweight and 946 (28%) participants were obese. Morbidly obese participants (BMI ≥40 kg/m²) accounted for 3% of the study sample. Age- and sex-adjusted mean plasma natriuretic peptide levels were lower in obese (P<0.001) and overweight (P<0.002) individuals compared with individuals with normal BMI (Table 1).

Obesity and Plasma Natriuretic Peptide Levels: Multivariable Analyses

After adjustment for age, clinical, and echocardiographic variables, BMI was inversely associated with plasma natriuretic peptide levels (Table 2). In men, each standard deviation increase in BMI (+4.4 kg/m²) was associated with an 18% decrement in BNP and a 12% decrement in N-ANP (P<0.001 for both). In women, each standard deviation increase in BMI (+5.7 kg/m²) was associated with a 16% decrement in BNP and a 10% decrement in N-ANP (P<0.001 for both).

There was also a progressive decrease in plasma natriuretic peptide levels with increasing BMI category (P for trend <0.001; Table 2). Obese men had 40% lower plasma BNP levels and 26% lower plasma N-ANP levels compared with men with normal BMI (P<0.001 for both). Corresponding differences in women were 38% and 26% (P<0.001 for both). Significant reductions in plasma natriuretic peptide levels were observed in both class 1 (BMI 30 to 34.9 kg/m²) and class 2 or greater (BMI ≥35 kg/m²) obesity (P<0.001 for comparisons with normal BMI). Multivariable-adjusted mean levels of plasma BNP and N-ANP are shown in Figure 1 for each BMI category.

Results were similar in all analyses excluding participants taking ACE inhibitors, β-blockers, or diuretics. Interaction terms of BMI with age, sex, systolic blood pressure, and diabetes were not significant (with adjustment for multiple testing).

Obesity and Low Plasma Natriuretic Peptide Levels

We performed multivariable logistic regressions examining predictors of low plasma natriuretic peptide levels (Table 3). After multivariable adjustment, being overweight was associated with a 1.4- to 3.5-fold increase in the odds of having low plasma natriuretic peptide levels. Obesity was associated with a 1.8- to 4.8-fold increase in the odds of having low plasma natriuretic peptide levels.

Joint Influences of Obesity, Hypertension, and Diabetes

The progressive decrease in adjusted plasma natriuretic peptide levels across BMI categories was observed in both hypertensive and nonhypertensive individuals (Figure 2). Overall, plasma

TABLE 1. Participant Characteristics

	Normal BMI (n=1033)	Overweight (n=1410)	Obese (n=946)
Age, y	58±10	59±10	58±9
Male, %	31	55	51
BMI, kg/m^2	22.7±1.7	27.4±1.4	34.3±4.2
Waist circumference, cm	84.6±8.1	97.1±7.1	112.8±10.4
Hypertension, %	29	42	53
Antihypertensive therapy, %	18	27	39
Diabetes, %	4	8	18
Smoker, %	18	14	15
Prior myocardial infarction, %	2	4	4
Atrial fibrillation, %	0.5	1	2
Left atrial diameter,* cm	3.7±0.5	4.0±0.5	4.2±0.5
Left ventricular mass,* g	142.4±36.4	169.1±44.1	184.4±46.5
Left ventricular systolic dysfunction,* %	4	6	6
Plasma natriuretic peptide levels			
BNP,† pg/mL	18.4	15.9‡	14.8‡
N-ANP,† pmol/L	428	376‡	348‡

Entries are mean±SD or percents.

*Not available in 120 (4%), 832 (24%), and 221 (7%) participants for left atrial diameter, left ventricular mass, and left ventricular systolic dysfunction, respectively.

†Adjusted for age and sex.

