International Journal of Medicine and Medical Sciences Vol 1.(11) pp. 473-494, November, 2009
Available online http://www.academicjournals.org/ijmms
ISSN 2006-9723 ©2009 Academic Journals

Review

Biosynthesis, physiology and main diagnostic and therapeutic potentials of cardiac natriuretic peptides

Melpomeni Ntalapascha[1], Zoi Daniil[2] and Epaminondas Zakynthinos[1]*

[1]Critical Care Department, School of Medicine, University Hospital of Thessaly, Greece.
[2]Pulmonary Department, School of Medicine, University Hospital of Thessaly, Greece.

Accepted 02 November, 2009

Cardiac natriuretic peptides (NPs) is a family of peptide hormones, circulating in blood, originating from three prohormones: The atrial natriuretic peptide (ANP) prohormone synthesizes four active peptides (ANPs: Long-Acting Natriuretic Peptide, Vessel Dilator, Kaliuretic Peptide and ANP). B type natriuretic (BNP) and C type natriuretic (CNP) prohormones are cleaved in only one active peptide hormone each (BNP and CNP, respectively). ANPs and BNP bind to Natriuretic Peptide Receptor A (NPR-A) and CNP to NPR-B, which are transmembrane, guanylcyclase enzymes, in order to exert their biological effects. All NPs bind to a third receptor, NPR-C, which acts to clear them from the circulation. Activation of NPR-A mediates inhibition of renin-aldosterone system and natriuresis, as well as vasorelaxant, antifibrotic, anti-hypertrophic and anti-inflammatory and independent lipolytic effects. NPR-B activation is responsible for long bone growth. The properties of NPs to regulate plasma volume, through NPR-A activation, have been used for management of decompensated heart failure (HF) and acute renal failure. Human recombinant BNP (nesiritide) is commercially available for therapy of acute HF. Nesiritide improves hemodynamic profile and the clinical status of the patient. However, it may worsen renal function indicating a worse prognosis. Finally, plasma measurement of BNP has emerged as a useful, cost-effective biomarker for the diagnosis and prognosis of HF. However, other cardiovascular diseases as ischemia, arrhythmias and cardiac hypertrophy, as well as disorders of no cardiac origin, as sepsis and septic shock may cause elevated BNP levels.

Key words: Atrial natriuretic peptide, brain natriuretic peptide, C-type natriuretic peptide, natriuretic peptide receptors, nesiritide, anaritide, cardiovascular diseases, cancer.

INTRODUCTION

Since the discovery of atrial granules by Kisch (1956) and the atrial natriuretic peptide (ANP) by de Bold et al. (1981) new members of this growing family were identified and investigated, that is brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP), dendroaspis natriuretic peptide (DNP) and urodilatin (URO) (Candace et al., 2007). However, ANP, BNP and CNP are the main representatives of natriuretic peptides (NPs) group.

The NPs are a group of endogenous hormones (Candace et al., 2007) that exert significant role in the regulation of cardiovascular, renal and endocrine homeostasis (Levin et al., 1998). Growing evidence suggests that they also play significant role in the regulation of lipid metabolism (Sengenes et al., 2005), in the stimulation of long bone growth (Potter et al., 2005) and in the course of cancer as well (Vesely et al., 2005). Finally, a few study suggest immunological (Kiemer et al., 2000) and neurological effects (Antunes-Rodrigues et al., 1985). All NPs exert their actions through ligation in cell surface natriuretic peptide receptors.

This review will focus on the biosynthesis and physiology of NPs and will highlight the potential diagnostic options of BNP in cardiac and non-cardiac diseases; yet, the present role of NPs in the treatment of renal and heart failure, and their future as anticancer agents will be mentioned.

NATRIURETIC PEPTIDE RECEPTORS

The natriuretic peptides are ligands for three different cell

*Corresponding author. E-mail: ezakynth@yahoo.com. Tel: +32410-681280 Fax: +32410-670838.

