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Review article

NATRIURETIC PEPTIDES IN CARDIOVASCULAR DISEASES

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Abstract: The natriuretic peptide family comprises atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP), dendroaspis natriuretic peptide (DNP), and urodilatin. The activities of natriuretic peptides and endothelins are strictly associated with each other. ANP and BNP inhibit endothelin-1 (ET-1) production. ET-1 stimulates natriuretic peptide synthesis. All natriuretic peptides are synthesized from polypeptide precursors. Changes in natriuretic peptides and endothelin release were observed in many cardiovascular diseases: e.g. chronic heart failure, left ventricular dysfunction and coronary artery disease.

Key words: Atrial natriuretic peptide, Brain natriuretic peptide, C-type natriuretic peptide, Dendroaspis natriuretic peptide, Urodilatin, Endothelin-1

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Abbreviations used: ACTH – adrenocorticotropic hormone; ANP – atrial natriuretic peptide; AVP – arginine vasopressin; BNP – brain natriuretic peptide; CHF – chronic heart failure; CNP – C-type natriuretic peptide; cGMP – cyclic guanosine monophosphate; DNP – dendroaspis natriuretic peptide; ET – endothelin; FGF – fibroblast growth factor; NO – nitric oxide; NYHA – New York Heart Association; PAI – plasminogen activator inhibitor; PGDF – platelet derived growth factor; TGF – transforming growth factor; TIMP – tissue inhibitor of matrix metalloproteinase; TNF – tumor necrosis factor

INTRODUCTION

The natriuretic peptide family comprises atrial natriuretic peptide (ANP; A-type natriuretic peptide), brain natriuretic peptide (BNP; B-type natriuretic peptide), C-type natriuretic peptide (CNP), dendroaspis natriuretic peptide (DNP), and urodilatin. Atrial natriuretic peptide was the first to be identified, in 1981 [1]. In 1984, Kangawa and Matsuo published the full amino acid sequence of human ANP [2]. ANP is a peptide made up of 28 amino acids, and it is first secreted by the heart atria. Brain natriuretic peptide was identified in 1988 [3, 4]. It was primarily isolated from the pig brain, and thus was called brain natriuretic peptide. However, it was soon found that BNP is synthesized in the ventricular myocytes. In humans, this peptide is made up of 32 amino acids. In 1990, C-type natriuretic peptide was isolated from the pig brain. It is produced mainly in the central nervous system and vessels [5, 6]. In humans, the CNP chain consists of 22 amino acids [7]. D-type natriuretic peptide was isolated from the venom of the green mamba. Structurally, it is similar to ANP, BNP and CNP [8, 9]. In humans, DNP is present in the atrial cells and the plasma [10]. Urodilatin is also included in the family of natriuretic peptides. It is a 32-amino acid paracrine hormone that was isolated from human urine in 1988. Its structure is nearly identical to that of ANP; the difference is the 4 additional amino acids in the N-terminal fragment, urodilatin. This is not surprising, because ANP and urodilatin are formed as the results of cleavage of the same peptide: proANP (1-126). Urodilatin is produced by the renal tubule cells and acts exclusively in the kidneys. Some authors consider it to be a renal form of ANP.

A peptide with the function of constricting the blood vessels was first discovered by Hickey *et al.* [11]. A few years later, the sequence of this peptide was determined [12]. Called endothelin (ET), it appeared to be identical in humans, dogs, rats and pigs.

The activities of natriuretic peptides and endothelins are relatively strictly associated with each other. ANP and BNP are peptides that inhibit endothelin-1 production. On the other hand, ET-1 stimulates natriuretic peptide synthesis [13]. This specific self-control is found in many diseases of the circulatory system. In pathological conditions, the predominance of one of these systems in patients can be identified, and sometimes counteracted effectively, after the determination of the plasma concentrations of the defined natriuretic peptides and endothelins.

NATRIURETIC PEPTIDES

All natriuretic peptides are synthesized from polypeptide precursors. ANP, BNP and CNP have very similar structures. Each of them has a ring consisting of 17 amino acids, of which 11 are identical [14]. Urodilatin and ANP have an identical ring (Fig. 1).

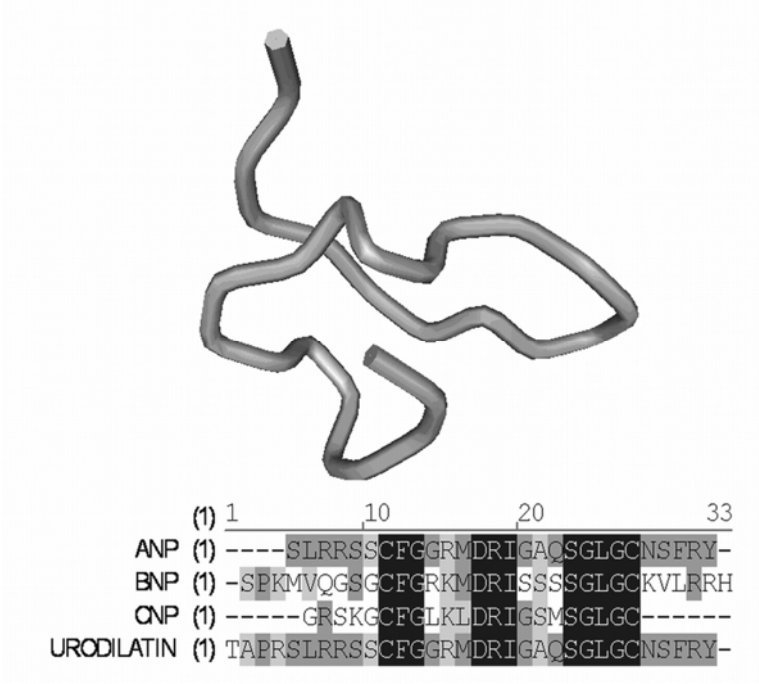

Fig. 1. PDB model of an antrial natriuretic peptide var 1 (DOI 10.2210/pdb1anp/pdb), and a sequence homology of a loop structure of three main natriuretic peptides with the precursor, peptide, Urodilatin. Sequence similarity is indicated by dashed lines, and identical sequences of a loop are in black.