‡$P<0.002$ compared with normal BMI.

natriuretic peptide levels were 6% to 27% higher in hypertensive compared with nonhypertensive individuals. However, overweight and obese individuals with hypertension still had lower plasma BNP and N-ANP levels compared with nonhypertensive individuals with normal BMI. Additionally, the inverse relation between BMI category and natriuretic peptide levels was observed within normal, prehypertensive, and hypertensive subgroups, as classified by Joint National Committee VII (data not shown).[16]

Adjusted mean plasma natriuretic peptide levels in individuals with and without diabetes mellitus are shown in Figure 2. Participants with diabetes had lower adjusted plasma N-ANP levels (17% lower in men, $P<0.001$; 15% lower in women, $P<0.001$) than participants without diabetes. There was a trend toward lower adjusted plasma BNP levels in men (17% lower, $P=0.06$) but not in women (8% lower, $P=0.39$). The effects of diabetes and obesity on plasma natriuretic peptide levels were additive; thus, obese

TABLE 2. Multivariable Linear Regression Results

Models	Men, β Coefficient (SE)	Women, β Coefficient (SE)
Log plasma BNP		
Continuous BMI, per SD increment	−0.200 (0.042)*	−0.169 (0.028)*
BMI categories		
Normal (<25 kg/m^2)	Referent	Referent
Overweight (25.0 to 29.9 kg/m^2)	−0.318 (0.080)*	−0.254 (0.059)*
Obese (≥30 kg/m^2)	−0.519 (0.095)*	−0.474 (0.074)*
Log plasma N-ANP		
Continuous BMI, per SD increment	−0.133 (0.018)*	−0.103 (0.012)*
BMI categories		
Normal (<25 kg/m^2)	Referent	Referent
Overweight (25.0 to 29.9 kg/m^2)	−0.187 (0.034)*	−0.182 (0.027)*
Obese (≥30 kg/m^2)	−0.300 (0.040)*	−0.295 (0.033)*

The multiplicative effect on plasma natriuretic peptide levels may be estimated by exponentiating the β coefficient. For instance, obesity is associated with a 40% reduction in BNP levels in men, because $e^{(-0.519)}=0.60$. All models are adjusted for age, prior myocardial infarction, atrial fibrillation, diabetes, smoking, blood pressure category (defined in text), serum creatinine, left atrial size, left ventricular systolic dysfunction, and left ventricular mass.
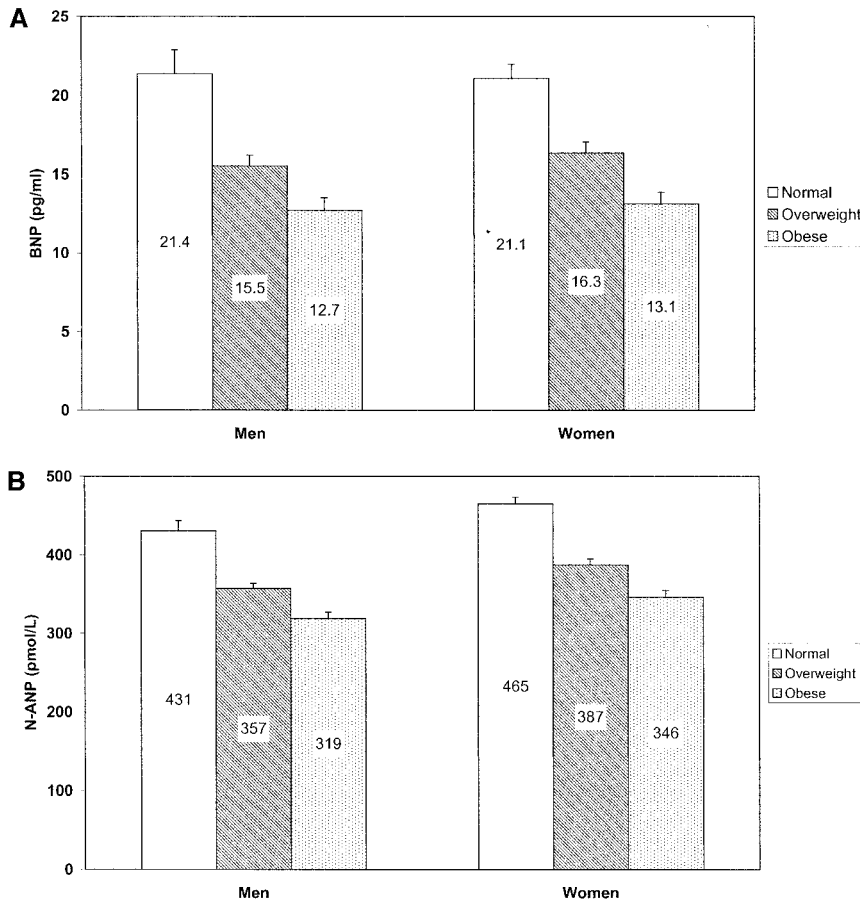
*$P<0.001$.