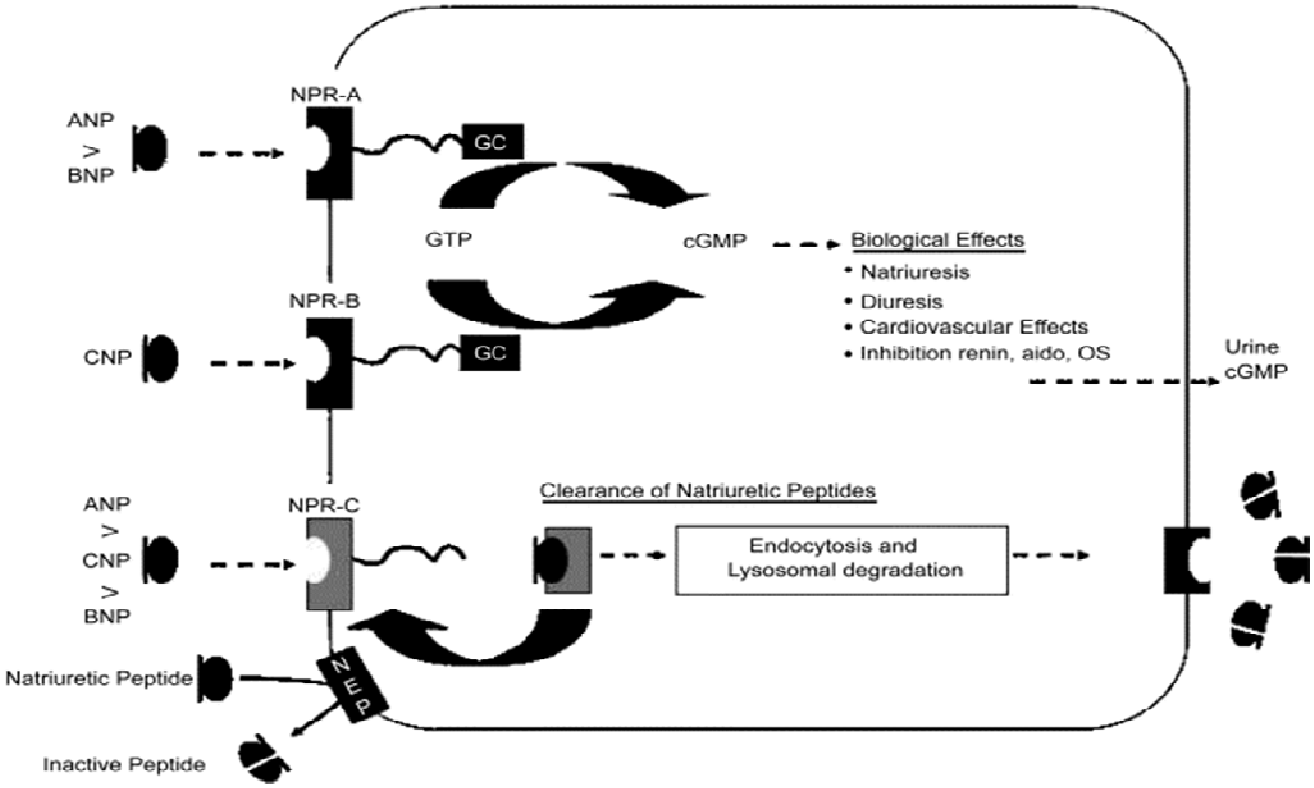

Figure 1. Natriuretic peptide receptor topology and ligand preferences. Action of natriuretic peptides at target cells. GC; guanylyl cyclase, NPR-A; natriuretic peptide receptor A, NPR-B; natriuretic peptide receptor B, NPR-C; natriuretic peptide receptor C, NEP; neutral endopeptidase, aldo; aldosterone, OS; orthosympathetic system (Modified from: Vanderheyden, et al. Brain and other natriuretic peptides: molecular apects. Europ J Heart Fail.2004; 6:261-268)

surface receptors - called natriuretic peptide receptor NPR-A, NPR-B and NPR-C - that mediate physiological effects (Vanderheyden et al., 2004) (Figures 1 and 2). They are also known as Guanylyl Cyclase (GC) GC-A, GC-B, and the clearance receptor, or as NPR1, NPR2, NPR3, respectively. NPR-A and NPR-B are trans-membrane, guanylyl cyclase, enzymes that catalyze the synthesis of 3´, 5´- cyclic guanosine monophosphate (cGMP); NPR-C does not possess a GC activity (Lafontan et al., 2005) (Figure 1). cGMP activates signal transduction elements such as low and high-affinity cGMP dependent protein kinases (Kuhn et al., 2003), phosphodiesterases (PDE) and cyclic nucleotide-gated channels (CNG).It has been shown that ATP is absolutely necessary for the activation of both NPR-A and NPR-B (Chinkers et al., 1991; Marala et al., 1991; Wong et al., 1995). However, ATP does not activate natriuretic peptides but it stabilizes them (Duda et al., 1993).

