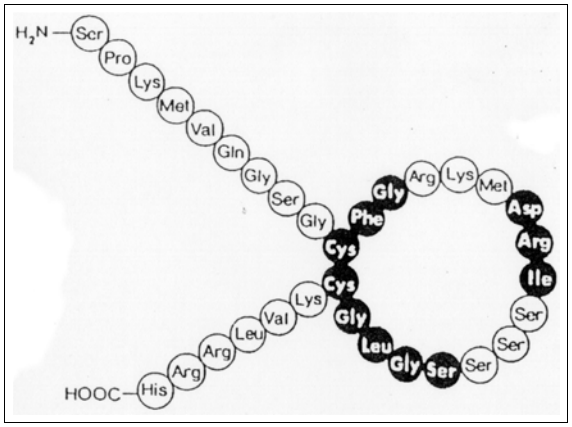
BRAIN NATRIURETIC PEPTIDES (BNP)

1. Characteristics of BNP

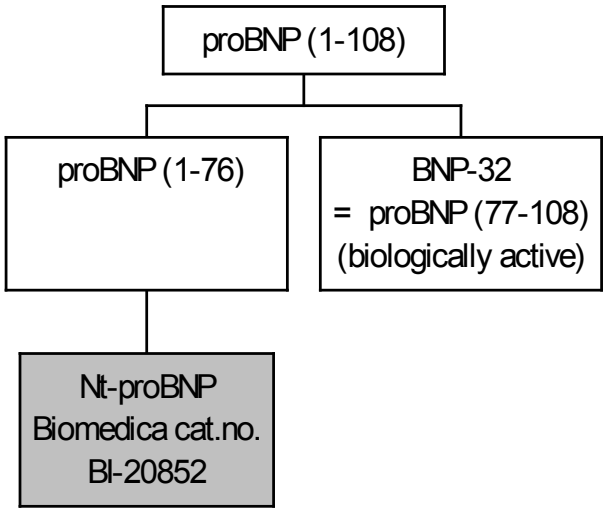
The circulating (biological active) form of human BNP, as shown in the figure, comprises a 32 amino acid peptide with a 17 amino acid ring closed by a disulfide bond between two cysteine residues. Its amino acid sequence is highly conserved across species.



BNP-32 - the biologically active hormon

2. Biosynthesis of BNP

The brain natriuretic peptide, also known as ventricular natriuretic peptide, is a cardiac hormone which is secreted predominantly from the ventricle. BNP is stored in human cardiac tissue mainly as a low molecular weight form, BNP-32, with a lesser amount of the precursor peptide, proBNP (1-108).
The circulating plasma forms of BNP are BNP-32, and the amino-terminal portion of proBNP (1-108).
The site of processing of proBNP (1-108) to BNP-32 (amino acids 77-108) and amino-terminal proBNP (1-76) is not known.



3. Function of Natriuretic Peptides

The natriuretic peptides can affect systemic blood pressure by several mechanisms, including modification of renal function and vascular tone, counteracting of the renin-angiotensin-aldosterone system and action on brain regulatory sites. These systems maintain a balance which ensures relative constancy of body electrolyte and water content and circulatory homeostasis.

Main biologic actions of natriuretic peptides
•cause of natriuresis
•cause of vasodilatation
•suppression of renin action
•suppression of aldosterone action
•suppression of sympathetic activity
•inhibition of growth of vascular smooth muscle

4. Relevance of proBNP

Plasma levels of proBNP and BNP-32 are similar in normal subjects.
In NYHA Class I, II and III subjects, the levels of proBNP are 4-fold higher than concomitant BNP-32 levels.
It was shown, that left ventricular ejection fraction (LVEF), exercise test time and creatinine clearance were independent predictors of proBNP plasma concentrations. The levels of proBNP and BNP-32 were highly correlated (2).

Conclusion:
The proportional and absolute increment above normal levels of proBNP exceeds that for BNP-32 in cardiac impairment, and suggests that proBNP may be a more discerning marker of early cardiac dysfunction than BNP-32.