Figure 1. Adjusted means and SEs for plasma BNP (A) and N-ANP (B) by BMI category. Covariates used for adjustment are listed in Table 2.

participants with diabetes had the lowest natriuretic plasma peptide levels of any subgroup (Figure 2).

In logistic regressions adjusting for all covariates including BMI and hypertension categories, diabetes was significantly associated with low plasma BNP levels (adjusted odds ratios, 1.51; 95% CI, 1.00 to 2.27 for men; adjusted odds ratios, 1.95; 95% CI, 1.26 to 3.02 for women) and low plasma N-ANP levels (adjusted odds ratios, 1.85; 95% CI, 1.15 to 2.96 for men; adjusted odds ratios, 2.29; 95% CI, 1.47 to 3.56 for women).

Waist Circumference and Plasma Natriuretic Peptide Levels

Substituting waist circumference for BMI yielded similar results in multivariable analyses. In men, each standard deviation increase in waist circumference was associated with a 16% decrement in BNP ($P<0.001$) and a 10% decrement in N-ANP ($P<0.001$). Corresponding values in women were also 16% and 10% ($P<0.001$ for both). In models incorporating both waist circumference and BMI, waist circumference added incremental information in women ($P=0.001$ for log BNP, $P=0.003$ for log N-ANP) but not in men ($P>0.10$ for both peptides).

Discussion

Obesity is a burgeoning public health problem in the United States. The prevalence of obesity-related conditions will likely increase if present trends continue. Obesity and excess weight account for approximately 40% of the population

TABLE 3.   Influence of Obesity on Odds of Having Low Plasma Natriuretic Peptide Levels

BMI Categories	Low Plasma BNP		Low Plasma N-ANP	
	Men	Women	Men	Women
Normal	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
Overweight	1.64 (1.18–2.27)†	1.43 (1.08–1.88)*	3.47 (2.26–5.32)‡	1.89 (1.41–2.53)‡
Obese	2.51 (1.71–3.68)‡	1.84 (1.32–2.58)‡	4.81 (2.98–7.76)‡	2.85 (2.01–4.04)‡

