B-Type Natriuretic Peptides and Their Relation to Cardiovascular Structure and Function in a Population-Based Sample of Subjects Aged 70 Years

Kai M. Eggers, MD, PhD a,*, Bertil Lindahl, MD, PhD a, Per Venge, MD, PhD b, and Lars Lind, MD, PhD c

The aim of the present study was to evaluate whether B-type natriuretic peptides (BNPs) could serve as screening markers for the detection of preclinical vascular disease in the community. BNP and N-terminal–pro-BNP were analyzed in 1,000 subjects aged 70 years participating in the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study and were related to different measures of endothelial function and activation, arterial compliance, carotid atherosclerosis, and echocardiographic findings. The median levels were 42.0 ng/L for BNP and 110.7 ng/L for N-terminal–pro-BNP. On adjusted multivariate analysis, the 2 BNPs were related to increased left ventricular mass and impaired left ventricular systolic and diastolic function but not to any of the other assessed entities reflecting preclinical vascular disease. In conclusion, BNPs are strong markers of increased left ventricular mass and impaired cardiac performance but cannot be regarded as useful screening markers for the detection of preclinical states of vascular disease in elderly subjects. © 2009 Published by Elsevier Inc. (Am J Cardiol 2009;103:1032–1038)

Natriuretic peptide levels are elevated in many cardiovascular pathologies, including left ventricular (LV) hypertrophy, arrhythmias, coronary disease, and heart failure, and they have also been linked to preclinical states of vascular damage, such as endothelial dysfunction and atherosclerosis. 1–3 To further elucidate the associations of B-type natriuretic peptide (BNP) and N-terminal–pro-BNP (NT–pro-BNP), the N-terminal fragment of the prohormone pro-BNP, with different measures of cardiovascular structure and function, we conducted this analysis in apparently healthy 70-year-old subjects included in the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. Specifically, we aimed to assess the relations of the 2 natriuretic peptides to measures of vascular integrity (i.e., endothelial function, arterial compliance, biomarkers of endothelial activation and vascular inflammation, and atherosclerosis in the carotid arteries) and to echocardiographic abnormalities, with the hypothesis that BNP and NT–pro-BNP are related to both vascular and cardiac status.

Methods

All subjects aged 70 years and living in the community of Uppsala, Sweden, were eligible for participation in the PIVUS study. 4 Subjects were chosen in a randomized way from the register of community inhabitants. Of the 2,025 subjects invited, 1,016 participated in the study from April 2001 to June 2005. Written informed consent was obtained from all participants, and the study protocol was approved by the local ethics committee.

NT–pro-BNP was determined using the Elecsys pro-BNP immunoassay on an Elecsys 2010 instrument (Roche Diagnostics GmbH, Mannheim, Germany). BNP was analyzed using the Architect BNP immunoassay (Abbott Laboratories, Abbot Park, Illinois). The intra-assay variation was 3.2% at 217 ng/L for NT–pro-BNP and 4.2% for BNP at 94 ng/L. C-reactive protein was measured with an ultrasensitive particle-enhanced immunoturbidimetric assay (Orion Diagnostica, Espoo, Finland). Interleukin-6 was determined with an enzyme-linked immunosorbent assay (Quantikine; R&D Systems, Minneapolis, Minnesota). Cardiac troponin I was analyzed using the refined version of the AccuTnI assay (Beckman-Coulter, Inc., Fullerton, California) and dichotomized at 0.01 ng/L. 5 Biomarkers of endothelial activation (E-selectin, P-selectin, intercellular adhesion molecule–1, and vascular adhesion molecule–1) were determined using the Evidence biochip array analyzer (Randox Laboratories, Crumlin, United Kingdom). The glomerular filtration rate was estimated using the 4-variable Modification of Diet in Renal Disease (MDRD) equation. 6