Atrial natriuretic peptide is first synthesized in the atrial cells. A low concentration of ANP was also found in the ventricular cells and kidneys. However, compared to the myocardium, the ANP concentration in the kidney is negligible. ANP is synthesized in the form of a biologically inactive propeptide, proANP, which consists of 126 amino acids. This peptide undergoes cleavage by endoprotease (membrane serine protease) in the endoplasmic reticulum, into the biologically active C-terminal fragment, proANP (99-126) (also called alpha-ANP) (1-98). Alpha ANP is rapidly eliminated from the plasma; its half-life is 3-4 minutes. The Nt-pro-ANP half-life is significantly longer (60-120 min).

Brain natriuretic peptide is mainly synthesized in the ventricular cells. BNP derives from the prepro-BNP precursor consisting of 134 amino acids. After cleavage, prepro-BNP splits into a 108-amino acid pro-BNP (1-108) and a 26-amino acid signal peptide (109-134). In turn, pro-BNP splits into the biologically active 32-amino acid C-terminal fragment, BNP (77-108), and the inactive 76-amino acid N-terminal fragment, Nt-proBNP (1-76) [15-19]. BNP has a half-life of about 20 minutes. The half-life of Nt-pro-BNP is significantly longer (60-120 min).

C-type natriuretic factor is found in the central nervous system, the endothelial cells and in low concentrations in the blood plasma. It plays the role of the

paracrine hormone. CNP is produced from the precursor pro-CNP as the result of cleavage by endoprotease. The atrial and ventricular cells are potent stimuli of ANP and BNP release. Both ANP and BNP are stored in granules and secreted via regulatory pathways from the atria. They are also secreted via the constitutive pathway from the ventricles. ANP is immediately released from atrial cell granules, which, coupled with its very short half-life, results in dynamic changes in its concentration in the blood. The secretion of BNP is mainly from the left ventricular cardiomyocytes, is controlled at the transcription level, and requires longer-lasting stimuli. An increased BNP concentration in the blood remains for a significantly longer time than an increased ANP concentration.

Tachycardia is a factor that intensifies natriuretic peptide synthesis. Glycocorticosteroids, thyroid hormones, endothelin-1 and angiotensin II also increase this synthesis. Endothelin-1 and angiotensin II intensify the synthesis independently of their haemodynamic activity. CNP secretion is regulated by growth factors and cytokines, mainly by TNF-α, interleukin-1, basic fibroblast growth factor, and transforming growth factor β. Increased CNP secretion is observed as the result of tissue damage or hypoxia.

Natriuretic peptides are ligands for three types of natriuretic receptors: type-A, type-B and type-C. These receptors are localized on the target cell surfaces. Type-A and type-B receptors have two extracellular domains binding the ligand, and two intracellular domains containing guanyl cyclase and kinase, which condition the formation of cGMP (cyclic guanosine monophosphate). Type-A and type-B receptors are responsible for the majority of the known biological activities of natriuretic peptides [20, 21]. Type-C receptors clear the natriuretic peptide from the circulation (clearance receptors). ANP and BNP mainly bind with type-A receptors, and CNP with type-B receptors [22]. ANP has the highest affinity to type-A receptors. It also shows a high affinity to type-C receptors. Natriuretic peptides are cleared from the circulation with the help of a clearance receptor (type-C receptor), and thanks to endopeptidases present on the surfaces of the epithelial cells, smooth muscles, myocytes, renal epithelium and fibroblasts.

ANP and BNP are secreted from cardiac myocytes in response to atrial or ventricular wall stretch. The activity of ANP and BNP is similar. They increase glomerulal filtration and natriuresis, suppressing sodium reabsorption, they relax the vessels' smooth musculature causing a decrease in the cardiac preload and afterload and a decrease in blood arterial pressure. They reduce the noradrenergic and renin-angiotensin-aldosterone system activities. Besides their renal and vascular effects, natriuretic peptides exert effects on the suprarenal cortex, decreasing the secretion of mineralocorticoids and glicocorticoids.

ANP hipotensive activity lies in the relaxation of the resistance vessels, mainly the precapillary arterial vessels and, to a lesser degree, the extracapillary venous vessels. Suppressing venous return, ANP reduces blood flow to the heart and decreases cardiac output leading to a decrease in arterial pressure. However, in

patients with chronic heart failure (CHF), the infusion of ANP significantly increased the stroke volume index. The permeability of endothelium to plasmic fluid increases under the effect of ANP, causing its outflow from vessels to the extravascular space and thus increasing the hematocrit and plasma protein concentration. Then, hypovolemia occurs, which is intensified by the simultaneous natriuretic activity of ANP [23]. ANP is assumed to play an important role in organism adaptation to an acute elevation of the plasma volume, increasing sodium and water excretion, but it is less important in conditions of chronic hypervolemia. Atrial natriuretic peptide does not exert any significant effect on the renal blood flow, but at higher plasma concentrations, it may cause blood redistribution to deeper layers of the cortex and to the renal medulla. ANP has a relaxing effect on the preglomerular vessels, which may increase glomerular filtration and decrease the sensitivity of tubulo-glomerular feedback counteracting angiotensin II.

