Atrial and Brain Natriuretic Peptides in Cardiovascular Diseases

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Abstract The human heart secretes both atrial natriuretic peptide and brain natriuretic peptide. This study attempts to clarify the pathophysiological significance of the peptides in cardiovascular diseases. Using immunoradiometric assay, plasma brain natriuretic peptide and atrial natriuretic peptide levels in essential hypertension, various secondary hypertension, chronic renal failure, chronic heart failure during cardiac pacing, and acute myocardial infarction were determined. Mean plasma brain natriuretic peptide and atrial natriuretic peptide levels in healthy subjects were 3.7±0.3 and 5.7±0.3 pmol/L, respectively, and increased as a function of age. Plasma brain natriuretic peptide levels showed a larger increase than atrial natriuretic peptide levels in various cardiovascular diseases. In chronic renal failure, whereas plasma atrial natriuretic peptide levels decreased significantly after hemodialysis and were correlated with the changes in body weight, changes in plasma brain natriuretic peptide levels were less prominent and did not show such a correlation. In chronic heart failure, both basal plasma brain natriuretic peptide and atrial natriuretic peptide levels were also significantly elevated. However, in response to acute ventricular or atrial pacing, brain natriuretic peptide levels did not show any increase in contrast to the marked increase of atrial natriuretic peptide levels. In acute myocardial infarction, brain natriuretic peptide levels showed more prominent changes than atrial natriuretic peptide levels and were correlated with serum levels of creatine kinase and cardiac myosin light chain I in most patients. These results suggest that both brain and atrial natriuretic peptides play an important role in the regulation of cardiovascular homeostasis. The two natriuretic peptides appear to take partial charge of their respective roles in responding to various hemodynamic overloads to the heart. (Hypertension. 1994;23 [suppl I]:I-231-I-234.)

Key Words • natriuretic peptide • aging • hypertension, essential • heart failure • myocardial infarction • cardiac pacing

Recent advances in natriuretic peptide research have demonstrated that the human heart is an endocrine organ secreting two kinds of natriuretic peptides: atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP).1,2 Because ANP is produced mainly in the atrium and BNP mainly in the ventricle, they may reflect the effects of different cardiac overloads. Although both natriuretic peptides share similar biologic actions,3,4 clearance of BNP from the circulation is slower than that of ANP.5 In addition, the extent of the increase of plasma BNP levels is larger than ANP in various disease states.6-9 These results suggest that the regulatory mechanism and pathophysiological significance of BNP differ from those of ANP.

To further elucidate the physiological and pathophysiological significance of BNP, we determined plasma BNP and ANP levels in healthy subjects and in patients with various cardiovascular diseases.

Methods

Subjects

Plasma BNP and ANP levels were determined in 142 healthy subjects and in patients with various cardiovascular diseases: essential hypertension (EH, n=32), primary aldosteronism (n=20), pheochromocytoma (n=4), and chronic renal failure (n=20), pheochromocytoma (n=4), and chronic renal failure.

Blood samples were collected from a peripheral vein in the morning after an overnight fast and after 30 minutes of recumbency.

The effects of cardiac pacing on plasma BNP and ANP levels were studied in 11 patients (10 men and 1 woman, 31 to 73 years of age) who had chronic heart failure caused by various underlying diseases. After routine left ventriculography, right ventricular and right atrial pacing for 5 minutes at a rate of 150 beats per minute were performed sequentially with an interval of more than 20 minutes. Blood samples were obtained from the coronary sinus and aortic root before and soon after each cardiac pacing and also during the recovery period of each patient. Written informed consent was obtained from each patient.

Plasma BNP and ANP levels were serially determined in six patients (five men and one woman, 31 to 72 years of age) with acute myocardial infarction over a period of 2 weeks. The location of the infarction was anterior in three patients, inferior in two patients, and segmental in one patient. Hemodynamic parameters were determined with a Swan-Ganz catheter. Serum glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, and creatine kinase were measured by autoanalyzer. Serum cardiac myosin light chain I levels were determined by radioimmunoassay kits (Yamasa-Shoyu Co, Choshi, Japan).