Particulate GC receptors require a single transmembr-ane domain, composed of a ligand-binding domain in the extracellular side, a small hydrophobic region, a kinase-homology domain (KHD) and an intrinsic GC activity on the intracytoplasmic side (Moro et al., 2006).

Natriuretic peptides are degraded through two processes that have different mechanisms (Anand-Srivastava et al., 1993): enzymatic degradation by neutral endopeptidase 24.11 (neprilysin-NEP) and NPR-C mediated internalization followed by lysosomal degradation (Figure 1). Even though there is no specific antagonist that completely blocks the GC activity, a polysaccharide known as HS-142-1, was found to inhibit ligand bindingand activation of both NPR-A and NPR-B but not NPR-C (Morishita et al., 1991; Sano et al., 1992; Poirier et al., 2002).

Natriuretic peptide receptor A (NPR-A)

The human NPR-A gene contains 22 exons and 21 introns and is located in chromosome 1q21 - 22 23 (Takahashi et al., 1998).

Human and rat NPR-A mRNA are highly expressed in kidney, terminal ileum, adrenal gland, adipose, spleen, lung tissues, in vascular smooth muscle cells and in the heart (Lowe et al., 1989; Chang et al., 1989; Schulz et al., 1989; McGregor et al., 1993). NPR-A has a growth factor receptor-like topology consisting of an intracellural domain of approximately 570 amino acids [26], an extra-cellular domain of approximately 450 amino acids and a 20 - 25 residue single hydrophobic membrane-spanning