The data indicated the presence and important role in the body fluid homeostasis of brain atrial natriuretic peptide (ANP) in all the vertebrate species examined. The peptide is localized in neurons in the hypothalamic and brain stem areas involved in body fluid volume and blood pressure regulation, and its receptors are located in the regions that contain the peptide. Most, if not all of the actions of ANP are mediated by the activation of particulate guanylyl cyclase with the generation of guanosine 3',5'-cyclic monophosphate, which mediates its actions in the brain as in the periphery. Although atrial stretch releases ANP from cardiac myocytes, the experiments indicate that the response to acute blood volume expansion is markedly reduced after the elimination of neural control. Volume expansion distends baroreceptors in the right atria, carotid-aortic sinuses, and kidneys, altering the afferent input to the brain stem and hence the hypothalamus, resulting via ANPergic neurons in the hypothalamus in the stimulation of oxytocin release from the neurohypophysis that circulates to the right atrium to stimulate ANP release. The ANP circulates to the kidney and induces natriuresis. Atrial natriuretic peptide also induces vasodilatation, compensating rapidly for increased blood volume by increased vascular capacity. Atrial natriuretic peptide released into hypophysial portal blood vessels inhibits the release of adrenocorticotropic hormone (ACTH), thereby decreasing aldosterone release and enhancing natriuresis. Furthermore, the ANP neurons inhibit AVP (arginine vasopressin) release, leading to diuresis and decreased ACTH release. The activation of hypothalamic ANPergic neurons via volume expansion also inhibits water and salt intake. These inhibitory actions may be partially mediated via ANP neurons in the olfactory system altering salt taste. Atrial natriuretic peptide neurons probably also alter fluid movement in the choroid plexus and in other brain vascular beds. Therefore, brain ANP neurons play an important role in modulating not only the intake of body fluids, but also their excretion to maintain body fluid homeostasis [24].

The natriuretic and hypotensive effect of BNP is more pronounced than that of ANP [25]. Both peptides similarly suppress the renin activity of the plasma and

aldosterone secretion [26]. Moreover, BNP exerts myocardial relaxing activity, and antiproliferative and antifibrinolytic activity [27, 28]. BNP has a direct effect on the cardiac fibroblasts by inhibiting fibrotic responses via extracellular signal-related kinase signaling. BNP opposes TGF-β-regulated genes related to fibrosis (collagen 1, fibronectin, CTGF, PAI-1, and TIMP3), myofibroblast conversion (a-smooth muscle actin 2 and non-muscle myosin heavy chain), proliferation (PDGFA, IGFI, FGF18, and IGFBP10), and inflammation (COX2, IL6, TNFα-induced protein 6, and TNF superfamily, member 4) [29].

CNP, produced by the endothelial cells, is thought to play an important role in the local dilation of vessels. Unlike other natriuretic peptides, CNP acts only locally. It affects the smooth muscles of both the venous and arterial vessels. CNP does not demonstrate natriuretic properties.

Urodilatin is an important regulator of renal sodium excretion. Natriuretic peptides, besides their direct vasodilating effect, also exert an indirect prohypotensive activity inhibiting the vasoconstricting effect of noradrenaline, angiotensin II and vasopressin [30]. Furthermore, they weaken the angiotensin II and vasopressin central pressor effect and the central stimulation of the sympathetic system.

The level of Nt-pro ANP circulating in the plasma is more stable than that of the pulsatively secreted alpha-ANP. Nt-pro ANP better reflects the chronic level of ANP secretion, whereas alpha-ANP reflects its level at a given moment. Nt-pro ANP is more useful in medium- and long-term diagnostics and prognosis [31]. Witthaut *et al*., investigating among other things the level of ANP, obtained mean ANP concentrations in healthy subjects of 14.9 ± 1.2 pg/ml [32]. In the studies of Hoffmann *et al*. mean concentration of Nt-proANP measured with the ELISA method in healthy persons was 1404 pmol/l.

Under physiological conditions, the concentration of BNP in the blood serum is low. Maisel *et al*. observed that the level of BNP depends on the patient's age and race and not on the patient's gender [33]. The suggested range of normal values of BNP concentration is 0.5-30 pg/ml (0.15-8.7 pmol/l) [34]. In the immunoenzymatic method (Biomedica), the reference values of Nt-pro BNP in healthy subjects are < 600 pg/ml (250 pmol/ml). In the studies of Cosin *et al*., the Nt-pro BNP level was found to depend on the patient's age and gender [35]. The range of normal blood BNP and Nt-pro BNP concentration depends on the method of determination and even on the producer of the reagents used.

The form of BNP found in the plasma is of significant importance. Determining the Nt-pro BNP level is recommended for risk assessment because of its more stable form and longer half-life. However, a biologically active BNP fragment of a markedly shorter half-life may be useful in monitoring the clinical condition over the course of therapy [36].

ENDOTHELINS

Endothelins are 21-amino acid peptides synthesized by a wide variety of cell types, above all by the vascular wall cells and in the brain, kidneys and endocrine glands [37-40]. So far, 3 peptides coded by 3 different genes have been identified: endothelin-1 (ET-1), endothelin-2 (ET-2) and endothelin-3 (ET-3) [41]. Endothelin-1 is formed from a polypeptide precursor – big ET-1. Big ET-1 consists of 38 amino acids (1-38). After cleavage, ET-1 (1-21) and the C-terminal fragment (22-38) are formed [42]. ET-1's vasoconsticting potency is 140 times higher than that of big ET-1 [43].

