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## Natriuretic peptides and their usefulness in clinical practise

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### Summary:

Natriuretic peptides are peptic hormones produced by atrial and ventricular myocytes, and by endothelium of blood vessels, that take part in homeostatic control of water and sodium levels, but also potassium transport, lipolysis in adipocytes and blood pressure regulation.

Three different natriuretic peptides are distinguished: atrial natriuretic peptide (ANP), b-type natriuretic peptide (BNP) and c-type natriuretic peptide (CNP). Those peptides are responsible mostly for water-sodium homeostasis and regulation of blood pressure. Levels of natriuretic peptides increase significantly in diseases and disorders such as congestive heart failure and pulmonary hypertension, that is why natriuretic peptides were found useful in

diagnosis and monitoring of said diseases. In clinical practise, BNP and NT-proBNP levels are mostly used.

**Key words:** natriuretic peptide, atrial natriuretic peptide, brain natriuretic peptide, heart failure, hypertrophic cardiomyopathy

### **Introduction:**

First reports about the endocrine feature of heart tissue are dated around 1956 when Kish discovered osmophilic granularities inside the cells of a guinea pig's atria [1]. Functions of heart peptides were uncovered wider in 1981 by de Bold and his associates. They have noted substantial rise in sodium and water secretion of kidneys after intravenous injection of rat atrial tissue extract. Ultimately, in 1984, the structure of the human brain natriuretic peptide was isolated and studied [1].

A family of natriuretic peptides consists of three structurally connected paracrine factors: atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-type natriuretic peptide.

Because of the involvement of natriuretic peptides in homeostatic control of many aspects inside human body, such as water and sodium levels, potassium transport, lipolysis in adipocytes and blood pressure regulation, it can be suggested that natriuretic peptides have an influence on metabolic syndrome development. Disorder in natriuretic peptide system can cause development of high blood pressure, lipid dysfunction and obesity [2].

The objective of our workpiece is introduction of newest reports regarding usefulness of natriuretic peptides in clinical practise.

### **Atrial natriuretic peptide (ANP)**

First of the natriuretic peptide group, ANP, is synthesized and stored mostly by atrial myocytes, however it also occurs in lower concentration in other tissues, such as heart chamber tissue and kidney tissue. The stimulus of ANP secretion is extension of the atrial muscle that is caused by higher endovascular capacity or higher intramural heart pressure. After secretion ANP penetrates into the coronary sinus, which helps with distribution to destined organs. Hormones such as endothelin, angiotensin II and arginine-vasopressin also have the role of stimulating the ANP secretion. ANP works as an endogenous ligand through natriuretic peptide receptor A (NPR-A). NPR-A activation induces cyclic guanosine monophosphate's diuretic, natriuretic and vasodilatory functions.

ANP's function highly affects kidneys, where sodium and water absorption, and renin secretion is increased. ANP increases GFR directly through dilation of afferent arterioles, which leads to better blood supply of renal corpuscles and ultrafiltration. ANP also lowers the constriction of arterioles caused by noradrenaline. Spasmolytic function of ANP that influences smooth muscle of blood vessels consists of one or more of the following mechanisms: suppression of  $Ca^{2+}$  secretion from sarcoplasmic reticulum, suppression of  $Ca^{2+}$  supply and reinforcement of active secretion of  $Ca^{2+}$  [2].

Beside the influence on heart and kidneys, ANP also stimulates dilation of airways and lung's blood vessels - it was proven that infusion or inhalation of ANP leads to dilation of bronchi, both in healthy patients' cases and patients suffering from bronchial asthma. Higher concentration of ANP leads to higher encumbrance of the right heart ventricle in cases of pulmonary hypertension [3].

Apart from systemic functions, ANP also has pleiotropic effect on the heart and circulatory system, that happens regardless of blood pressure regulation that occurs through autocrine and paracrine mechanisms. It was proven using tests on lab mice that loss of ANP functions (through ANP's gene deletion or its receptor) leads to heart's hypertrophy and dysfunction as a response to tension overload. It is said that ANP intake improves heart's activity in response to rebuilding, and it also reduces ischemia-reperfusion injury. In addition, ANP works as a proangiogenic, anti-inflammatory and antiatherosclerotic factor in the circulatory system [4].

Concentration of ANP and its ending fragment NT-proANP in plasma can be used as a marker of asymptomatic dysfunction of the left ventricle. Standard range for ANP is around 10 fmol / ml (20 pg / ml) and is exceeded 10-100 times in patients suffering from congestive heart failure, and is positively correlated with severity of disease, and also with higher atrial pressure and other parameters of left heart ventricle's dysfunction. The highest concentration of ANP in circulation occurs in the advanced stage of heart failure, when the levels of ANP rise because of increased production of ANP in the heart, and not because of lowered clearance. ANP is a sensitive indicator of heart failure, but in recent years, because of higher stability and longer half-life, BNP is preferred in diagnostics [4].

### **B-type natriuretic peptide (BNP)**

BNP is synthesised in cardiomyocytes of heart ventricles, initially as a prohormone composed of 134 amino acid residues and containing signal sequence that is cut up in purpose of creating a 108-amino acid prohormone. As a result of enzymatic processing, ultimately three clinically substantial forms of hormone are created: proBNP, biologically active BNP and N-terminal peptide NT-proBNP. Similar to ANP, BNP works through a membrane receptor of b-type natriuretic peptide (NPR-B) and catalyzes the synthesis of cGMP that works as a mediator in natriuretic and vasodilatory effects [4]. Apart from

systemic functions, BNP also shows local effects on muscle tissue in the heart. It was proven that BNP infusion suppresses TGF- $\beta$  infused fibroblast proliferation and reduces expression of fibrosis-related genes, myofibroblasts conversion and inflammation [5].