5. Clinical Applications and Pathophysiology

Circulating plasma levels of proBNP are elevated in a number of diseases and have shown to be important markers for:

⇒ diagnosis of left ventricular dysfunction (LVD), even in NYHA Class I patients:
- ⇒ left ventricular ejection fraction (LVEF)
- ⇒ left ventricular end diastolic pressure (LVEDP)

⇒ diagnosis of ventricular hypertrophy

⇒ diagnosis of congestive heart failure

⇒ prognosis after acute myocardial infarction (AMI)

⇒ prognosis of the general cardiac status

⇒ diagnosis of essential hypertension

Circulating plasma levels of BNP-32 have been proven to be good markers for:

⇒ optimisation of ACE-I (Angiotensin Converting Enzyme-Inhibitors) therapy:
  ⇒ selecting patients who may benefit from ACE-I
  ⇒ better therapy efficacy by increasing ACE-I doses as long as BNP doesn't decrease (except if toxic doses are achieved before)

⇒ diagnosis of hypertrophic obstructive cardiomyopathy (HOCM) earlier than echocardiography

⇒ prognosis of the mortality, independently of cardiovascular diseases

⇒ diagnosis of chronic renal failure (CRF)

⇒ diagnosis of liver disease

In the past decade there have been many reports on how the assay of natriuretic peptides might influence the management of patients with heart failure. However, the studies have differed in design, methods, statistical analysis and, in particular, the population studied. Research interest has focused on the use of these assays in screening, diagnosis, assessment of clinical status, assessment of therapeutic efficacy, and prognosis with regard to both morbidity and mortality. Since studies differ, careful evaluation of the methods used, especially the peptide assay, is required to interpret the clinical importance of the findings for primary care. For this purpose, Biomedica offers an enzyme immunoassay kit, which measures an immunoreactive proBNP fragments, comprising an epitope from the sequence (8-29) with high sensitivity (down to 1 fmol/ml) and high specifity.

6. Implications

Natriuretic Peptides: Physiology, Therapeutic Potential, and Risk Stratification in Ischemic Heart Disease

(1) *Stein et al., Am Heart J. (1998) 135 (5), 914-923*

Review publication. BNP may be the superior prognosticator for risk stratification after myocardial infarction and is independent of left ventricular ejection fraction.

Immunoreactive amino-terminal pro-brain natriuretic peptide (NT-proBNP): a new marker of cardiac impairment

(2) *Hunt et al., Clinical Endocrinology (1997) 47, 287-296*

In cardiac impairment the proportional and absolute increment above normal levels of the aminoterminal BNP peptide exceeds that for BNP-32 and suggest that amino terminal-proBNP may be a more discerning marker of early cardiac dysfunction than BNP-32.

The role of the circulation in processing pro-brain natriuretic peptide (proBNP) to amino-terminal BNP and BNP-32

(3) *Hunt et al., Peptides (1997) 18 (10), 1475-1481*

Human proBNP (purified from cardiac tissue) was incubated at 37 °C in whole blood, serum and plasma and the products analyzed by size exclusion high pressure liquid chromatography and radioimmunoassay (RIA). Incubation with serum resulted in the formation of a 9 kDa and a 3 kDa peptide, consistent with the N-terminal and the C-terminal peptides of the propeptide.

Significance of raised natriuretic peptides after bicaval and standard cardiac transplantation

(4) *Gamel et al., Ann. Thorac. Surg (1997) 63, 1095-1100*

High levels of ANP and BNP are synthesized and secreted by the transplanted denervated human heart regardless of the surgical technique. The level of BNP correlates with ventricular performance and afterload. The bicaval technique seems to be associated with better left ventricular and right ventricular diastolic performance.

Evaluation of plasma natriuretic peptides as markers for left ventricular dysfunction

(5) *Muders et al., Am Heart J. (1997) 134, 442-449*

In this study cANP (99-126), BNP and nANP (26-55) were significantly correlated with LV dysfunction, and were independent predictors in detecting LV dysfunction in addition to clinical variables such as pathologic ECG findings, and history of diabetes or coronary artery disease.

Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care

(6) *Cowie et al., Lancet (1997) 350, 1347-1351*

In patients with symptoms suspected by a general practitioner to be due to heart failure, plasma BNP concentration seems to be a useful indicator of which patients are likely to have heart failure and require further clinical assessment.

Analytical and clinical evaluation of new diagnostic tests for myocardial damage

(7) *Wu, Clinica Chimica Acta (1998) 272, 11-21*

New tests are needed in the area of early diagnosis of acute myocardial infarction (AMI), detection of reinfarction or myocardial extension after AMI, risk stratification of patients with unstable angina, and therapeutic monitoring of patients with congestive heart failure. The most promising new markers are glycogen phosphorylase BB, free fatty acid binding protein, and brain natriuretic peptide.

A new, fast and reliable radioimmunoassay of brain natriuretic peptide in human plasma. Reference values in healthy subjects and in patients with different diseases
(8) *Jensen et al., Scand. J. Clin. Lab. Invest. (1997) 57, 529-540*

A new, fast and reliable radioimmunoassay for measurement of brain natriuretic peptide (BNP) in human plasma has been developed and its application is reported in healthy subjects and in patients with congestive heart failure, chronic renal failure, liver cirrhosis and essential hypertension.

Plasma N-terminal pro-brain natriuretic peptide and adrenomedullin
(9) *Richards et al., Circulation (1998) 97, 1921-1929*

Nt-proBNP measured 2 to 4 days after myocardial infarction independently predicted left ventricular function and 2-year survival. Stratification of patients into low- and high-risk groups can be facilitated by plasma Nt-proBNP or BNP measurements, and one of these could reasonably be included in the routine clinical workup of patients after myocardial infarction.

Different secretion patterns of adrenomedullin, brain natriuretic peptide, and atrial natriuretic peptide during exercise in hypertensive and normotensive subjects
(10) *Nishikimi et al., Clin. and Exper. Hypertension (1997) 19(4), 503-518*

Plasma levels of all three peptides at rest were significantly higher in hypertensives than in controls. Plasma concentrations of BNP increased only in patients with hypertension and the levels of increase correlated with basal plasma BNP levels and with left ventricular mass determined by echocardiography.

Brain natriuretic peptide is stable in whole blood and can be measured using a simple rapid assay: implications for clinical practice
(11) *Murdoch et al., Heart (1997) 78, 594-597*

Routine assay of BNP is feasible in ordinary clinical practice and may be of value to general practitioners and hospital based physicians in the diagnosis and management of patients with LVSD (left ventricular systolic dysfunction).

Brain natriuretic peptide concentrations in patients with aortic stenosis
(12) *Prasad et al., American Heart Journal (1997) 133, 477-479*

Plasma BNP and ANP concentrations are elevated in patients with AS (aortic stenosis). BNP rises as the severity of the AS increases but its predictive value is poor.

Rapid assay of plasma brain natriuretic peptide in the assessment of acute dyspnoea
(13) *Fleischer et al., New Zealand Medical Journal (1997) 110, 71-74*

Rapid BNP assays are practicable and provide accurate information on cardiac status - heart failures could be distinguished from primary lung disorders.

Secretion of brain natriuretic peptide in patients with aneurysmal subarachnoid haemmorrhage
(14) *Berendels et al., Lancet (1997) 349, 245-249*

The patients with subarachnoid haemorrhage had much higher plasma concentrations of BNP than controls, accompanied by normal plasma concentrations of ANP and CNP.

Brain natriuretic peptide predicts mortality in the elderly
(15) *Wallen et al., Heart (1997) 77, 264-267*

In an elderly population, measurements of BNP may add valuable prognostic information and may be used to predict mortality in the total population as well as in patients with known cardiovascular disorders. In subjects without any known cardiovascular disorder, BNP was a strong and independent predictor of total mortality.