Endothelin-1 structure and function is the best understood. Only two amino acids differentiate endothelin-2 from ET-1 (6-Trp, 7-Leu). Endothelin-2 effector activity does not differ from that of ET-1. Six amino acid residues (2-Thr, 4-Phe, 5-Thr, 6-Tyr, 7-Lys, 14-Tyr) differentiate ET-3 from ET-1. Endothelin-3 also demonstrates a different affinity than ET-1 to receptors, and thus a different function in the organism's physiology [44]. Adrenaline, angiotensin II, vasopressin, thrombin, insulin, interleukin 1, platelet-derived growth factor (PGDF), TNF-α and epidermal growth factor (EGT) are among the other factors stimulating endothelin secretion.

ET-A and ET-B are two types of receptor that are bound with G proteins and that mediate endothelin action [45]. The activation of ET-A results in an increase in the activity of phospholipase C, phospholipase D and sometimes phospholipase A2. Thus, it results in the elevation of the cytoplasm calcium ion concentration, yielding a vasoconstrictive effect. The activation of the receptors of ET-B and its recognized subtypes (endothelial ET-B1 and muscular ET-B2) causes an increase in the production of compounds which relax the vascular smooth muscles (e.g. nitric oxide or adrenomedulline), and an increase in endothelin gene expression, locally stimulating its own synthesis. ET-1 secreted by epithelial cells activates both types of receptor [46]. The induction of endothelial ET-B receptors causes vascular relaxation through the stimulation of NO synthesis activity with a subsequent increase in guanyl cyclase and increased cGMP release. Furthermore, through the stimulation of prostacyline synthesis, it results in the activation of adenyl cyclase and increased cAMP release. These simultaneous processes lead to a decrease in the intracellular calcium ion concentration. However, the vasoconstrictive effect predominates in the vessels [47]. In the circulatory system, ET-A receptors are found in smooth muscle and cardiomyocyte cells, whereas ET-B receptors are found in endothelial and muscular cells [48].

Endothelin-1 acts both as a paracrine-autocrine hormone strongly constricting vessels and as a mitogenic hormone released by the vascular endothelium [49]. Thusfar, studies have demonstrated a strong effect of endothelins on coronary, cerebral, renal and mesenteric microcirculation.

In the heart, endothelin-1 is a potent constrictor of coronary vessels [50]. An effect on heart rate has also been observed. Intravenous administration of ET-1

leads to spontaneous slight tachycardia associated with a temporary drop in arterial pressure, followed by long-lasting bradycardia evoked by stimulation of baroreceptors by increasing arterial pressure. This effect predominates despite the direct positive inotropic and chronotropic activity that ET-1 exerts on the cardiomyocytes. ET-2 and ET-3 demonstrate similar inotropic activity; however, it is significantly weaker than that of ET-1 [51, 52].

Under the conditions of activated shear stress caused by the elevated afterload, and under the effect of angiotensin II, the secretion of endothelins in the myocardium increases. Blocking angiotensin II production with convertase inhibitors results in ET-1 secretion inhibition [53]. By increasing aldosterone secretion, endothelin participates with angiotensin II in cardiac muscle fibrosis [54]. The haemodynamic effect of ET-1 on kidneys leads to an increase in sodium resorbtion [55, 56]. ET-1 potentiates the secretion of natriuretic peptides and stimulates cardiomyocyte and fibroblast proliferation.

The reference values of ET-1 have not been determined precisely for healthy subjects via the immunoenzymatic method. It is recommended that each laboratory should determine their own reference levels. Biomedica reports that in 70 healthy subjects the median serum ET-1 concentration obtained by this method was 0.65 pg/ml (0.26 fmol/ml).

NATRIURETIC PEPTIDES IN CIRCULATORY SYSTEM DISEASES

Increased ANP release was observed in patients with chronic heart failure, left ventricular dysfunction or coronary artery disease. In some clinical situations, an increase in BNP concentration was observed. The following are included: aortic stenosis, chronic heart failure, left ventricular dysfunction or hypertrophy, hypertension, ischemic heart disease, pulmonary embolism, primary pulmonary hypertension, myocarditis, heart transplant rejection, arrhythmogenic right ventricular dysplasia with decreased ejection fraction, Kawasaki's disease, renal failure, hyperaldosteronism, Cushing's syndrome, and decompensated cirrhosis. Advanced age and female gender were also observed to be associated with increased BNP. However, lower concentrations of BNP may result from the coexistence of mitral stenosis, dehydration, therapy with diuretics or angiotensin-converting enzyme inhibitors [57-61]. Increased CNP secretion is observed as the result of tissue damage or hypoxia and in the course of chronic renal failure.

Endothelins are thought to participate in the pathogenesis of: arterial hypertension, pulmonary hypertension, dilated cardiomyopathy, idiopathic pulmonary fibrosis, asthma, food allergies, and cerebral vasospasm after subarachnoid haemorrhage [62-65].

HEART FAILURE

An infusion of atrial ANP significantly decreased pulmonary capillary wedge pressure and increased the stroke volume index in all of the patients with CHF.