Values shown are adjusted odds ratios (95% CIs) for having low plasma BNP or N-ANP levels (defined in text). Odds ratios are adjusted for age, prior myocardial infarction, atrial fibrillation, diabetes, smoking, blood pressure categories (defined in text), serum creatinine, left atrial size, left ventricular systolic dysfunction, and left ventricular mass.
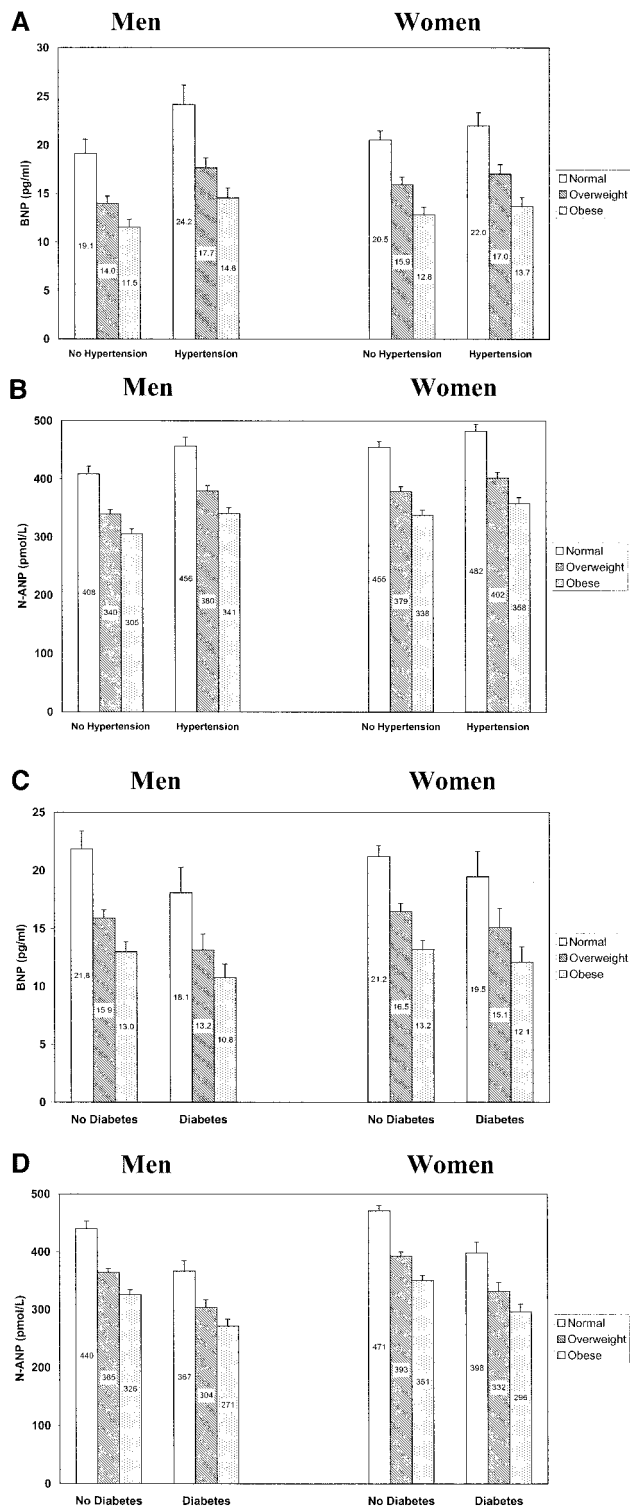
*$P<0.05$; †$P<0.01$; ‡$P<0.001$.

Figure 2. Adjusted means and SEs for plasma BNP and N-ANP by BMI category and presence of hypertension (A and B) or diabetes mellitus (C and D). Covariates used for adjustment are listed in Table 2.

burden of hypertension.[19] Low plasma natriuretic peptide levels in obese individuals have been invoked as a potential mechanism for obesity-related hypertension by several investigators.[5,6] An inverse association between BMI and natriuretic peptide levels has been noted in select groups, including

hypertensive persons,[5] healthy nonobese individuals,[13] and patients with acute coronary syndromes.[20] The present study extends prior observations to a cohort of more than 3000 individuals who were not selected on the basis of BMI or the coexistence of another condition. The size of our study ensured adequate statistical power and enabled the use of multivariable analyses to account for potential confounding factors. Another novel aspect of the present study was the examination of clinical correlates of low plasma natriuretic peptide levels using predefined criteria.

Principal Findings

Obese and overweight individuals have considerably lower plasma natriuretic peptide levels than individuals with a normal BMI, a finding that is not attributable to underlying differences in cardiovascular risk factors or cardiac structure between obese and nonobese subjects. The validity of this observation is supported by its consistency across both natriuretic peptides, in both sexes, and in separate analyses focusing on low natriuretic peptide values. In women, an abdominal pattern of obesity additionally predicted lower natriuretic peptide levels, even after adjustment for BMI.

