N-Terminal Pro Brain Natriuretic Peptide Is Inversely Related to Metabolic Cardiovascular Risk Factors and the Metabolic Syndrome

Michael H. Olsen, Tine W. Hansen, Marina K. Christensen, Finn Gustafsson, Susanne Rasmussen, Kristian Wachtell, Knut Borch-Johnsen, Hans Ibsen, Torben Jørgensen, Per Hildebrandt

Abstract—We wanted to investigate the relationship of N-terminal pro brain natriuretic peptide (Nt-proBNP) to metabolic and hemodynamic cardiovascular (CV) risk factors in the general population. From a population-based sample of 2656 people 41, 51, 61, or 71 years of age, we selected 2070 patients without previous stroke or myocardial infarction who did not receive any CV, antidiabetic, or lipid-lowering treatment in 1993 to 1994. Traditional CV risk factors, 24-hour blood pressures, left ventricular (LV) mass, and ejection fraction by echocardiography, pulse wave velocity, urine albumin/creatinine ratio (UACR), and serum Nt-proBNP were measured in 1993 to 1994. The metabolic syndrome was defined in accordance with the definition of the European Group for the Study of Insulin Resistance (EGIR). Higher log(Nt-proBNP) was in multiple regression analysis related to female gender ($\beta=-0.37$), older age ($\beta=0.32$), higher clinic pulse pressure ($\beta=0.20$), lower serum total cholesterol ($\beta=-0.15$), lower LVEF ($\beta=-0.08$, all $P<0.001$), lower log(serum insulin) ($\beta=-0.07$), lower log(plasma glucose) ($\beta=-0.06$, both $P<0.01$, lower log(serum triglyceride) ($\beta=-0.06$), lower body mass index ($\beta=-0.05$); lower heart rate ($\beta=-0.05$), higher logUACR ($\beta=0.04$, all $P<0.05$) and higher log(LV mass index) ($\beta=0.04$, $P=0.07$), adjusted $R^2=0.35$, $P<0.001$). The metabolic syndrome was associated with lower Nt-proBNP (35 pg/mL versus 48 pg/mL; $P<0.001$) and shifted the positive relationship between pulse pressure and Nt-proBNP to the right (ie, higher blood pressure for a given level of Nt-proBNP). The metabolic syndrome was associated with lower Nt-proBNP levels and shifted the positive relationship between Nt-proBNP and pulse pressure to the right, creating a possible link between the metabolic syndrome and hypertension. (Hypertension. 2005;46:660-666.)

Key Words: risk factors  ■  albuminuria  ■  hypertrophy  ■  natriuretic peptides  ■  obesity

Brain natriuretic peptide (BNP) is synthesized in myocar dial cells as a response to increased wall stress in relation to heart failure or acute myocardial ischemia as a prohormone that is cleaved into BNP and N-terminal proBNP (Nt-proBNP). High BNP as well as high Nt-proBNP are new promising cardiovascular (CV) risk markers and have been associated with high blood pressure (BP), left ventricular (LV) hypertrophy, and albuminuria. Because Nt-proBNP as well as BP, LV mass, and albuminuria increase with aging, it is unclear whether these associations merely rely on aging. Wang et al demonstrated recently an inverse relationship between serum BNP and body mass index that could be a potential link between obesity and hypertension if obese patients have lower BNP levels at given levels of wall stress. However, others have not found this association, and it has been suggested recently that the inverse relationship between BNP and body mass index may only reflect an increase in BNP and a decrease in body mass index with aging. No studies of the effect of obesity or other elements of the metabolic syndrome on Nt-proBNP are available.

Therefore, the aim of the present study was to evaluate the association of Nt-proBNP to metabolic and hemodynamic CV risk factors, including the metabolic syndrome, 24-hour ambulatory BP, LV hypertrophy, pulse wave velocity (PWV), and urine albumin/creatinine ratio (UACR) in 4 different age groups to control for age.

