The ABC of Natriuretic Peptides

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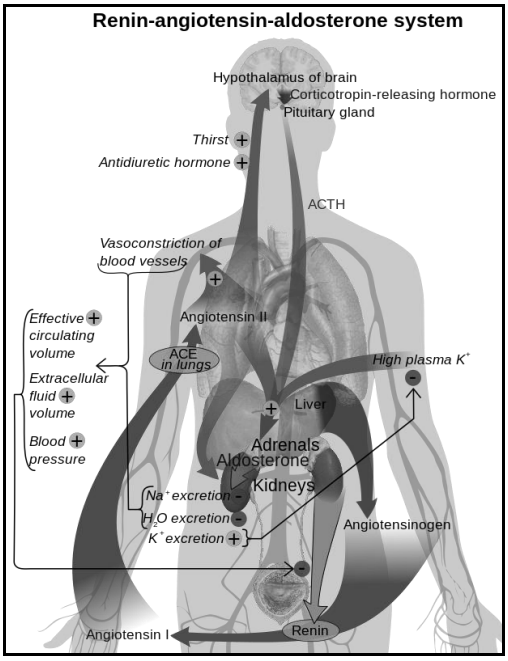
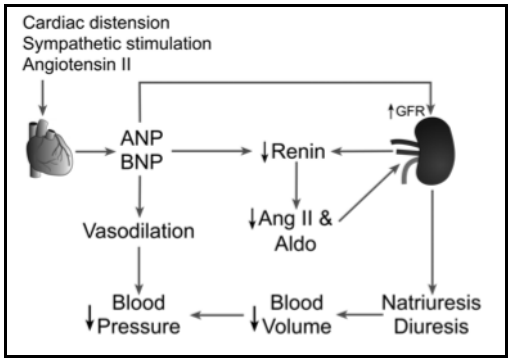
The natriuretic peptide system forms part of the regulation of extracellular fluid composition and volume. It not only impacts on the salt and water handling but also influence pressure regulation. Natriuretic peptides (NP) also have an influence on the myocardial structure and function. The main physiological action is a reduction in blood volume and systemic vascular resistance that lead to reduction in arterial pressure.

To understand the importance of the natriuretic peptides, we need to revise the RAAS (Renin-Angiotensin-Aldosterone-System).



The extracellular fluid volume is determined by the osmotically active solute in the extracellular fluid (ECF). Sodium and chloride are the most abundant solutes and the changes in chloride are usually secondary to changes in sodium. Thus the most important determinant of the ECF volume is sodium. The control of water excretion is controlled by volume, and a rise in the volume will inhibit Vasopressin secretion and vice versa. The osmotic regulation of Vasopressin secretion is overridden by volume stimuli.

Angiotensin II (ATII) has got an important role in the response to hypovolemia. Angiotensin II will stimulate Vasopressin and Aldosterone secretion. It causes blood vessel constriction and thirst that will help to maintain the blood pressure. With the expansion of the ECF volume, the natriuretic peptides ANP and BNP are secreted. This will lead to natriuresis and diuresis.



The focus will be on two natriuretic peptides secreted by the heart: ANP and BNP.

ANP

This was the first hormone isolated and is primarily released from atrial myocardial cells and in some cases the ventricles in response to atrial stretch from volume expansion. ATII, endothelin and sympathetic stimulation especially ß adrenergic mediated, carotid and baroreceptors also stimulates ANP release. Both atria participates in the release of ANP but it appears that the right is more important in quantity. ANP can be isolated from other tissues like the brain where ANP- containing neural pathway projects from the anteromedial part of the hypothalamus to the lower brainstem which controls neural regulations of the cardiovascular system. ANP opposes ATII and the ANP-containing neural circuits is involved in lowering the BP and promoting natriuresis.

BNP

Brain natriuretic peptide is homologous to ANP and initially identified in the brain but also present in the cardiac ventricles. This 32 amino acid molecule is present in circulation in concentrations 20% lower than that of ANP in normal subjects but exceed ANP in diseased states. The prohormone proBNP gets cleaved and then produces the active hormones BNP and N-terminal proBNP(NT-proBNP).

CNP

C-type natriuretic peptide is a paracrine mediator and is produced by vascular endothelial cells and present in the pituitary and kidneys with very little in the circulation and heart. The function may involve regulation in blood flow but its physiological role remains to be determined.

Mechanism of action

The two major actions of NP is

- Vasodilatory effects
- Natriuresis and Diuresis via the renal system

1. Vasodilator effects

ANP and BNP causes systemic vasodilation via cGMP on vascular smooth muscle. Venodilation with the increased venous compliance will lead to a decrease the central venous pressure and preload and thus a reduction in the cardiac output. Arterial dilatation leads to decrease in systemic vascular resistance (SVR) and arterial blood pressure

2. Renal effects

ANP and BNP increase sodium excretion by the kidney through dilatation of the afferent arterioles and relaxation of the mesangial cells. This then leads to an increase in glomerular filtration and inhibition of sodium reabsorption in the renal tubules. Additional actions of the natriuretic peptides include an increase in capillary permeability that leads to the extravasation of fluid and a decrease in blood pressure. In the RAAS these peptides inhibit renin secretion and counteract the pressor effects of the catecholamines and ATII.