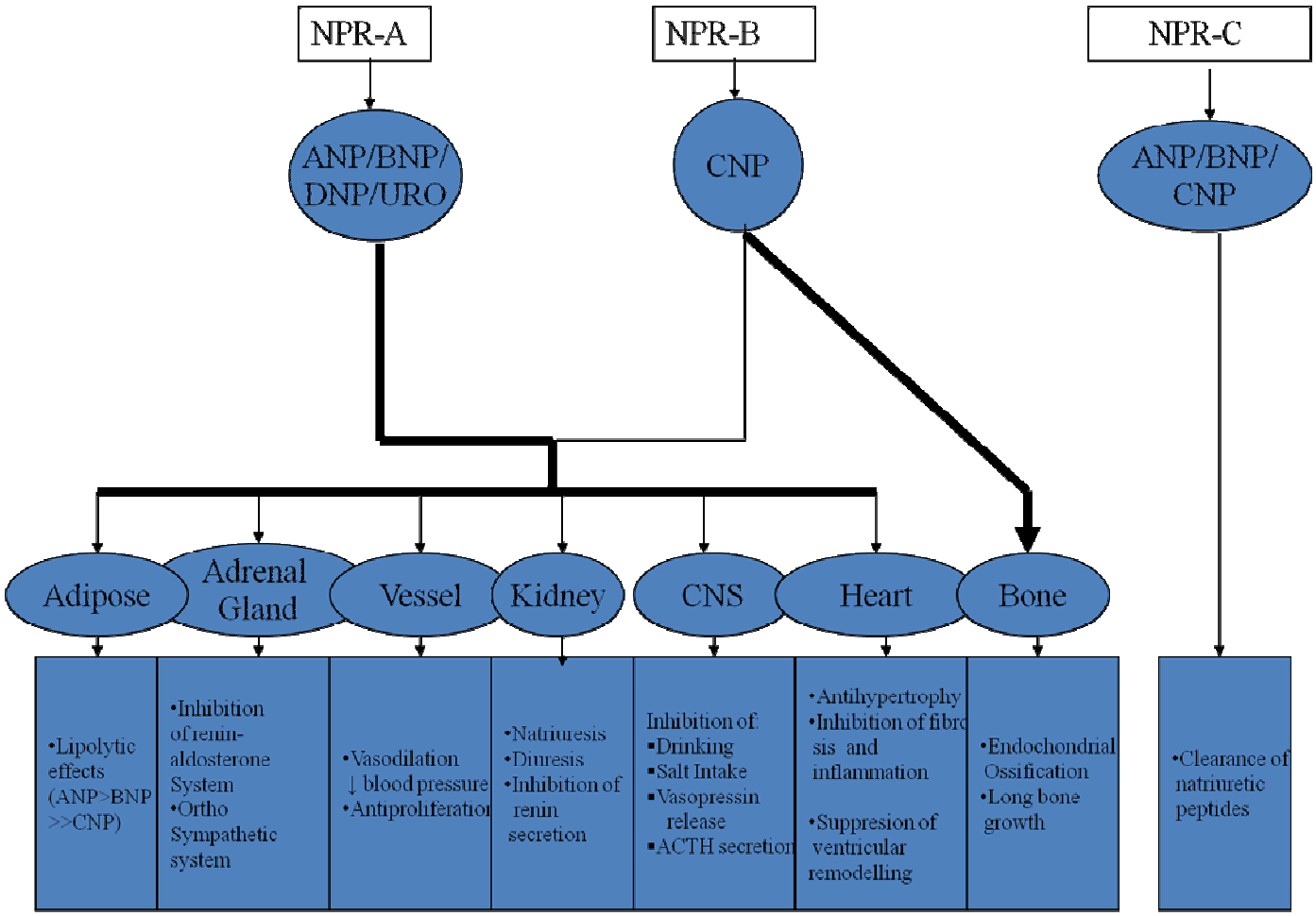

Figure 2. Main actions of natriuretic peptides at target cells. (Other significant actions, activated mainly by only one NP, are analyzed in the text). NPR-A; natriuretic peptide receptor A, NPR-B; natriuretic peptide receptor B, NPRC; natriuretic peptide receptor C, ANP; atrial natriuretic peptide, BNP; brain natriuretic peptide , CNP; C-type natriuretic peptide, DNP; Dendroaspis natriuretic peptide, URO; urodilatin

spanning region. NPR-A is mainly activated by ANP and BNP (Koller et al., 1991; Suga et al., 1992) (Figures 1 and 2). NPR-A forms a head-to-head, A- like dimer with a stoichiometry of one molecule of ANP to two molecules of receptor (Ogawa et al., 2004). Therefore, the binding of ANP to NPR-A is asymmetric.

Under basal conditions, NPR-A is phosporylated on four serines and two theonines within a stretch of 17 amino acids at the amino-terminal portion of its kinase homology domain (Potter et al., 2005). Phosphorylation of NPR-A is absolutely required for hormonal activation because it is found that conversion of any phosphorylated residue to alanine reduces hormone-dependent GC activity (Potter et al., 1989; Fethiere et al., 1993). Furthermore, the mutation of four or more phosphorylation sites to alanine leads to a hormonally unresponsive receptor (Potter et al., 2002).

NPR-A is dephosphorylated by two separate phosphatase activities. One is inhibited by microcystin, without repuiring magnesium, whereas the other one is not inhibited by microcystin but requires magnesium or manganese for activity (Bryan et al., 2002).

NPR-A is negatively regulated by its cognate ligand ANP (homologous downregulation) through a mechanism that requires cGMP (Cao et al., 1995). It is also regulated by 1, 25 dihydroxyvitamin D through a single vitamin D response element between -498 and -484 in the promoter. Finally, NPR-A is positively regulated by osmotic stimuli. NPR-A exhibits ligand selectivity in the order: ANP>BNP>>CNP (Figures 1 and 2).

Natriuretic peptide receptor B (NPR-B)

The human NPR-B contains 22 exons and is located on chromosome 9p21 - 12 (Rehemudula et al., 1999). NPR-B was identified in the kidney, adrenal, lung, uterus, ovary tissue, skin and in the brain and particularly in the