In experimental studies, reductions in natriuretic peptide secretion are associated with salt-sensitive hypertension and left ventricular hypertrophy.[21,22] Heterozygous ANP knockout mice, which have basal ANP levels that are 9% lower than wild-type mice, have increased susceptibility to hypertension after a sodium load.[21] These observations provide indirect evidence that the reductions in circulating natriuretic peptide levels observed in our study (20% to 40% in obese individuals compared with lean individuals) may be physiologically significant.

Mechanisms for Reduced Natriuretic Peptide Levels in Obesity

Obesity is associated with salt retention and increased cardiac output,[23] which would be expected to produce elevated natriuretic peptide levels. That obesity seems to have the opposite effect is counterintuitive and presumably attributable to nonhemodynamic factors. Natriuretic peptide clearance receptors (NPR-C) are abundant in adipose tissue, suggesting that adipocytes participate in the removal of natriuretic peptides from the circulation.[24,25] In experimental animals, caloric deprivation through fasting results in dramatic decreases in NPR-C gene expression[26] and increased circulating ANP levels.[27] Elevated NPR-C gene expression has been documented in the adipose tissue of humans with obesity and hypertension,[5] and allelic variants of this gene have been associated with lower plasma natriuretic peptide levels.[28]

Reduced secretion of natriuretic peptides from diminished myocardial hormone release[6] or impaired synthesis[29] may also be an important explanation for low plasma natriuretic peptide levels. The finding of reduced N-ANP levels in our investigation supports this possibility. N-ANP is not cleared by clearance receptors in adipose tissue, and as such is an indirect indicator of preclearance levels. Additional data are needed to understand the relative importance of these mechanisms to the reduction in natriuretic peptide levels in obese

individuals. Simultaneous measures of plasma N-terminal pro-BNP (a propeptide) and BNP in obese and lean individuals may provide added insight.

Although the evidence noted above supports the hypothesis that low natriuretic peptide levels may be the consequence of obesity, recent investigations raise the interesting possibility that these relations may be bidirectional. Adipocytes also express NPR-A receptors, which mediate the biologic effects of natriuretic peptides.[25] Investigators have demonstrated that binding of ANP to NPR-A receptors on adipocytes induces lipolysis.[30] Thus, low natriuretic peptide levels may lead to reduced lipolysis, additionally perpetuating the obese state.

Separate and Joint Influences of Obesity, Hypertension, and Diabetes

Our data indicate that the influence of obesity on natriuretic peptide levels is independent of hypertension and diabetes. However, because obesity frequently coexists with hypertension and diabetes, it is important to consider the joint influences of these conditions on natriuretic peptide levels.

As in most reports, we observed that hypertension was associated with elevated plasma natriuretic peptide levels.[7,8] It is noteworthy that obese and overweight participants with hypertension still had relatively low plasma natriuretic peptide levels compared with lean, nonhypertensive participants. Obese individuals may have circulating natriuretic peptide levels that are inappropriately low for the degree of hypertension. Loss of this protective mechanism may predispose to salt retention and excessive adrenergic tone, leading to persistent elevations in blood pressure.[4]

Of note, we observed lower adjusted plasma N-ANP levels in participants with diabetes in our samples. We regard this finding as hypothesis generating because of the relatively small number of participants with diabetes in our sample. Others have reported elevated plasma natriuretic peptide levels in individuals with diabetes.[9] Additional investigations of a larger sample are warranted to better elucidate the effect of diabetes on natriuretic peptide levels.

Strengths and Limitations

Strengths of the present investigation include the large sample size, routine measurement of both plasma N-ANP and BNP, standardized ascertainment of clinical and echocardiographic covariates, and use of multivariable analyses.

Several limitations deserve comment. Plasma BNP levels in ambulatory individuals are frequently below the detection limit of present assays. We used Tobit models and logistic regression analyses to account for the left censoring of the BNP distribution. Misclassification of BNP levels above and below the detection limit would be expected to cause a conservative bias. Additionally, the consistency of our results across both BNP and N-ANP supports the validity of our findings, because only 2% of plasma N-ANP levels are below the detection limit.