Natriuretic peptide Receptors (NPR)

Three receptors have been identified: NPR-A, NPR-B and NPR-C. NPR-A and B is expressed on cell membranes and has guanyl cyclase domains. ANP has greatest affinity for NPR-A and CNP for NPR-B. NPR-C binds all 3 natriuretic peptides. It acts via G proteins, activates phospholipase C and inhibits adenylcyclase. Some sources however say that the receptors has no intracellular change and is a clearance receptor that removes natriuretic peptides form the circulation and releases them later to maintain a steady level of these hormones in the blood.

Summary of Cardiovascular and Renal Actions of Natriuretic peptides

- ❑ Arterial hypotension
- ❑ ↓ venous pressure
- ❑ Systemic vasodilation
- ❑ Natriuresis
- ❑ Diuresis
- ❑ ↑ GFR and filtration fraction
- ❑ Inhibition of renin release
    - ❑ ↓ ATII
    - ❑ ↓ Aldosterone
- ❑ ↓ Pulmonary capillary wedge pressure

To summarise: Natriuretic peptides is a counter-regulatory system for the RAAS.

Biomarkers

BNP as biomarker has important role in diagnosis, disease severity, risk stratification, therapeutic decision-making and prognosticator in the preoperative as well as postoperative period.

BNP binds to NPR-C and through proteolysis by the NEP, is cleared from the plasma. A small proportion of BNP and NT-proBNP is cleared by the kidneys. The half-life of BNP is 20 min and NT-proBNP, 120 minutes. Due to its wider detection range and its stability for 72 hours in the plasma, NT-proBNP is a more useful biomarker.

Their baseline values are influenced by a number of factors: higher values in female, elderly, anaemia and patients with atrial fibrillation and lower values in obese patients.

Clinical application in cardiac disease

ANP and BNP release is increased in cardiac failure (CF) in response to ventricular filling pressures. Both hormones have increased concentrations in patients with symptomatic LV dysfunction as well as asymptomatic patients. ANP and BNP have diuretic, natriuretic and hypotensive effects as well as inhibit the RAAS system, endothelin secretion and renal sympathetic activity. ANP and BNP in patients with heart failure will counteract the effects of noradrenaline, endothelin and ATII that will limit the vasoconstriction and sodium retention. BNP has an added role in protecting the heart against collagen accumulation and pathological remodelling in progressive cardiac failure.

The values of BNP and NT-proBNP in CF correlate with disease severity and functional class of New York Heart Association. It is inversely related to the cardiac output.

NT-pro-BNP is a prognosticator of unfavourable outcome such as cardiovascular death, readmission and cardiac events in chronic heart failure patients as well as those with asymptomatic left ventricular dysfunction.

This table[3] demonstrates the cut off values for diagnostic purposes in cardiac failure (CF).

	Rule out (CF unlikely)	Rule in (CF likely)
BNP (pg/ml)	100	500
NT-proBNP (pg/ml) age < 50 yr	300	450
NT-proBNP (pg/ml) age > 50 yr	300	900

In patients with ischaemic heart disease the degree of myocardial damage is linked to the rise in NT-proBNP and this correlates with the LV ejection fraction as well.

As marker in maternal cardiac disease, NT- proBNP is an early marker of decompensation and worsening of cardiac disease. Patients with pre-eclampsia has a significantly higher level than the normotensive patients due to elevated LV filling pressures and the underlying LV diastolic dysfunction.

The ACC/AHA HF guidelines recommend the measurement of natriuretic peptide levels in evaluation and risk stratification in the urgent care setting in whom clinical diagnosis of CF is uncertain. It is part of the total evaluation but should not be used in isolation to confirm/exclude suspected CF. The use of BNP in differentiating cardiac vs. non-cardiac cause of dyspnea is difficult and remains uncertain. It may be useful as part of clinical evaluation in patients with dyspnoea of uncertain etiology and a history of cardiomyopathy induced CF versus a non-cardiac cause of dyspnoea.

Perioperative use

In cardiac surgery especially in the patient with aortic stenosis, the levels of BNP and NT-proBNP correlate with severity but also decline after successful valve replacement. Pre-operative levels correlate with the long-term outcome after cardiac surgery.

NT-proBNP in the non-cardiac surgery setting, predict mortality, as well as the Major Adverse Cardiac Events (MACE) peri-operatively. Perioperative myocardial ischemia is difficult to diagnose, and its early recognition, as well as the detection of heart failure versus dyspnoea from a pulmonary origin, might be guided by post-operative NT-proBNP levels. This is important to make early therapeutic decisions in these patients.

There is good evidence to support the perioperative use of BNP as biomarker in diagnosis, risk assessment and prognosticator. Ongoing research will assess whether the perioperative use NT-proBNP levels will influence patient outcome.

Pharmacology

Neutral endopeptidase (NEP) degrades natriuretic peptides and inhibition of this enzyme increases the circulating levels of natriuretic peptides and potentiate their effects. In animal studies NEP inhibitors is effective for the treatment of heart failure especially when combined with an ACE inhibitor.

Recombinant BNP, Nesiritide, is used for the acute decompensated congestive cardiac failure due to systolic dysfunction.

To summarise: Natriuretic peptides have an important role in counter regulation of the RAAS system and can be used as biomarkers with a wide application in clinical use.

References

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