Although it decreased pulmonary capillary wedge pressure, it caused no significant change in the stroke volume index in the patients without CHF. Concomitant significant reductions in total systemic resistance were observed in both groups of patients. The ANP infusion significantly increased the urine volume, the excretion of sodium, and the endogenous creatinine clearance in patients without CHF. In patients with CHF, it showed a tendency to increase all these variables, but the urine volume did not correlate with the reduction in pulmonary capillary wedge pressure. Although no significant difference was observed in the decrement of the plasma aldosterone concentration in the patients with and without CHF, the ANP infusion also decreased the plasma aldosterone concentrations. These findings indicate that the ANP infusion improves left ventricular function in patients with CHF, and suggest that this improvement mainly results mainly from the vasodilating activity of ANP [66].

Brain natriuretic peptide is of prognostic importance in cardiovascular diseases [67, 68]. In patients with heart failure, serum BNP concentrations are found to increase proportionally to the severity of the clinical condition evaluated according to the New York Heart Association (NYHA) classification, and may be 25 times higher than the values in subjects without this pathology [69]. In studies by Cosin *et al*., authors observed that NT-proBNP correlates with the patient's condition in NYHA classification [70]. In the studies of McDonagh *et al*., the plasma level of the Nt-pro BNP concentration was 15.2 ± 14.2 pg/ml in healthy subjects, while in patients with chronic heart failure, it increased on average 45-fold to 691 ± 49 pg/ml [71]. In the studies of Dao *et al*., in patients with chronic heart failure, the mean values of serum BNP were: 95 pg/ml (NYHA I), 221 pg/ml (NYHA II), 459 pg/ml (NYHA III) and 1006 pg/ml (NYHA IV) as compared to 12 pg/ml found in healthy subjects [72]. BNP at the cut-off point of 80 pg/ml demonstrates a very high sensitivity and specificity in the diagnosis of chronic heart failure. The predictive value of BNP concentrations of less than 80 pg/ml for the diagnosis of chronic heart failure was 98% [73]. Cowie *et al*., based on a study of 122 patients, showed that BNP concentrations exceeding 76.8 pg/ml (22.2 pmol/l) allow the diagnosis of chronic heart failure with 97% sensitivity and 84% specificity [74]. Berger *et al*. confirmed the importance of BNP concentration as a predictive factor of sudden death in the course of chronic heart failure [75]. Observing 452 patients with an ejection fraction < 35% for 3 years, they found out that BNP concentration was the only independent indicator of the risk of sudden death. Their accepted cut-off value of 130 pg/ml is similar to the 80 pg/ml value applied by Dao. Tsutamoto *et al*. [76] demonstrated on the basis of a group of patients with CHF that the increase in plasma BNP concentration by 10 pg/ml was associated with a 3% risk of death in the period of further observation.

So far, the determination of one limiting value of BNP confirming or excluding chronic heart failure has been unsuccessful. Values between 80 and 130 pg/ml (the decisive value) are most frequently mentioned. Elevated BNP concentrations enable the precise diagnosis of both systolic and diastolic heart

failure [77]. In the study of Marsel *et al*., the BNP concentration in patients with left ventricular diastolic dysfunction was 391 ± 89 pg/ml, whereas in the group of patients with systolic dysfunction, it was higher: 567 ± 113 pg/ml [78]. The plasma BNP concentration was demonstrated to correlate with the value of pulmonary artery wedge pressure and with left ventricular end-diastolic pressure [79-84].

In patients with severe heart failure, the kinetics of natriuretic peptide secretion and excretion is disturbed, which leads to prolongation of the time of retention of these peptides in the plasma and to an increase in the partially degraded fraction of hormones. Thus, the increase in peptide concentration is not equivalent to the increase in hormone activity or to the increase in its plasma secretion because both of these effects depend on other physiological processes. Left ventricular dysfunction is manifested by a deepening imbalance between the system of sodium retention and the mechanisms leading to vasoconstriction and mechanisms of sodium excretion and vasorelaxation. This may be caused by the impairment of the hormone mechanisms associated with the process of sodium excretion caused by the impaired function of the vascular receptors for the system of natriuretic peptides and possibly also by disordered feedback between the plasma concentration of these peptides and their excretion. This mechanism may partly be the cause of the increase in natriuretic peptide concentration and the overlapping effects of the increased secretion and retention of natriuretic peptides making it impossible to easily interpret the mechanisms causing the elevation in concentration [85]. Furthermore, it is assumed that the factors capable of initiating cardiac hypertrophy induce numerous pathways of signal transduction and transcription factors, leading to increased expression of fetal genes in cardiomyocytes and thus the increase of ANP gene promotor activity [86].

BNP concentration demonstrates strict correlation with the class of heart failure according to NYHA. The diagnostic value of insignificantly and moderately elevated BNP concentrations is made difficult by the fact that they may result from, for example, cardiac hypertrophy. However, this measurement seems to be useful in the diagnostics of diastolic heart failure. In subjects with elevated blood pressure and right ventricular structural dysfunction (primary pulmonary hypertension, cor pulmonale, pulmonary embolism, congenital diseases and right ventricular arrhythmogenic dysplasia), BNP concentration increases to a lesser degree than in those with left ventricular dysfunction. BNP concentration appears to be of prognostic value, and as it is suggested in the most recent studies, it can enable the determination of risk of death including sudden death and hospitalization to a higher degree than NYHA class or ejection fraction.

The highest values of Nt-pro BNP are observed in left ventricular systolic dysfunction. Elevated values of Nt-pro BNP were observed in patients who had in their history pulmonary oedema or had an ejection fraction < 40% [87]. Determination of BNP and N-terminal BNP concentrations may help in the

qualification of patients with heart failure for transplantation or cardioverter-defibrillator implantation [88, 89].