It is also important to acknowledge that the physiological interactions of the natriuretic peptides, sodium intake, and other environmental and endogenous factors are complex.[1,31] Despite the large sample size, our study was cross-sectional, so we cannot determine whether low plasma natriuretic

peptide levels followed or preceded obesity. Additionally, the demonstration of low basal natriuretic peptide levels in ambulatory subjects may not signify an inadequate natriuretic peptide response to hemodynamic stress. Lastly, our criteria for low plasma natriuretic peptide levels, although established a priori, were empirical.

Implications

Our findings may have several implications. First, the observation of lower natriuretic peptide levels in obese individuals underscores the potential role of this pathway in the pathogenesis of obesity-related hypertension. Additional research is needed to elucidate the relations between low plasma natriuretic peptide levels and the chronic cardiovascular sequelae of obesity. Second, plasma natriuretic peptide levels may be a less useful marker for heart failure or left ventricular dysfunction in obese individuals, a speculation that merits investigation. Third, the response to exogenous natriuretic peptide therapy for congestive heart failure may be modified in the setting of obesity, in part because of increased peripheral clearance of these molecules.[32] Lastly, our findings raise the possibility that augmentation of the natriuretic peptide system may reduce the susceptibility of obese individuals to hypertension. Although the role of pharmacological manipulation of the natriuretic peptide axis remains to be defined, it is possible that weight loss could enhance endogenous natriuretic peptide activity in such individuals.[26,32] Additional prospective studies in well-characterized samples will be required to confirm our findings and to evaluate these hypotheses.

References

1. Hall JE. The kidney, hypertension, and obesity. *Hypertension.* 2003;41: 625–633.
2. Lauer MS, Anderson KM, Kannel WB, et al. The impact of obesity on left ventricular mass and geometry: the Framingham Heart Study. *JAMA.* 1991;266:231–236.
3. Rocchini AP, Key J, Bondie D, et al. The effect of weight loss on the sensitivity of blood pressure to sodium in obese adolescents. *N Engl J Med.* 1989;321:580–585.
4. Landsberg L. Obesity and hypertension: experimental data. *J Hypertens Suppl.* 1992;10:S195–S201.
5. Dessi-Fulgheri P, Sarzani R, Tamburrini P, et al. Plasma atrial natriuretic peptide and natriuretic peptide receptor gene expression in adipose tissue of normotensive and hypertensive obese patients. *J Hypertens.* 1997;15: 1695–1699.
6. Licata G, Volpe M, Scaglione R, et al. Salt-regulating hormones in young normotensive obese subjects: effects of saline load. *Hypertension.* 1994; 23:I20–I24.
7. Sagnella GA, Markandu ND, Shore AC, et al. Raised circulating levels of atrial natriuretic peptides in essential hypertension. *Lancet.* 1986;1: 179–181.
8. Buckley MG, Markandu ND, Miller MA, et al. Plasma concentrations and comparisons of brain and atrial natriuretic peptide in normal subjects and in patients with essential hypertension. *J Hum Hypertens.* 1993;7: 245–250.
9. Yano Y, Katsuki A, Gabazza EC, et al. Plasma brain natriuretic peptide levels in normotensive noninsulin-dependent diabetic patients with microalbuminuria. *J Clin Endocrinol Metab.* 1999;84:2353–2356.
10. Chattington PD, Anderson JV, Rees LH, et al. Atrial natriuretic peptide in type 2 diabetes mellitus: response to a physiological mixed meal and relationship to renal function. *Diabet Med.* 1998;15:375–379.

11. Kannel WB, Feinleib M, McNamara PM, et al. An investigation of coronary heart disease in families: the Framingham offspring study. *Am J Epidemiol*. 1979;110:281–290.