Endothelial function was studied with the brachial ultrasound technique for the assessment of flow-mediated vasodilation in the conduit arteries and the invasive forearm technique assessing forearm blood flow for the determination of endothelium-dependent and endothelium-indepen-
Results for NT-pro-BNP and BNP were available in 1,000 subjects. The median NT-pro-BNP and BNP levels were 111 ng/L (interquartile range 65 to 184) and 42 ng/L (interquartile range 25 to 71), respectively. Higher BNP tertiles were significantly associated with female gender, hypertension, and histories of myocardial infarction, coronary revascularization, and stroke. Higher tertiles of NT-pro-BNP, moreover, were related to current smoking and a history of heart failure (Table 1). NT-pro-BNP and BNP were strongly interrelated (r = 0.86, p < 0.001). NT-pro-BNP was weakly correlated to cardiac troponin I (r = 0.12, p < 0.001), C-reactive protein (r = 0.08, p = 0.009), interleukin-6 (r = 0.08, p = 0.01), vascular adhesion molecule-1 (r = 0.08, p = 0.009), and the estimated glomerular filtration rate (r = −0.11, p < 0.001). BNP was weakly correlated to cardiac troponin I (r = 0.08, p = 0.02), vascular adhesion molecule-1 (r = 0.09, p = 0.007), and the estimated glomerular filtration rate (r = −0.08, p = 0.01) but not to C-reactive protein or interleukin-6. Neither NT-pro-BNP nor BNP was correlated to E-selectin, P-selectin, or intercellular adhesion molecule-1.

Results for the 3 methods for the assessment of endothelial function were available in 703 subjects. Compared with the remaining 297 subjects, this subcohort had lower median levels of NT-pro-BNP (105 vs 123 ng/L, p = 0.002) and BNP (41 vs 45 ng/L, p = 0.02), attributable to a lower prevalence of cardiovascular disease (98 subjects [14%] vs
Table 1
Clinical characteristics and biochemical marker results in relation to B-type natriuretic peptide tertiles

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Sample (n = 1,000)</th>
<th>NT–pro-BNP (ng/L)</th>
<th>p Value</th>
<th>BNP (ng/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;81 (n = 333)</td>
<td>≥149 (n = 333)</td>
<td></td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td></td>
<td>81–148 (n = 334)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>502 (50%)</td>
<td>212 (64%)</td>
<td>149 (45%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>723 (72%)</td>
<td>215 (65%)</td>
<td>242 (73%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus†</td>
<td>129 (13%)</td>
<td>37 (11%)</td>
<td>42 (13%)</td>
<td>0.32</td>
</tr>
<tr>
<td>Hyperlipidemia‡</td>
<td>628 (63%)</td>
<td>209 (63%)</td>
<td>211 (63%)</td>
<td>0.98</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27 (24–30)</td>
<td>27 (25–30)</td>
<td>27 (24–30)</td>
<td>0.10</td>
</tr>
<tr>
<td>Current smoking</td>
<td>107 (11%)</td>
<td>25 (7.5%)</td>
<td>35 (11%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>72 (7.2%)</td>
<td>12 (3.6%)</td>
<td>11 (3.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous heart failure</td>
<td>35 (3.5%)</td>
<td>8 (2.4%)</td>
<td>6 (1.8%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Previous coronary revascularization</td>
<td>54 (5.4%)</td>
<td>7 (2.1%)</td>
<td>9 (2.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>36 (3.6%)</td>
<td>6 (1.8%)</td>
<td>9 (2.7%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Previous cardiovascular diagnosis§</td>
<td>165 (17%)</td>
<td>30 (9.0%)</td>
<td>37 (11%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Biochemical markers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac troponin I &gt;0.01 μg/L</td>
<td>217 (22%)</td>
<td>63 (19%)</td>
<td>58 (17%)</td>
<td>0.001</td>
</tr>
<tr>
<td>C-reactive protein (mg/dl)</td>
<td>1.2 (0.6–2.3)</td>
<td>1.1 (0.6–2.2)</td>
<td>1.2 (0.6–2.3)</td>
<td>0.10</td>
</tr>
<tr>
<td>Interleukin-6 (ng/L)</td>
<td>4.3 (2.2–15)</td>
<td>3.9 (2.1–15)</td>
<td>3.7 (2.0–13)</td>
<td>0.01</td>
</tr>
<tr>
<td>P-selectin (μg/L)</td>
<td>101 (85–119)</td>
<td>100 (84–119)</td>
<td>102 (85–120)</td>
<td>0.92</td>
</tr>
<tr>
<td>E-selectin (μg/L)</td>
<td>15 (11–19)</td>
<td>15 (12–19)</td>
<td>15 (11–19)</td>
<td>0.32</td>
</tr>
<tr>
<td>Intercellular adhesion molecule–1 (μg/L)</td>
<td>346 (303–403)</td>
<td>341 (299–400)</td>
<td>343 (298–406)</td>
<td>0.20</td>
</tr>
<tr>
<td>Vascular adhesion molecule–1 (μg/L)</td>
<td>519 (456–601)</td>
<td>506 (456–599)</td>
<td>520 (449–594)</td>
<td>0.17</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate (ml/min/1.73 m²)</td>
<td>79 (67–95)</td>
<td>81 (67–97)</td>
<td>80 (66–95)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Continuous variables are expressed as median (interquartile range). Categorical variables are expressed as number (percentage).