Methods

Study Design
In 1982 to 1984, 4807 individuals 30, 40, 50, or 60 years of age selected randomly from the population near Glostrup University Hospital were invited to participate in a population survey. In 1993...
to 1994, 4444 were reinvited, and 2656 came and participated in subsequent investigations. An echocardiogram was performed, PWV and 24-hour ambulatory BP were measured, blood samples were obtained for analysis of plasma glucose, serum Nt-proBNP, insulin, and lipid profile, and a morning urine sample was collected to calculate UACR. On the basis of self-reported physical activity, subjects were divided in 3 groups: those without physical activity, those with light physical activity (daily walking, frequent bicycling, or <30 minutes of sport activity each day), and those participating in sport activities >30 minutes each day. To be able to examine relationships between Nt-proBNP and CV risk factors, we excluded people receiving any CV, lipid-lowering, or antidiabetic treatment that potentially could influence some of the CV risk factors and selectively disturb correlations; this left 2113 subjects. Furthermore, we excluded patients with previous stroke or myocardial infarction because they represented a subgroup of survivors despite lack of treatment, which very well could present unusual, nonrepresentative relationships, leaving 2051 subjects for analysis. Within this subpopulation, 47.3% (970) were daily smokers and 25.8% (528) ex-smokers. The study was approved by the local ethical committee, and subjects gave informed consent.

The metabolic syndrome was defined using the definition from the European Group for the Study of Insulin resistance (EGIR) as hyperinsulinemia (serum insulin ≥ upper quartile of 44 pmol/L) together with ≥2 of the following: obesity (body mass index >30 kg/m² or waist/men/women ≥/94/80 cm), dyslipidemia (serum triglyceride >2.0 mmol/L or serum HDL cholesterol <1.0 mmol/L), hyperglycemia (plasma glucose ≥6.1 mmol/L), or hypertension (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg).

Echocardiography
Studies were performed using M-mode and 2D echocardiographs. Studies were read by an experienced technician blinded for all other information. LV internal dimension and interventricular septal and posterior wall thicknesses (PWTs) were measured at end-diastole and end-systole according to American Society of Echocardiography (ASE) recommendation on up to 3 cycles. When optimal orientation of the LV could not be obtained by M-mode, correctly oriented 2D linear dimensions were made by the leading-edge convention according to ASE recommendation. End-diastolic ASE LV dimensions were used to calculate LV mass by a formula that yields values closely related (r = 0.90; P < 0.001) to necropsy LV weight and that showed excellent reproducibility (p = 0.93; P < 0.001) between 2 separate echocardiograms in 183 hypertensive patients. The ability to substitute ASE 2D LV measurements for M-mode measurements has resulted in yields of LV mass measurements of 91% to 98% in previous studies. LV mass was considered an unadjusted variable and also after traditional normalizations for body surface area (BSA). LV mass/BSA partition values of 116 g/m² in men and 104 g/m² in women were used as the upper gender-specific normal 95% confidence intervals, as described previously. Relative wall thickness (RWT) was calculated as 2 × end-diastolic PWT/LV internal dimension. Increased RWT was present when this ratio exceeded 0.43, which represents the 97.5th percentile in previously described normal subjects. Normal geometry was present when LV mass/BSA and RWT were normal, whereas normal LV mass/BSA and increased RWT was classified as concentric remodeling. Increased LV mass/BSA but normal RWT identified eccentric hypertrophy, whereas increases in both variables identified concentric LV hypertrophy. LV internal dimension and wall thickness were measured at end-diastole and end-systole following ASE recommendations on ≥3 cardiac cycles. When optimal orientation of the M-mode cursor could not be obtained, correctly oriented linear dimension measurements were made using 2Dimensional imaging by the leading-edge ASE convention. End-diastolic LV dimensions were used to calculate LV mass, which was corrected for body size by dividing with BSA. Standard methods were used to calculate endocardial ejection fraction.

Pulse Wave Velocity
Two transducers connected to a printer were placed over the common carotid artery and the femoral artery. PWV was calculated as the distance between the 2 transducers divided by the calculated time delay for the pulse wave between the 2 transducers.