12. Sahn DJ, DeMaria A, Kisslo J, et al. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation*. 1978;58:1072–1083.

13. Wang TJ, Larson MG, Levy D, et al. Impact of age and sex on plasma natriuretic peptide levels in healthy adults. *Am J Cardiol*. 2002;90: 254–258.

14. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. Bethesda, Md: National Heart, Lung, and Blood Institute; 1998.

15. Tobin J. Estimation of relationships for limited dependent variables. *Econometrica*. 1958;26:24–36.

16. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289: 2560–2572.

17. Vaziri SM, Larson MG, Lauer MS, et al. Influence of blood pressure on left atrial size: the Framingham Heart Study. *Hypertension*. 1995;25: 1155–1160.

18. Hosmer DW, Lemeshow S. *Applied Logistic Regression*. New York: John Wiley; 1989.

19. *World Health Report 2002: Reducing Risks, Promoting Healthy Life*. Geneva, Switzerland: World Health Organization; 2002.

20. James SK, Lindahl B, Siegbahn A, et al. N-terminal pro-brain natriuretic peptide and other risk markers for the separate prediction of mortality and subsequent myocardial infarction in patients with unstable coronary artery disease: a Global Utilization of Strategies To Open occluded arteries (GUSTO)-IV substudy. *Circulation*. 2003;108:275–281.

21. John SW, Krege JH, Oliver PM, et al. Genetic decreases in atrial natriuretic peptide and salt-sensitive hypertension. *Science*. 1995;267: 679–681.

22. Tamura N, Ogawa Y, Chusho H, et al. Cardiac fibrosis in mice lacking brain natriuretic peptide. *Proc Natl Acad Sci U S A*. 2000;97:4239–4244.

23. Messerli FH, Ventura HO, Reisin E, et al. Borderline hypertension and obesity: two prehypertensive states with elevated cardiac output. *Circulation*. 1982;66:55–60.

24. Sarzani R, Paci VM, Dessi-Fulgheri P, et al. Comparative analysis of atrial natriuretic peptide receptor expression in rat tissues. *J Hypertens Suppl*. 1993;11(suppl 5):S214–S215.

25. Sarzani R, Dessi-Fulgheri P, Paci VM, et al. Expression of natriuretic peptide receptors in human adipose and other tissues. *J Endocrinol Invest*. 1996;19:581–585.

26. Sarzani R, Paci VM, Zingaretti CM, et al. Fasting inhibits natriuretic peptides clearance receptor expression in rat adipose tissue. *J Hypertens*. 1995;13:1241–1246.

27. Crandall DL, Ferraro GD, Cervoni P. Effect of experimental obesity and subsequent weight reduction upon circulating atrial natriuretic peptide. *Proc Soc Exp Biol Med*. 1989;191:352–356.

28. Sarzani R, Dessi-Fulgheri P, Salvi F, et al. A novel promoter variant of the natriuretic peptide clearance receptor gene is associated with lower atrial natriuretic peptide and higher blood pressure in obese hypertensives. *J Hypertens*. 1999;17:1301–1305.

29. Morabito D, Vallotton MB, Lang U. Obesity is associated with impaired ventricular protein kinase C-MAP kinase signaling and altered ANP mRNA expression in the heart of adult Zucker rats. *J Invest Med*. 2001;49:310–318.

30. Sengenes C, Berlan M, De Gliszinski I, et al. Natriuretic peptides: a new lipolytic pathway in human adipocytes. *FASEB J*. 2000;14:1345–1351.

31. Engei S, Sharma AM. The renin-angiotensin system and natriuretic peptides in obesity-associated hypertension. *J Mol Med*. 2001;79:21–29.

32. Dessi-Fulgheri P, Sarzani R, Serenelli M, et al. Low calorie diet enhances renal, hemodynamic, and humoral effects of exogenous atrial natriuretic peptide in obese hypertensives. *Hypertension*. 1999;33:658–662.