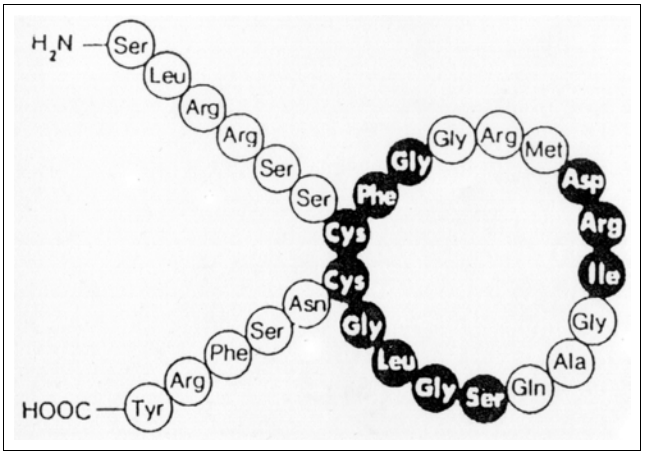
ATRIAL NATRIURETIC PEPTIDES (ANP)

1. Characteristics of ANP

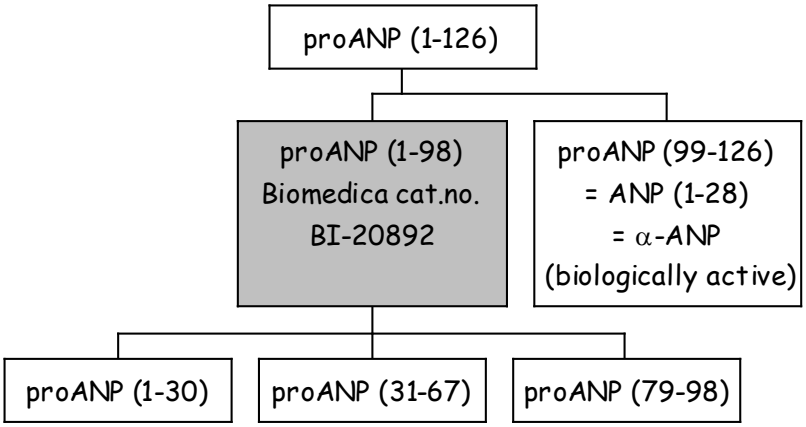
The circulating (biological active) form of human ANP, as shown in the figure, comprises a 28 amino acid peptide with a 17 amino acid ring closed by a disulfide bond between two cysteine residues. Its amino acid sequence is highly conserved across species.



ANP (1-28) - the biologically active hormon

2. Biosynthesis of ANP

proANP is stored in membrane-bound granules in atrial cardiocytes. Upon stimulation, these granules move to the cell surface, releasing the stored proANP (1-126). The precise location and identity of this mechanism are still the subject of some debate. This prohormone is cleaved into the mature 28 amino acid peptide ANP, also known as ANP (1-28) or α-ANP, and the amino terminal fragment ANP (1-98). The 98 aminoacid N-terminus is further processed proteolytically within the circulation to form proANP (1-30), proANP (31-67) and proANP (79-98).



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 and diuresis
•cause of vasodilatation
•suppression of renin action
•suppression of aldosterone action
•suppression of sympathetic activity
•suppression of antidiuretic hormone (ADH)
•inhibition of growth of vascular smooth muscle

4. Relevance of proANP

proANP has a significantly longer half-life compared to α-ANP, which is very short lived (half-life 2.5 minutes) and thus has up to 50 times the plasma concentration of α-ANP. As circulating levels of immunoreactive proANP moieties are less sensitive to rapid fluctuations of α-ANP levels, they better reflect the total amount of secreted ANP.
Samples are directly assayed to measure proANP, and need no prior extraction as with α-ANP.

Conclusion:
Several studies reported that plasma-levels of α-ANP and proANP were significantly elevated even in asymptomatic patients with left ventricular dysfunction and support a clinical relevance for proANP as an important non-invasive marker.