Ambulatory BP
Immediately after recording of office BP, an automatic BP device measuring ambulatory BP (BP) by the cuff-oscillometric method (Takeda TM-2421; A&D Co. Ltd.) was applied and worn for 24 hours. BP recordings were made every 15 minutes between 7 AM and 11 PM, and every 30 minutes between 11 PM and 7 AM. Means of 24-hour ambulatory BP were computed with weights according to the time interval between successive readings.

Assays
Urine albumin concentration was determined by standard methods using a turbidimetric method (Hitachi 717 analyzer; Roche Diagnostics) on a single urine specimen taken in the morning. Urine creatinine was analyzed using the Jaffé reaction without deproteinizing and then quantified by a photometric method (Hitachi 717 analyzer, Roche Diagnostics). UACR was calculated.

Serum was frozen immediately at −20°C to be examined in July 2003. To assess the stability of Nt-proBNP in the frozen samples, we plotted serum Nt-proBNP as a function of the time the samples had been frozen, which varied from 8.5 to 10.5 years, and found no association between Nt-proBNP level and the time from which the sample was obtained. Ruling out a systemic change in Nt-proBNP over this time interval, together with findings by others, suggests that the peptide is likely to be stable when preserved as described in the present protocol. Serum Nt-proBNP concentration was determined using Elecsys proBNP sandwich immunoassay on an Elecsys 2010 (Roche Diagnostics). The analytical range extended from 5.1 to 34 927 pg/mL. Between-assay coefficients of variation in low and high ranges of Nt-proBNP are reported to be 4.8% and 2.7%.

Fasting concentrations of serum insulin and lipids were measured using well-established methods. Plasma glucose concentrations were measured using a Beckman glucose analyzer (Beckman Instruments Inc.) and a glucose oxidase method.

Statistics
Data management and analysis were performed using SPSS 12.0 (SPSS) software. Data are presented as mean±SD for continuous variables with normal distribution, median, and interquartile range for continuous variables without normal distribution and proportions for categorical variables. Variables with skewed distributions underwent logarithmic transformation to create normal distributions. Unpaired Student’s t test was used to determine differences in continuous variables between groups. Pearson’s χ² test or Fisher’s exact test was used to determine differences in categorical variables between groups. Using multiple regression analyses, correlations were adjusted for age and gender, lifestyle (daily exercise, alcohol consumption, and smoking status), body composition (body mass index and waist circumference), metabolic CV risk factors (glucose, insulin, and lipid levels), hemodynamic CV risk factors (heart rate, clinic BP, 24-hour systolic BP), and subclinical CV damage (LV mass index, LV ejection fraction, UACR, and PWV), calculating the standardized regression quotient (β). Only variables with P values <0.10 entered the final multiple regression models, in which we performed by stepwise, backward selection. The 4 age groups were described by a categorical variable assigned a value from 1 to 4. Two-tailed P <0.05 indicated statistical significance.

Results
Nt-proBNP in Relation to Age, Gender, and the Metabolic Syndrome
Serum Nt-proBNP was higher in women throughout the 4 age groups, but the difference decreased with aging because of a
A steeper increase in men shown by a significant gender modulation of the relationship between age and Nt-proBNP (P < 0.001; Figure 1). Serum Nt-proBNP was lower in subjects with dyslipidemia, hyperinsulinemia, and high body mass index but not in subjects with wide waist or hyperglycemia (Table 1). Serum Nt-proBNP was also lower in subjects with the metabolic syndrome (Table 1), with a weak interaction with age (P < 0.01) and no interaction with gender (Figure 2).