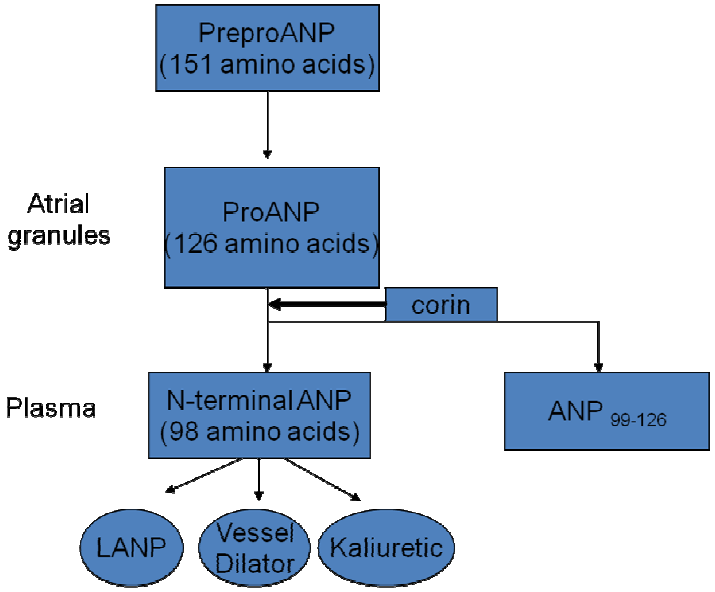

Figure 3. Human preproANP is 151 amino acids in length. Cleavage of the amino terminal signal sequence results in the 126-amino-acid proANP, which is the predominant form stored in atrial granules. ProANP is cleaved by corin to form the biologically active carboxy-terminal 28-aminoacid peptide (ANP 99-126). Within the 126 amino-acid proANP are three more peptide hormones (numbered by their amino acid sequence): amino acids 1-30 (long-acting natriuretic peptide; LANP), amino acids 31-67 (vessel dilator), amino acids 79-98 (kaliuretic peptide

pituitary gland (Sudoh et al., 1990; Paul et al., 1987; Nagase et al., 1997; Chrisman et al., 1993). It is also distributed in messangial cells and in cardiac fibroblasts (Lincoln et al., 1993) (The main sites of NPR-B are depicted in Figure 2). It has some common characteristics as NPR-A: it has the same overall topology and mutation in some of its residues leads to a decrease in hormone dependent guanylyl cyclase activity (Hirsch et al., 2003; Tamura et al., 2003). It has been noted that mutations in the alleles can lead to dwarfism and female sterility in mouse models. Mutations of NPR-B are also identified in patients with dwarfism called acromesomelic dysplasia, type Maroteaux (Bartels et al., 2004).

NPR-B shows binding selectivity in the order: CNP>>ANP>BNP (Tremblay et al., 2002; Misono et al., 2002) (Figures 1 and 2).

Natriuretic peptide clearance receptor (NPR-C)

The human NPR-C gene is located on chromosome 5p14-p13 and contains 8 exons and 7 introns (Rahmutula et al., 2002).

NPR-C mRNA is found in mesentery, placenta, lung, kidney, atrial and venous tissue (Wilcox et al., 1991; Porter et al., 1990), aortic smooth muscle and aortic endothelial cells (Fuller et al., 1988) and adrenal and cerebellum tissue (Herman Jet al., 1996) (Figure 2). Although NPR-C has some common characteristics as NPR-A and NPR-B, such as the fact that the extracellular domain is about 30% identical (Van den et al., 2001), it has some differences as well. It is a disulfide-linked homodimer containing only 37 intracellular amino acids and no guanylyl cyclase activity (Kuno et al., 1986) (Figure 1).

The major function of NPR-C is to clear natriuretic peptides from the circulation or extracellular milieu through receptor-mediated internalization and degradation (Jaubert et al., 1999; Matsukawa et al., 1999) (Figures 1 and 2).

The serum half-life of BNP is longer in comparison with ANP. This is justified of the lower affinity of NPR-C for BNP (Bennett et al., 1991) (Figure 1).