5. Clinical Applications and Pathophysiology

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

⇒ discriminating NYHA Class I CHF subjects

⇒ left ventricular dysfunction in asymptomatic patients

⇒ prediction of the general cardiac status

⇒ prediction of early heart failure in asymtomatic patients

⇒ prognosis after acute myocardial infarction (AMI)

⇒ diagnosis of chronic renal failure (CRF)

⇒ optimisation of ACE-I (Angiotensin Converting Enzyme-Inhibitors) therapy

⇒ diagnosis of preeclamsia

⇒ diagnosis of liver disease

⇒ diagnosis of volume overload in patients undergoing continuous ambulatory peritoneal dialysis

7. Implications

proANP and the HEART CARDIOLOGY

Adrenomodullin, endothelin, neuropeptide Y, atrial, brain, and C-natriuretic prohormone compared as early heart failure indicators
(1) *Daggubati et al., Cardiovascular Research (1997), 246-255*

pro ANPs (31-67), (1-30) and (79-98) had 100%, 83% and 50% sensitivity in differentiating Class I CHF subjects from healthy subjects. proANP (31-67) is the most sensitive marker in discriminating NYHA Class I CHF subjects from healthy individuals.

Prognostic Significance of N-terminal pro-atrial natriuretic factor (1-98) in acute myocardial infarction: comparison with atrial natriuretic factor (99-126) and clinical evaluation
(2) *Omland et al., Br Heart Journal (1993) 70, 409-414*

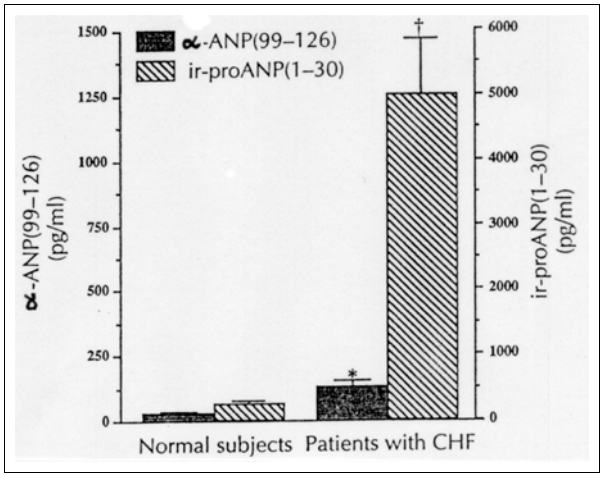
Determination of plasma N-terminal proatrial natriuretic factor (1-95) in the subacute phase of myocardial infarction may provide clinically relevant prognostic information that is superior to that obtained from atrial natriuretic factor (99-126) measurements and clinical evaluation.

Comparison of Atrial Natriuretic Peptide, B-Type Natriuretic Peptide, and N-Terminal Proatrial Natriuretic Peptide as Indicators of Left Ventricular Systolic Dysfunction
(3) *Davidson et al., Am J Cardiol (1996) 77, 828-831*

Plasma concentrations of Nt-proANP provides a sensitive indicator of moderate to severe LV dysfunction; both peptides are objectively superior to ANP for identifying patients with LVEF < 35%. These simple tests could be used to screen patients with suspected ventricular dysfunction to reduce the demand for further cardiac investigations.

Plasma levels and molecular forms of proatrial natriuretic peptides in healthy subjects and in patients with congestive heart failure.
(4) *Azizi et al., Journal of Endocrinology (1996) 148, 51-57*

The rise of immunoreactive proANP (1-39) levels is more pronounced than the variation of immunreactive α-ANP (99-126). Nt-proANP (1-30) plasma levels may prove to be a more sensitive marker of left ventricular dysfunction than ANP.
See also figure on next page.



α-ANP and Nt-proANP as markers for CHF

Plasma Proatrial Natriuretic Factor is Predictive of Clinical Status in Patients with Congestive Heart Failure
(5a) *Dickstein et al., Am J Cardiol (1995) 76, 679-683*

Concentration of proANP is related to the degree of clinical heart failure. Analysis is simple and should be of practical value as a supplement in the routine assessment of cardiac status in this heterogenous population.

Three Peptides From the Atrial Natriuretic Factor Prohormone Amino Terminus Lower Blood Pressure and Produce Diuresis, Natriuresis, and/or Kaliuresis in Humans
(5b) *Vesely et al., Circulation (1994) 90, 1129-1140*

proANP's (1-30) and (31-67) have significant blood pressure-lowering, diuretic properties. Natriuretic properties in humans are significantly prolonged compared with ANP.

Serum N-terminal proatrial natriuretic factor in children with congenital heart disease
(6) *Holmström et al., European Heart Journal (1996) 17, 1737-1746*

Elevation of Nt-proANP (= proANF) level is related to atrial pressures, heart failure and a high pulmonary to systemic flow ratio. These findings make proANP a potential new diagnostic tool in heart disease in children.