Nt-proBNP in Relation to Other CV Risk Factors
Median Nt-proBNP was elevated in subjects with elevated BP (Table 1), and higher Nt-proBNP was associated with higher clinic (r = 0.17; P < 0.001) and higher 24-hour ambulatory systolic BP (r = 0.07; P < 0.05) as well as higher clinic (r = 0.30) and higher 24-hour ambulatory pulse pressure (r = 0.19; both P < 0.001). Both relationships were modulated by age (P < 0.001) and were much stronger in the older age groups (r = 0.19 and r = 0.29 both P < 0.001 versus r = 0.07 and r = 0.07 both P < 0.05). The metabolic syndrome did not modulate the relation to pulse pressure. However, the metabolic syndrome shifted the positive relationship between pulse pressure and Nt-proBNP to the right (P < 0.001), allowing subjects with the metabolic syndrome to have higher pulse pressure for a given level of Nt-proBNP (Figure 3). The relationship between Nt-proBNP and pulse pressure as well as systolic BP were also shifted to the right in subjects with hyperinsulinemia (Figure 4) and dyslipidemia (Figure 5).

<table>
<thead>
<tr>
<th>Metabolic Subgroup</th>
<th>No.</th>
<th>With (pg/mL)</th>
<th>Without (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyslipidemia* (≥ 44 pmol/L)</td>
<td>444 (22%)</td>
<td>29 (10.5–65)</td>
<td>51 (24–90)†</td>
</tr>
<tr>
<td>Hyperinsulinemia (≥ 44 pmol/L)</td>
<td>519 (26%)</td>
<td>36 (16.4–70)</td>
<td>50 (23–89)‡</td>
</tr>
<tr>
<td>Body mass index &gt; 30 kg/m²</td>
<td>264 (13%)</td>
<td>40 (16.8–73)</td>
<td>46 (21–86)†</td>
</tr>
<tr>
<td>Waistmen/women ≥ 94/80 cm</td>
<td>933 (45%)</td>
<td>45 (20–86)</td>
<td>46 (21–83)</td>
</tr>
<tr>
<td>Obesity (high body mass index or high waist)</td>
<td>933 (45%)</td>
<td>45 (20–86)</td>
<td>46 (21–83)</td>
</tr>
<tr>
<td>Hyperglycemia (≥ 6.1 mmol/L)</td>
<td>71 (3.5%)</td>
<td>41 (10.7–91)</td>
<td>46 (21–84)</td>
</tr>
<tr>
<td>Elevated BP (≥ 140/90 mm Hg)</td>
<td>639 (31%)</td>
<td>52 (23–107)</td>
<td>43 (20–79)‡</td>
</tr>
<tr>
<td>The metabolic syndrome</td>
<td>318 (16%)</td>
<td>34 (11.7–71)</td>
<td>48 (22–86)‡</td>
</tr>
</tbody>
</table>

*Serum triglyceride > 2.0 mmol/L or serum HDL cholesterol < 1.0 mmol/L.
†P < 0.05; ‡P < 0.001.
After adjusting for age and gender using multiple regression analyses, higher log(Nt-proBNP) was unrelated to lifestyle measures but associated with better metabolic profile and higher BP (Table 2). In multiple regression analyses, higher log(Nt-proBNP) was after adjustment for age (β = 0.33), and female gender (β = −0.33) related to higher clinic pulse pressure (β = 0.20), lower serum total cholesterol (β = −0.16; all P < 0.001), lower log(serum insulin) (β = −0.07), lower log(plasma glucose) (β = −0.06; both P < 0.01), lower log(serum triglyceride) (β = −0.06), lower body mass index (β = −0.05), lower heart rate (β = −0.05; all P < 0.05; adjusted R² = 0.34; P < 0.001).

**Nt-proBNP in Relation Subclinical CV Damage**

After adjusting for age, female gender, and metabolic and hemodynamic CV risk factors, log(Nt-proBNP) was correlated independently to LV ejection fraction (β = −0.08; P < 0.001), logUACR (β = 0.04; P < 0.05) and log(LV mass index) (β = 0.04; P < 0.07; adjusted R² = 0.35; P < 0.001) in multiple regression analyses. Because of a significant modulation by age on the relationship between log(Nt-proBNP), logUACR, and log(LV mass index) (P < 0.001), we divided the population in younger subjects 41 or 51 years of age and older subjects 61 or 71 years of age. Only in the older group, log(Nt-proBNP) was positively related to log(LV mass index) (β = 0.10) and logUACR (β = 0.09; both P < 0.01; adjusted R² = 0.29) after adjusting for CV risk factors, suggesting that high Nt-proBNP was related to subclinical CV damage independently of BP in subjects 61 or 71 years of age.