Ventricular synthesis of BNP is regulated through stretching of the heart's walls caused by volumetric overload or higher transmural gradient. Peptide circulates in relatively low concentration among healthy patients (around 1 fmol / ml or 2,5 pg / ml), however in cases of congestive heart failure concentration of BNP and NT-proBNP rises around even 100 times. Both of those parameters have negative predictive value in heart failure diagnosis, but also work as a prognostic factor during the course of said illness. Heart failure is a set of typical symptoms such as dyspnoea, swelling of the lower limbs, lower exertion tolerance, that can be accompanied by aberrations in physical examination, such as jugular vein distention, crackles in above lung area, peripheral oedema, caused by irregular heart structure or heart function disorder.

The effects of these disorders are decreased cardiac output or increased intracardiac pressure at rest or during exercise. Acute heart failure is a condition of rapidly increasing symptoms of myocardial decompensation, which is life-threatening and requires urgent diagnosis and treatment. Chronic heart failure develops gradually, symptoms may go unnoticed for a long time, so laboratory tests enabling the initial diagnosis of this disease are helpful [6]. Borderline concentration of NT-proBNP among healthy patients leading to diagnosis of acute heart failure is around 300 pg / ml, and in case of chronic heart failure - 125 pg / ml. In the case of BNP, those levels are respectively 100 pg / ml for acute heart failure and 35 pg / ml for chronic heart failure. Higher concentration of BNP is observed also among patients suffering from pulmonary hypertension. Such a situation should be interpreted as higher encumbrance of the right heart ventricle. Base treatment of heart failure are three different types of drugs: angiotensin-converting-enzyme inhibitors,  $\beta$ -blockers and anti-mineralocorticoids.

In the course of heart failure, physiological reactions are disproportionately low in comparison to elevated levels of BNP in plasma. It is caused by the fact that most of BNP detected by conventional diagnostic tests is less biologically active. In consequence, heart failure can reflect a state of deficiency of biologically active natriuretic peptide. The fact that natriuretic peptide system is preventing adverse effects of hormonal systems retaining sodium and constricting blood vessels in cases of heart failure is suggesting that there is a possibility of natriuretic peptide usage as a therapeutic tool [4].

### **C-type natriuretic peptide (CNP)**

CNP, different then other two peptides, is not synthesized in cardiomyocytes, but in the endothelium of blood vessels as a response to its damage. CNP activates cyclase of b-type natriuretic factor receptor (NPR-B) that, similar to NPR-A, catalyzes cGMP synthesis. Biggest CNP expression occurs in the brain, chondrocytes and endothelium cells exposed to cytokines. This peptide has a vasodilatory function just like other peptides, but its effect is highly reliant on the diameter of the blood vessel. CNP is regarded as a hyperpolarizing

endothelial factor, taking part in paracrine functions of other vessel-relaxant endothelial mediators such as nitric oxide (NO) or prostacyclin. CNP also reduces pulmonary hypertension and fibrosis, therefore it is said that this mechanism impacts heart failure progression [4]. CNP's function that stimulates long bone growth is also known [1].

During tests on animals many other CNP functions were discovered. It was proven that CNP is secreted by fibroblasts of the heart as a reaction to stimuli inducing fibrosis. It causes collagen synthesis to stop in a cGMP-dependent way. An effect that was attained during tests on lab rats showed that after CNP administration on the 4th day after heart infraction and forward there was a significant reduction of cardiac hypertrophy of left ventricle after two weeks of treatment. Collected data is suggesting the role of NPR-B in cardiac hypertrophy regulation. It was also proven that CNP reduces proliferation of smooth muscle cells in vessels induced by platelet-derived growth factor and also reduces tunica interna damage in common carotid arteries among rats that suffered vessel damage [5].

### **BNP and NT-proBNP comparison**

Both BNP and NT-proBNP come from the same prohormone and are secreted by ventricular cardiomyocytes. BNP is biologically active, and NT-proBNP does not show such activity.

Proper concentration of BNP and NT-proBNP in blood depends on the testing method. Concentration is higher throughout women and older groups of patients, and lower in groups suffering from obesity. Both of those parameters are useful predictive factors in diagnosis of heart failure. Higher levels of BNP can also indicate pulmonary hypertension. In case of acute heart failure, borderline levels of BNP are 100 pg / ml, and NT-proBNP - 300 pg / ml; in chronic heart failure those levels are successively 35 pg / ml for BNP and 125 pg / ml for NT-proBNP. Most of BNP detected in standard diagnostic tests is less biologically active, which can indicate that heart failure is actually a biologically active natriuretic peptides deficiency state [4].

### **Summary**

Natriuretic peptides are a useful tool when it comes to diagnosing and monitoring heart failure and pulmonary hypertension. For this purpose levels of BNP and NT-proBNP are usually measured, while levels of ANP not so often. CNP is the least known of the natriuretic peptide family. More research is needed to understand all of the function of this hormone, and also to expand the spectrum of its diagnostic potential.

### **Contribution of authors:**

A. Skalecka - study concept and design; critical revision of the manuscript for important intellectual content; study supervision;

K. Krupa - acquisition of data; analysis and interpretation of data; technical support;  
A. Słabczynska- acquisition of data; analysis and interpretation of data; technical support;  
M. Romaniuk- acquisition of data; analysis and interpretation of data; technical support;  
K. Suswał- acquisition of data; analysis and interpretation of data; technical support.

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