* Antihypertensive treatment or blood pressure >140/90 mm Hg.
† Antidiabetic treatment, including diet, or fasting glucose >6.1 mmol/L.
‡ Antihyperlipidemic treatment, low-density lipoprotein cholesterol >3.5 mmol/L, or serum triglycerides >1.7 mmol/L.
§ Previous cardiovascular disease was defined as coronary artery disease (self-reported), heart failure (self-reported), previous stroke, or hypertension.
**Table 2**

<table>
<thead>
<tr>
<th>Variable</th>
<th>NT–pro-BNP (ng/L)</th>
<th>BNP (ng/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Flow-mediated vasodilatation (%)</strong></td>
<td>5.4 (3.0–7.3)</td>
<td>5.3 (3.2–7.5)</td>
</tr>
<tr>
<td><strong>Endothelium-dependent vasodilatation (%)</strong></td>
<td>0.09 (0.06–0.12)</td>
<td>0.09 (0.07–0.12)</td>
</tr>
<tr>
<td><strong>Endothelium-independent vasodilatation (%)</strong></td>
<td>1.3 (1.0–1.5)</td>
<td>1.2 (1.0–1.3)</td>
</tr>
<tr>
<td><strong>SV/PP ratio (ml/mm Hg)</strong></td>
<td>1.3 (1.0–1.7)</td>
<td>1.2 (1.0–1.5)</td>
</tr>
<tr>
<td><strong>Distensibility of the CCA (%/mm Hg)</strong></td>
<td>0.09 (0.06–0.13)</td>
<td>0.09 (0.07–0.13)</td>
</tr>
<tr>
<td><strong>LVMI (g/m²)</strong></td>
<td>88 (73–104)</td>
<td>86 (72–104)</td>
</tr>
<tr>
<td><strong>LV end-diastolic diameter (mm)</strong></td>
<td>46 (43–49)</td>
<td>47 (44–51)</td>
</tr>
<tr>
<td><strong>E/A ratio</strong></td>
<td>0.89 (0.71–1.0)</td>
<td>0.88 (0.72–1.0)</td>
</tr>
</tbody>
</table>

**Discussion**

The main finding of our analysis is that the information provided by BNP levels in elderly subjects from a general population is restricted to cardiac abnormalities. As in previous studies assessing general populations, the 2 BNPs were strongly and essentially similarly indicative for impaired LV systolic function, higher LV mass, and LV diastolic dysfunction, expressed as an increased E/A ratio. This is not surprising, given that BNP is produced predominantly in the ventricular myocardium in response to cardiomyocyte stretch to counterbalance volume or pressure overload. Of note, the multiple linear regression analysis demonstrated stronger associations...
NT–pro-BNP

Endothelial function
Flow-mediated vasodilatation (%) 
Endothelium-dependent vasodilatation (%) 
Endothelium-independent vasodilatation (%)
Arterial compliance
Distensibility of the CCA (%/mm Hg)
SV/PP ratio (ml/mm Hg)