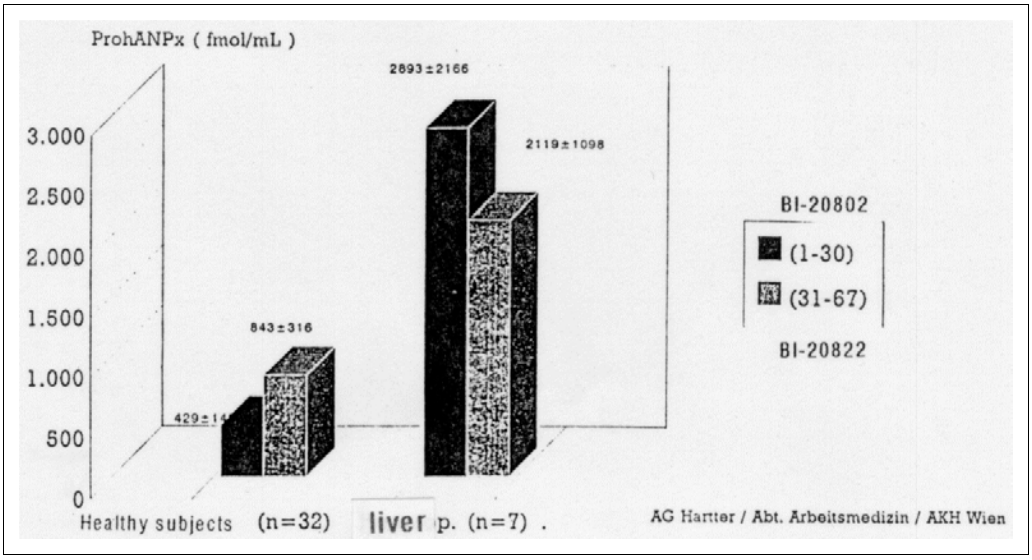
An Increase of the Plasma N-terminal Peptide of Proatrial Natriuretic Peptide in Preeclampsia

(7) *Anneli et al., Obstet Gynecol (1997) 89, 747-753*

A marked elevation in N-terminal peptide of proatrial natriuretic peptide may predict development of severe preeclampsia and/or in small for gestational age (SGA) infant.

(8) *Hartter et al., unpublished*

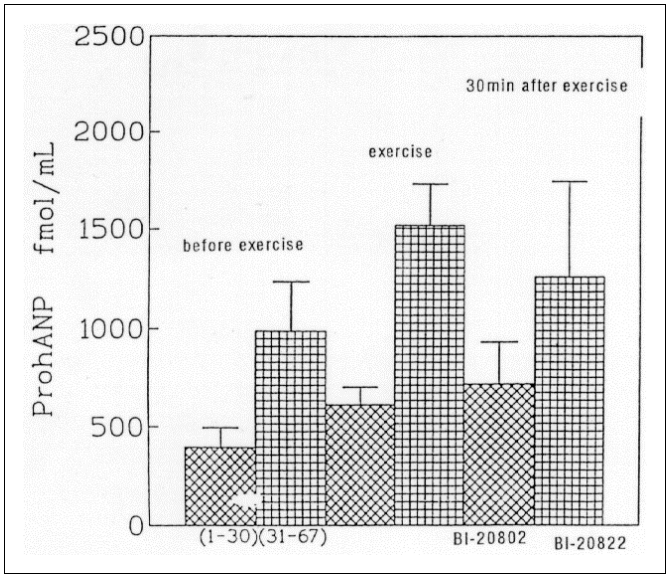
Data show marked elevated levels of proANP (1-30) and proANP (31-67) in liver disease patients. See also figure below.



proANP levels in liver disease

(9) *Hartter et al., unpublished*

See also figure below.



proANP levels during tread mill exercise

Plasma Atrial Natriuretic Peptide Levels in Continuous Ambulatory Peritoneal Dialysis Patients

(10) *Shiota et al., Nepron (1997) 75, 360-361*

The present study showed the plasma level of atrial natriuretic peptide to be a more reliable method for determination of the volume overload status in patients undergoing continuous ambulatory peritoneal dialysis.

Renal Actions of Atrial Natriuretic Peptide

(11) *Meyer et al., Contemporary Endocrinology: Natriuretic Peptides in Health and Disease, (1998) Chapter 9, 147-170*

α-ANP serves primarily as a regulator of the cardiovascular system with relatively little effect on the kidney, whereas proANP (95-126) (Urodilatin) serves as a physiological ligand for the receptors in the inner medullary collecting duct, relating to the intrarenal regulation of sodium excretion.