Hammerer-Lerches *et al*. carried out studies aiming to estimate the causes of variability observed in natriuretic peptide assays [90]. They compared the diagnostic effectiveness of BNP, Nt-pro BNP and Nt-pro ANP as indicators of cardiac performance in 130 patients with mild forms of left ventricular dysfunction, and simultaneously compared three competing methods for determining these parameters. It appeared that patients with mild left ventricular dysfunction are best identified by BNP and Nt-pro BNP analysis; the obtained diagnostic performance coefficients (AUC, area under curve ROC determining the probability of the correct classification of a patient based on a positive or negative test result) were 0.78 (95% Cl: 0.63-0.89) for BNP and 0.75 (95% Cl: 0.58-0.87) for Nt-pro BNP. However, the determination of the Nt-pro ANP level demonstrated a significantly lower diagnostic performance (AUC 0.64; 95% Cl: 0.48-0.77). We also discovered that patients with isolated left ventricular diastolic dysfunction had a BNP diagnostic performance that was significantly better than in the case of Nt-pro BNP. The cut-off value and diagnostic performance of BNP determination depends on the applied method. Mild left ventricular dysfunction without group differentiation as regards to gender and age was associated with a BNP concentration exceeding 50 ng/l (14 pmol/l). The obtained Nt-pro BNP values differed significantly depending on the test producer. The Nt-proBNP test by Roche Diagnostics correlated significantly better with the results of the functional tests than the Biomedica version, which detected left ventricular dysfunction less successfully. The peptide diagnostic parameters determined by immunochemical methods with the application of a panel of highly specific monoclonal antibodies may present different results because many of these peptides undergoing rapid plasma proteolytic degradation lose epitopes essential for recognizing an analyte by antibodies in the first stage of the reaction.

The results of the mentioned studies are in agreement with the results of the survey on the determination of natriuretic peptide levels in subjects with mild heart failure [91]. The authors of the survey assessed about 12,000 studies devoted to this problem, published in the years 2000-2004. About 7,000 studies directly concerned ANP determination, and 800 BNP determination. 151 studies fulfilled the accepted criteria of credibility. The authors revealed enormous discrepancies in research assumptions, patient selection criteria and even the standards of clinical condition assessment. Therefore, although numerous authors point to the usefulness of natriuretic peptide determinations in screening examinations and in the classification of patients with heart failure, it is currently difficult to determine what examinations could be substituted and when in the diagnostics of heart failure for the determination of natriuretic peptide levels. Similar conclusions concern the application of natriuretic peptide determinations as prognostic factors in patients with heart failure. In various centers, different natriuretic peptides were analysed (ANP, BNP, Nt-pro ANP, Nt-pro BNP,

CNP); these differ in origin, structure and role in the pathophysiological processes. Also, many different immunochemical methods were used varying in the ways of detection of natriuretic peptides.

In 2002, the Working Group on Heart Failure of the European Society of Cardiology recommended that natriuretic peptides be assessed as screening markers of heart failure equally with chest electrocardiograms and radiograms [92]. BNP determination is in the European Society of Cardiology guidelines aiming at the improvement of the diagnosis of chronic heart failure [93].

Patients with high long-term BNP concentrations, despite aggressive treatment, have exceptionally high risk of cardiac events. The effect of the applied drugs on serum BNP concentrations in patients with chronic heart failure was proved in the Valsartan-Heart Failure Trial (Val-HeFT) and the Randomized Aldactone Evaluation Study (RALES). The best prognosis was for the patients with the most significant decrease in BNP concentration (in relation to the initial value), whereas the highest mortality was observed in the group of patients with the highest increase in this concentration [94]. In RALES, the decrease in mortality rate in the group treated with spironolactone was proportional to the decrease in BNP concentration as compared to the initial values. The lack of its evident decrease during effective therapy with a b-adrenolytic drug was puzzling. Troughton *et al*. demonstrated a lower number of deaths and repeated hospitalizations in a group of patients with chronic heart failure whose treatment (with a diuretic and angiotensin convertase inhibitors) was controlled by determining Nt-pro BNP concentration [95].

Defining the role of BNP in the treatment of patients with chronic heart failure appeared to be equally important. Intravenous administration of BNP was found to improve hemodynamic parameters and to decrease regional sympathetic activity in heart failure [96]. Similarly, intravenous application of recombined human brain natriuretic peptide (nesiritid) to patients with decompensated CHF resulted in a beneficial hemodynamic effect in the form of a cardiac output increase, a decrease in the mean wedged pressure and pulmonary artery pressure, an improvement in the cardiac index and renal flow without an accompanying non-beneficial effect of heart rate increase or the occurrence of other cardiac arrhythmias [97].

Numerous authors emphasize the usefulness of BNP concentration determination in the differentiation of the causes of acute dyspnoea other than chronic heart failure. Based on a study comprising 250 patients, Quyen *et al*. [98] found that this determination confirmed or excluded acute heart failure as a cause of dyspnoea: the positive prognostic value was 95%, and the negative was 97%. In the Breathing Not Properly Study, performed on 1586 patients who reported to the hospital for sudden dyspnoea, the highest BNP values (675 ± 450 pg/ml) were observed for subjects who presented symptoms caused by an intensification of chronic heart failure. Lower values were found in patients with a history of this disease, but the presented symptoms were non-cardiac (346 ± 390 pg/ml). The lowest BNP concentrations (110 ± 225 pg/ml) were

detected in subjects without heart failure, with a non-cardiac cause of dyspnoea [99].
Decreased BNP concentrations in the course of treatment of acute heart failure were observed to be associated with a good prognosis. Deaths were more frequent among patients in whom, despite the introduced therapy, these concentrations remained unchanged or increased [100, 101].
CNP is found in the endothelium of the heart. It has a very low concentration in the plasma, and elevations in CNP concentration are not associated with congestive heart failure.