Atherosclerosis in the carotid arteries
Intima-media thickness (mm)
LV size and function
LVEF (%) 
LVMi (g/m²)
LV end-diastolic diameter (mm)
Isovolumetric relaxation time (ms)
E/A ratio

BNP

Endothelial function
Flow-mediated vasodilatation (%) 
Endothelium-dependent vasodilatation (%) 
Endothelium-independent vasodilatation (%)
Arterial compliance
Distensibility of the CCA (%/mm Hg)
SV/PP ratio (ml/mm Hg)

Atherosclerosis in the carotid arteries
Intima-media thickness (mm)
LV size and function
LVEF (%) 
LVMi (g/m²)
LV end-diastolic diameter (mm)
Isovolumetric relaxation time (ms)
E/A ratio

The p values were derived from regression analyses with NT–pro-BNP and BNP as the dependent variables. Results for NT–pro-BNP, BNP, the LVEF, flow-mediated vasodilatation, endothelium-dependent and endothelium-independent vasodilatation, the distensibility of the CCA, and the SV/PP ratio were natural log transformed before the analyses.

* Unadjusted analysis.
† Analysis adjusted for classic risk factors (male gender, hypertension, current smoking, diabetes, and hyperlipidemia).
‡ Analysis adjusted for classic risk factors and biochemical markers independently associated with NT–pro-BNP and BNP in Table 1.

between BNPs and the assessed echocardiographic variables compared with tertile analysis. This underlines the problems related to analyses based on thresholds in apparently healthy populations with results for the targeted variables within a small range. Lower LVEFs or higher LVMIs across BNP tertiles were evident only in subjects who had elevated levels of cardiac troponin I, another biomarker that has been related to impaired cardiac performance in healthy populations. Elevated troponin levels in the absence of acute coronary syndromes indicate progressive cardiomyocyte loss due to decreased subendocardial perfusion, with a mismatch of oxygen supply and demand or apoptotic processes. Troponin elevation in a general population, therefore, probably needs to be recognized as an indicator of more adverse processes affecting cardiomyocyte integrity compared with BNPs.

Besides natriuresis and the inhibition of the renin-angiotensin-aldosterone axis, the physiologic actions of the natriuretic peptides also include regulation of the vascular tone by activation of the particulate isoform of guanylate cyclase after binding to natriuretic peptide receptor A. This cyclic guanosine monophosphate–guanylate cyclase after binding to natriuretic peptide receptor A. This cyclic guanosine monophosphate pathway, which may be impaired in cardiovascular disease associated with endothelial dysfunction and deficiencies in nitric oxide production (i.e., hypertension and atherosclerosis). Consequently, some investigators have linked increased BNP levels to endothelial dysfunction, an entity associated with increased cardiovascular risk. However, according to our results, levels of BNPs were not related to endothelial integrity, even when different measures of endothelial function or activation were assessed, thus preclud-
ing them from application as a screening tool for the detection of endothelial dysfunction.

Even for other indicators of early cardiovascular disease, such as elevated biomarkers of vascular inflammation, impaired arterial compliance, or carotid atherosclerosis, no independent associations with BNP levels could be observed. This contrasts a previous study demonstrating higher NT–pro-BNP levels in subjects with a greater burden of coronary atherosclerosis determined by electron-beam computed tomography. This obvious discrepancy might be explained by the known association between BNPs and myocardial ischemia, which in turn is determined by the degree of underlying coronary stenosis.

The present study was limited to Caucasians aged 70 years. Caution should therefore be taken in drawing conclusions for other ethnic or age groups. Although our results did not demonstrate an association between BNPs and different measures of endothelial function, we cannot exclude the possibility that our results are biased because of a lower prevalence of cardiovascular pathologies in the subjects participating in this subanalysis. The number of patients with LVEFs ≤0.55 was rather small. However, although this requires some caution regarding the interpretation of our results, our findings clearly correspond to those of other studies assessing apparently healthy populations. Finally, we would also like to point out that the results of 1 BNP assay cannot be extrapolated to another, which limits the transferability of our results applying cutoffs.

**Acknowledgment:** The reagents for the analysis of cardiac troponin I were provided by Beckman-Coulter, Inc., Fullerton, California.