**Discussion**

**Nt-proBNP in Relation to Metabolic and Hemodynamic CV Risk Factors**

To our knowledge, we are the first to demonstrate that serum Nt-proBNP is lower in patients with the metabolic syndrome attributable to inverse relationships between serum Nt-proBNP and body mass index, serum insulin, cholesterol, and triglyceride independently of age and gender. An inverse relationship between serum BNP and body mass index has been described recently9,21 and has been hypothesized to be a potential link between obesity and hypertension because obese people may have lower (ie, inappropriately low) natriuretic peptides at a given pulse pressure,9 impairing the natural BP regulation. Our data support to some degree this hypothesis because the relationship between pulse pressure
and Nt-proBNP was shifted to the right in subjects with the metabolic syndrome, allowing subjects with the metabolic syndrome to have higher pulse pressure for a given level of Nt-proBNP. This is also supported by previous observations that hyperinsulinemic22 or obese23 subjects are more sensitive to sodium load because of reduced effect of atrial natriuretic peptide,24–26 partly attributable to an increased clearance in adipose tissue.27,28 This may also relate to Nt-proBNP, but the importance of the natriuretic clearance receptor C for clearance of Nt-proBNP is unknown.29 Alternatively, BNP or Nt-proBNP may, through lipolytic and lipomobilizing effects, change the metabolic state as demonstrated for atrial natriuretic peptide30 and reduce the incidence of overweight and obesity.31 This hypothesis is also, to some degree, supported by our study because low Nt-proBNP was more closely related to hyperinsulinemia and dyslipidemia than to high body mass index and obesity, indicating that it might be the metabolic state rather than the amount and localization of adipose tissue that was important for the Nt-proBNP level.

The inverse relationship between Nt-proBNP and body mass index was independent of age, contradicting the hypothesis made by McCord et al11 that lower body mass was associated with higher Nt-proBNP because of a common relation to older age.

In accordance with others, we found that Nt-proBNP increased with age and was higher in women.32 The gender difference decreased with age, probably because of a higher number of subjects with unrecognized CV disease with high Nt-proBNP independently of gender in the older age group.

### Nt-proBNP in Relation to Subclinical CV Damage

After adjustment for age, gender, and pulse pressure, high serum Nt-proBNP was related to reduced LV systolic function, LV mass index, and UACR but not to PWV, indicating that the previously demonstrated relationship between high serum Nt-proBNP and LV hypertrophy6 and albuminuria7,8 do not just reflect parallel age- or load-related changes. This BP-independent relationship was especially clear in the older age group and may reflect subclinical coronary artery disease.3 In hypertension, the relationship between serum Nt-proBNP and CV damage is not limited to old patients, probably because they all have increased cardiac load attributable to high BP.5 This may indicate that the heart has to be stressed beyond a threshold before the secretion of BNP in the heart is activated.1 Thereafter, the secretion is related to the stress load on the heart best reflected by pulse pressure. The relationship between higher serum Nt-proBNP and stiffer arteries was not independent of age and gender. The relative weak relationship between serum Nt-proBNP and LV hypertrophy as well as LV ejection fraction supports the limited use

### Figure 5.
Serum Nt-proBNP is positively related to systolic BP (A) in subjects with (black) and without (light gray) hyperinsulinemia, as well as to pulse pressure (B) in subjects with (black) and without (light gray) hyperinsulinemia, but the relationship was shifted to the right in subjects with hyperinsulinemia.