ISCHEMIC HEART DISEASE AND ITS COMPLICATIONS

B-type natriuretic peptide (BNP, Nt-pro BNP) is also an indicator of myocardial ischemia. Sabatine *et al*. discovered that transient myocardial ischemia was associated with a rapid increase in BNP concentration, and that this increase was proportional to the severity of the ischemia. A similar relationship was observed in the case of Nt-pro BNP. However, the changes in Nt-pro BNP concentration in response to ischemia were expressed less distinctly [102]. In patients with acute coronary syndrome, BNP is secreted by undamaged cardiomyocytes. The increase in BNP concentration reflects the extensiveness and intensity of myocardial ischemia and accompanying contractility impairment. An elevated concentration of BNP (and Nt-pro BNP) is observed in all forms of acute coronary syndrome.
James *et al*. assessed 6,809 patients with acute coronary events with non-ST-segment elevation in whom Nt-pro BNP was determined (GUSTO IV study). They found that the annual mortality of patients with an NT-pro BNP of less than 98 pg/ml was 0.4% and with values above 4,634 pg/ml was as high as 27.1% [103].
It was revealed in patients with acute coronary syndromes that the risk of death was associated with a markedly higher BNP concentration. Such elevated values, if maintained in the serum of patients for 48 hours after myocardial infarction, increase the risk of chronic heart failure or death within a year [104].
Bassan *et al*. analyzed the data of 631 patients diagnosed in the admission room with chest pain with no ST-segment elevation on the ECG. In the analyzed material, patients diagnosed with myocardial infarction with no ST-segment elevation had significantly higher BNP concentrations on admission compared to those with unstable angina and to those in whom coronary etiology was not confirmed (the median BNP concentrations were, respectively: 203.5, 77.9 and 27.7 pg/ml, $p < 0.0001$). Patients with positive troponin values on admission demonstrated higher initial BNP concentrations compared to patients with negative initial results. However, no linear correlation was observed between the concentrations of troponin and BNP. In a subgroup of patients with low troponin values (both for the cut-off < 0.28 and 1 ng/ml), high BNP concentrations additionally distinguished patients with a high risk of the development of

myocardial infarction. In multimarker analysis, BNP concentrations above 100 pg/ml were a prognostic marker of myocardial infarction risk, independent of other clinical parameters. The addition of the initial values of necrosis markers to a multimarker model did not increase its predictive power. According to the authors of the study, BNP provides additional prognostic value to traditional markers of necrosis, particularly in the case when the first determinations of the markers are non-diagnostic [105].

Jarai *et al*., working with patients with unstable angina/non-ST-elevation myocardial infarction and normal Nt-pro BNP concentrations, additionally determined the concentrations of atrial natriuretic factor (Nt-pro ANP), demonstrating that in the investigated group, these concentrations together with troponin were independent prognostic factors of 2-year mortality [106].

Elevated serum ANP concentrations in patients with unstable angina may reflect left ventricular diastolic and increased BNP concentrations – both systolic and diastolic dysfunction [107]. However, further studies should be performed to confirm this phenomenon.

Schnabel *et al*. assessed 904 patients subjected to coronary angiography and the AtheroGene study. Elevated BNP values were connected with an increased risk of cardiovascular death in follow-up observation, not only in the group of patients with unstable angina, but also with stable angina. This dependency was particularly distinct for the upper quartile of BNP concentrations (3.7-fold risk increase for patients with stable coronary artery disease). Furthermore, an additional consideration of C-reactive protein concentrations in the multimarker model did not improve the model's prognostic power. The results of this study correlate with those of other similar studies, and broaden the application of BNP onto a group of patients with stable angina [108]. The analysis of BNP concentration in acute myocardial infarction demonstrated its maximal values 21 hours after initial symptoms and moreover, the dependence was observed between maximal BNP concentrations and the concentration of creatinine kinase [109-111].

Schnabel *et al*. later showed that, if the BNP value of 100 pg/ml was accepted as the cut-off value, patients with higher BNP concentrations had an over 4-fold higher risk of negative events (myocardial infarction, cardiovascular death) as compared to the remaining studied population. In relation to all the analyzed markers (age, gender, acute state markers or left ventricular systolic function), the BNP measurement had the highest accuracy in the prognosis of negative events measured under ROC curve (0.671) [112]. Omland *et al*. demonstrated that N-terminal pro-B-type natriuretic peptide is a sensitive prognostic marker for short, medium- and long-term mortality in the acute coronary syndromes they investigated [113].

HYPERTENSION

Natriuretic peptides together with nitric oxide inhibit angiotensin, noradrenaline and above all endothelin pressor activity, thereby conditioning the normal vascular wall tone. Factors affecting endothelial balance play this basic role in systemic pressure regulation.