Assay Methods of Brain and Atrial Natriuretic Peptides

Blood samples collected in chilled tubes containing Na2EDTA (5 mmol/L) and aprotinin (0.15 mmol/L) were centrifuged at 4°C, and plasma was stored at -80°C until assayed. Plasma BNP and ANP levels were determined by immunoradiometric assay without prior extraction as described previously.10 Two monoclonal antibodies recognizing the ring structure and C-terminal of human BNP, respectively, were used for the assay.

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Plasma ANP levels were determined by immunoradiometric
assay kits (Shionogi & Co, Osaka, Japan). Two monoclonal
antibodies recognizing the ring structure and C-terminal of
α-human ANP, respectively, were used. Although the assay
system showed 100% cross-reactivity with α-human ANP, it
did not show any cross-reactivity with human BNP. The
sensitivity of the assay for both BNP and ANP was 0.15 fmol
per tube.

Results
Plasma BNP and ANP levels in healthy subjects were
3.7±0.3 and 5.7±0.3 pmol/L, respectively, and in-
creased as a function of age (Fig 1). Although both
peptides increased in various cardiovascular diseases,
the extent of the increase in BNP was larger than in
ANP (Fig 2), resulting in an increase of the ratio of BNP
to ANP.

The average age of patients with EH was 51±3 years.
Therefore, although plasma BNP levels in patients with
EH (6.1±2.4 pmol/L) were significantly higher than those of
the entire healthy subject group (P<.05) (Fig 2), they did not differ from those of healthy subjects
with a similar age composition (Fig 1). However, when
EH patients were divided into subgroups according to
World Health Organization (WHO) classifications, plasma
BNP levels in stages II and III (14.0±5.8 pmol/L,
n=16) were significantly higher than those in
stage I (2.1±0.5 pmol/L, n=16, P<.05).

In patients with chronic renal failure, both plasma
BNP and ANP levels significantly decreased after he-
modialysis. However, the extent of the decrease was
smaller for BNP than ANP. The decrement of ANP
levels was correlated with both body weight (P<.001)
and blood urea nitrogen (P<.05), whereas BNP levels
were not correlated with body weight, blood pressure,
serum creatinine, hematocrit, or blood urea nitrogen.

In patients with chronic heart failure, basal plasma
BNP and ANP levels were significantly elevated in the
peripheral vein (Fig 2). Plasma ANP levels in the
coronary sinus and aorta before cardiac pacing were
193.1±90.8 and 27.5±12.5 pmol/L, respectively; these
levels showed a rapid, significant increase after ventric-
ular pacing (coronary sinus: 328.7±81.5 pmol/L,
P<.05 versus before; aorta: 79.8±24.2 pmol/L, P<.01 versus
before) and a further increase after atrial pacing (cor-
onary sinus: 476.2±136.0 pmol/L, P<.01 versus before;
aorta: 135.2±41.4 pmol/L, P<.05 versus before).

Plasma BNP did not change at all in response to both
types of cardiac pacing (before, after ventricular pacing,
and after atrial pacing, respectively, 95.4±47.3,
85.8±32.2, and 73.1±30.7 pmol/L in the coronary sinus
and 29.6±11.0, 40.0±14.5, and 41.8±16.5 pmol/L in the
aorta). Fig 3 shows the results in two representative
cases.

In patients with acute myocardial infarction, plasma
BNP levels showed a significant and biphasic increase
after the onset (Fig 4, a through f). Although there was
a significant correlation between BNP and ANP
(P<.01), changes in the ANP levels were much less
prominent. The extent of the increase of both peptides
differed from case to case. Of the factors examined,
BNP correlated significantly with creatine kinase in five
patients, myosin light chain I in four patients, and blood
pressure in three patients, whereas ANP levels showed
a significant correlation with pulmonary arterial and/or
atrial pressure in three patients (data not shown).

Discussion
In addition to the previously reported increase in
plasma ANP levels in aged men, there was a slight but
significant age-dependent increase in the BNP levels in healthy subjects. No evidence of cardiovascular disease was found in the past histories, physical examinations, routine biochemical studies on serum and urine, chest radiograph examinations, or electrocardiograms for any of the healthy subjects. Thus, we suggest that the age-related changes in plasma BNP may be physiological rather than pathological, although the presence of latent cardiovascular lesions may not be completely excluded.