### Table 2. Relationships Between Log(Nt-proBNP) and CV Factors Adjusted for Age and Gender

<table>
<thead>
<tr>
<th>Cardiovascular Risk Factors</th>
<th>β</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lifestyle measures</strong></td>
<td></td>
</tr>
<tr>
<td>Daily exercise</td>
<td>0.01</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>0.02</td>
</tr>
<tr>
<td>Smoking status</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Body composition</strong></td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td>−0.13‡</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>−0.13‡</td>
</tr>
<tr>
<td><strong>Metabolic CV risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>−0.19‡</td>
</tr>
<tr>
<td>Serum LDL</td>
<td>−0.16‡</td>
</tr>
<tr>
<td>Log(serum HDL)</td>
<td>0.06*</td>
</tr>
<tr>
<td>Log(serum triglyceride)</td>
<td>−0.17‡</td>
</tr>
<tr>
<td>Log(plasma glucose)</td>
<td>−0.10†</td>
</tr>
<tr>
<td>Log(serum insulin)</td>
<td>−0.15‡</td>
</tr>
<tr>
<td><strong>Hemodynamic CV risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>Clinic heart rate</td>
<td>−0.09‡</td>
</tr>
<tr>
<td>Clinic systolic BP</td>
<td>0.06†</td>
</tr>
<tr>
<td>Clinic diastolic BP</td>
<td>−0.07‡</td>
</tr>
<tr>
<td>Clinic pulse pressure</td>
<td>0.17‡</td>
</tr>
<tr>
<td>24-hour heart rate</td>
<td>−0.12‡</td>
</tr>
<tr>
<td>24-hour systolic BP</td>
<td>0.07†</td>
</tr>
<tr>
<td>24-hour diastolic BP</td>
<td>0.01</td>
</tr>
<tr>
<td>24-hour pulse pressure</td>
<td>0.10‡</td>
</tr>
</tbody>
</table>

*P<0.05; †P<0.01; ‡P<0.001.
of serum Nt-proBNP in screening for LV hypertrophy and dysfunction in the general population demonstrated by Vasan et al.33

Clinical Implications
The fact that Nt-proBNP was unrelated to lifestyle measures but related to subclinical CV damage almost independently of traditional CV risk factors indicates that Nt-proBNP is a superior marker of subclinical CV damage and therefore suitable to detect subclinical disease before it develops into clinical disease.4 However, the inverse relationship between NT-proBNP and established metabolic CV risk factors may be a problem when defining cutoff values for NT-proBNP in patients with varying levels of obesity, dyslipidemia, or hyperinsulinemia. Longitudinal studies are required to address whether traditional cutoff levels for NT-proBNP can be used in patients with high body mass index, dyslipidemia, or hyperinsulinemia. Using BNP does not solve the problem because the same inverse relationship has been demonstrated for BNP as well.9,21

Limitations
Because data on previous CV disease was self-reported, we chose a conservative but probably accurate definition using only previous myocardial infarction or previous stroke as previous CV disease. Therefore, some of the subjects may have unrecognized CV disease. We did not have a direct measure of kidney function, but the correlations did not change significantly after excluding the 2% to 3% of the subjects with microalbuminuria or macroalbuminuria to ensure normal kidney function. The stability of NT-proBNP in frozen serum over a period of 10 years has never been tested. However, we documented stability of NT-proBNP between serum samples for 8.5 to 10.5 years and demonstrated that the expected relationships between NT-proBNP and age and gender and BP were preserved, supporting the assumption of stability of NT-proBNP throughout the whole period.

Conclusion
Serum NT-proBNP was lower in people with the metabolic syndrome and inversely related to serum cholesterol, triglyceride, and insulin. Serum NT-proBNP was positively related to pulse pressure, but the relationship was shifted to the right in subjects with hyperinsulinemia, dyslipidemia, or the metabolic syndrome who presented higher pulse pressure for a given level of NT-proBNP. This might support the hypothesis of a natriuretic peptide–related link between the metabolic syndrome and hypertension.

Acknowledgments
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References


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