The vascular endothelium, releasing a number of substances of vasodilating activity into the blood flow, such as nitric oxide (NO), prostacyclines, hyperpolarising factor (EDHF), or of vasoconstricting activity, such as thromboxan A2, prostaglandin H2, endothelin (ET-1), is not only a local regulator of vascular wall tone, but also plays an important role in the endogenic system of systemic arterial pressure control. Despite their vasodilating role, natriuretic peptides also have indirect hypotensive activity inhibiting the vasoconstricting effect of noradrenaline, angiotensin II and vasopressin. Furthermore, they weaken the angiotensin II and vasopressin central pressor effect and the central stimulation of the sympathetic system. The influence on the sympathetic system is connected with the intensification of the reflex from the baroreceptors. The reduction of vascular resistance and blood pressure, the increase in the cardiac index, and the decrease in vascular resistance in the pulmonary circulation and right atrium was observed during the venous infusion of BNP. The coronary and renal vessels are particularly sensitive to the vasodilating effect of natriuretic peptides. CNP, synthesized by the endothelium, probably plays an important role in the local vasodilating effect. Unlike other natriuretic peptides, CNP works on the smooth muscles of both venous and arterial vessels [114].

The effect of the same ANP and BNP doses was directly compared in patients with arterial hypertension in the studies carried out by Pigeon *et al*. The haemodynamic and endocrine influence of natriuretic peptides was assessed. In this study, the effects of equimolal ANP and BNP doses and the two peptides together were compared. The infusion of peptides increased natriuresis over the level observed before their administration, decreased arterial pressure, increased the hematocrit, and inhibited the RAA system and plasma norepinephrine concentration. ANP significantly elevated the plasma and urine second messenger (cGMP) levels relative to BNP. Both increased the norepinephrine concentration by about 30% [115].

Inhibition of the activity of neutral endopeptidase (NEP), which is involved in the elimination of natriuretic peptides, induced sodium-excreting activity in an animal model of arterial hypertension, and in humans. Conversely, sodium excretion and the hypotensive activity of natriuretic peptides is reduced significantly in patients with hypertension, or renal or heart failure. It is supposed that both increased natriuretic peptide metabolism and decreased expression of tissue receptors are the cause.

ET-1 demonstrates the strongest vasoconstrictor and pressor activity. Its increased concentration was observed in malignant hypertension and the pre-

eclamptic state [116]. An elevated ET-1 concentration increases central and peripheral sympathetic system tone and potentiates noradrenaline vasoconstricting activity [117]. Thus, it is assumed that a disturbed interaction between ET-1 and the sympathetic nervous system may be one of the factors determining the development of arterial hypertension.

SEPTIC SHOCK

BNP is a marker of left ventricular dysfunction. Myocardial dysfunction frequently accompanies severe sepsis and septic shock [118, 119]. Witthaut *et al*. also confirmed this in their studies [120]. In cases of septic shock, they found a significant increase in ANP (82.7 ± 9.9 vs. 14.9 ± 1.2 pg/ml) and BNP (12.4 ± 3.6 vs. 5.5 ± 0.7 pg/ml). The plasma ANP peaked together with IL-6. The peaks of ANP and IL-6 were significantly correlated ($r = 0.73$; $p < 0.01$). The BNP level was inversely correlated to the cardiac index ($r = -0.56$; $p < 0.05$). They suggest that BNP reflects left ventricular dysfunction and ANP is related to IL-6 production rather than to cardiovascular dysfunction. Chua *et al*. described a markedly elevated Nt-pro BNP level in patients with septic shock [121].

GENETIC ANALYSES IN CORONARY DISEASES

A lack of the ANP gene was observed to condition the development of sodium-sensitive hypertension, whereas increased expression of this gene in transgenic animals is associated with an excessive decrease in pressure. Studies on ANP gene polymorphism in patients with arterial hypertension resulted in the determination of allelic and genotypic distribution of ANP coding genes' molecular variants. The occurrence of idiopathic hypertension in close connection with the presence of ANP gene polymorphism has been confirmed in clinical trials in humans [122]. A detailed analysis of ANP gene structure allowed the detection of mutation within its coding sequence and 5' terminus. Increased cGMP release observed in the investigated group led to endothelial imbalance and in consequence to early vascular wall damage [123].

The ScaI ANP gene polymorphism: transition T2238 →C leads to the loss of ScaI restriction site. Among the patients with coronary disease, the TT genotype was associated with more frequent prevalence of myocardial infarction and a greater number of atherosclerotically changed vessels [124]. A mutation in 341 NPR-A leading to the replacement of isoleucine with methionine in the amino acid chain (Met 341 Ile) was also investigated. The mutation was significantly more frequently observed in the group of patients with myocardial infarction than in the controls [125]. No association was found between BNP gene C 1563 T polymorphism and the development of idiopathic dilated cardiomyopathy [126]. Polymorphism in intron 18 (insertion/deletion of 9 base pairs) and in intron 11 (C 2077 T) is described within the BNP receptor gene (NPR-B). Polymorphism within a 3' region not undergoing translation (G 2628 A) affects the occurrence of hypertension [127].

CONCLUSIONS

Every year, the depth and breadth of knowledge on the role and activity of natriuretic peptides and endothelins in the human organism is greater. The interactions between these peptides can be described more and more precisely. However, many mechanisms have yet to be elucidated. Explaining the processes taking place in the vascular internal membrane is of particular importance from the point of view of the diagnostics and therapy of cardiovascular diseases. It is of significance for the establishment of pathomechanisms of the numerous pathologies of this system and for the determination of new directions in their therapy [128]. In recent years, the idea of natriuretic peptide application in clinical practice has gained considerable support [129-131]. Unfortunately, the obtained results are not always encouraging [132], and further research is definitely required.

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