Plasma BNP in EH at stage II or stage III of the WHO classification was higher than stage I, suggesting a more important role of BNP than that of ANP in patients with target-organ failure. The increased plasma BNP may serve as a part of compensatory mechanisms in response to the cardiac overload associated with hypertension. The increased BNP in patients with primary aldosteronism is also suggested to reflect cardiac overload induced by hypertension itself and/or volume expansion induced by aldosterone excess.

Fig 3. Graphs show changes of plasma atrial natriuretic peptide (ANP, •) and brain natriuretic peptide (BNP, o) levels in coronary sinus (CS, —) and aortic root (AO, - - -) in response to cardiac pacing in two patients with chronic heart failure. Graph a represents a 43-year-old man with essential hypertension and graph b, a 55-year-old man with ischemic heart disease. RVp indicates right ventricular pacing, RAp, right atrial pacing.

Fig 4. Graphs show changes in plasma brain natriuretic peptide (BNP, -o-), atrial natriuretic peptide (ANP, -•-), serum creatine kinase (CK, - -a- -), and serum cardiac myosin light chain I (LC1, - - - -) levels in six patients with acute myocardial infarction. Location of the infarction and periods after onset are shown.
Significant elevation of plasma BNP and ANP levels and their subsequent decrease after hemodialysis in patients with chronic renal failure are consistent with a previous study. Because the changes in ANP were correlated with body weight during hemodialysis, increased plasma ANP levels are suggested to result from volume expansion. In contrast, changes in BNP levels were not correlated with any biochemical or hemodynamic parameters, suggesting that a factor or factors other than volume expansion were responsible for the increased plasma BNP levels in chronic renal failure.

In agreement with a previous report, plasma BNP levels increased more prominently than ANP levels in acute myocardial infarction. Interestingly, BNP levels were significantly correlated with creatine kinase and myosin light chain I in most of the patients. The increase of serum creatine kinase implies a leakage of cytoplasmic protein, and the increase of myosin light chain I implies a liberation of structural protein from the infarcted myofilaments. In addition, it was shown that the ventricular tissue contains a small but significant amount of BNP. Therefore, the increase of BNP levels, especially in the early phase, may be partly attributed to a mechanism similar to that which causes the increase of creatine kinase and myosin light chain I. However, it is noteworthy that changes in plasma ANP levels were much smaller than changes in BNP despite the previous finding that the ventricular content of ANP is approximately 10-fold higher than that of BNP in failing heart. It is also difficult to explain the biphasic increase of plasma BNP levels only on the basis of a simple leakage mechanism. It was demonstrated that the levels of myosin light chain I reflect the changes in left ventricular function and are correlated with the infarct size. These correlations along with those between BNP and myosin light chain I suggest that the changes in BNP depend mainly on its increased synthesis in response to the hemodynamic overload of the ventricle associated with acute myocardial infarction. Because exogenous BNP was demonstrated to improve left ventricular function in patients with chronic heart failure, the increased BNP levels may serve as a compensatory mechanism in maintaining hemodynamic homeostasis in acute heart failure. Because changes in ANP levels were less prominent and varied from case to case, BNP appears to be more important as a homeostatic factor in acute myocardial infarction.

It was reported that BNP is secreted more rapidly than ANP. In support of this, the BNP gene but not the ANP gene has the AT-rich sequence in its 3'-untranslated region. The rate of BNP secretion is regulated at this step of gene transcription. However, the amount of secretion depends not only on the rate of synthesis but also on the rate of secretion itself. A large amount of ANP is stored in the secretory granules and can be rapidly secreted by acute stimulation, as shown in the present and previous studies. In contrast, plasma BNP levels did not change at all in response to acute cardiac pacing. Furthermore, the plasma ANP levels measured soon after admission were higher than the BNP levels in all three patients for up to 5 hours after onset, whereas the initial plasma BNP levels were higher than ANP in two of three patients thereafter. Therefore, it is postulated that ANP may respond more quickly than BNP to acute stimuli probably because it is secreted from the granules even though it is surpassed by the synthesis-dependent increase of BNP secretion. The two natriuretic peptides appear to take partial charge of their roles in corresponding to different hemodynamic overloads.

Note added in proof. After we submitted our manuscript in April 1993, an article by Morita et al.13 describing plasma BNP levels in various cardiovascular diseases appeared in the July issue of Circulation (1993;88:82-91).

References