NATRIURETIC PEPTIDES

Atrial natriuretic peptide (ANP)

All natriuretic peptides are synthesized as prohormones (Potter et al., 2005). Human preproANP is a 151 aminoacids in length (Potter et al., 2005) (Figure 3). Cleavage of the aminoterminal signal sequence results in

the 126-amino-acid proANP, which is the predominant form stored in atrial granules. When secreted, proANP undergoes proteolytic processing in a specific hydrophobic sequence by corin, which is a serine protease. This gives the N-terminal proANP1-98 form and the 28-amino-acid carboxy-terminal fragment ANP99-126 which is the main biologically active ANP. Both forms circulate in plasma. In detail, the 126 amino acid ANP prohormone is finally divided in four peptide hormones (Vesely et al., 1987; Dietz et al., 2001; Vesely et al., 1994; Vesely et al., 1998). These peptide hormones, numbered by their amino acids sequences beginning at the N-terminal end of the ANP prohorme, consist of the first 30 amino acids of the prohormone (long acting natriuretic peptide –LANP), amino acids 31 - 67 (vessel dilator), amino acids 79 - 98 (kaliuretic peptide) and amino acids 99 - 126 (ANP) (Vesely et al., 2005; Vesely et al., 1992).

The human ANP gene is located on chromosome 1p36.2 and contains 3 exons. ANP is expressed in lung, brain, adrenals, kidney, gastrointestinal tract and thymus, but its level of expression is about 50-fold higher in the cardiac atrium (Misono et al., 1984; Rosenzweig et al., 1991). In cardiac ventricles of healthy adults, there is only 1% of the atrial ANP mRNA. ANP is released in response to atrial stretch consecutive to a rise in cardiac filling pressure (Saito et al., 1989; Rodeheffer et al; 1986). In addition, many factors such as arginine-vasopressin, endothelin and angiotensin stimulate ANP release [66]. As already mentioned, ANP physiological actions are mediated through NPR-A receptors; yet, ANP is cleared by NPR-C and degraded by NEP [67] (Figure 1).

Actions

The main known biological actions of ANP and ANP relatives -LANP, vessel dilator and kaliuretic peptide- are blood pressure downregulation and the maintenance of plasma volume in animals (Vesely et al., 1998; Vesely et al., 2005; Zeidel et al., 1995; Martin et al., 1990; Gunning et al., 1992) and in humans (Vesely et al., 1994). Mice completely lacking ANP, or NPR-A, have blood pressures 20 - 40 mmHg higher than normal (John Set al., 1995), whereas animals transgenically expressing higher than normal amounts of ANP have blood pressures 20 - 30 mmHg lower than normal (Steinhelper et al., 1990).

ANP regulates water and salt homeostasis protecting the body of fluid overload by decreasing intravascular fluid volume, through potent natriuretic and diuretic effects. It exerts its effects at the level of the glomerulus causing afferent arteriolar dilation together with efferent arteriolar vasoconsrrtiction and thus it increases glomelural filtration rate (Vesely et al., 1998; Vesely et al., 2005; Vesely et al., 1992). In the collecting duct, it decreases sodium reabsorption, thereby increasing sodium excretion. ANP can be considered an endogenous antagonist of the renin angiotensin- aldosterone system and the antidiuretic hormone (Zeidel et al., 1995; Martin et al.,1990) (Figure 2, Table 1).

Although ANP was initially suggested to regulate blood pressure in a salt sensitive manner, more recent data suggest that this is not the case (Lopez et al., 1995). Even if ANP does not cross the blood-brain barrier, it reaches cerebral areas outside this barrier near the third ventricle, where NPR-A is expressed. ANP reduces, through effects on hypothalamic and pituitary neurons, vasopressin and corticotrophin (Burrell et al., 1991; Chartier and Schiffrin, 1986); it also reinforces its peripheral effects on the cardiorenal system (Blackburn et al., 1995). Intracerebroventricular infusion of ANP inhibits water intake and suppresses salt appetite (Itoh et al., 1986; Samson et al., 1987). Finally, ANP modulates blood pressure and sympathetic nervous system activity via inhibition of neurons in the nucleus tractus solitari (Steele et al., 1991) (Figure 2).

Studies suggest that NPs may act as an autocrine/paracrine factor to modulate cardiac hypertrophy in response to various stimuli. Calderone et al investigated the effect of exogenously administered ANP on the cardiac cell hypertrophy induced by norepinephrine. ANP, as well as nitric oxide donor and 8-bromo-cGMP, decreased the norepineprine - stimulated incorporation of [3H] leucine in ventricular myocytes (Calderone et al., 1998). Moreover, ANP inhibited the increase by the Ca2+ channel agonist BAY K8644 of norepinephrine-stimulated incorporation of [3H] leucine in myocytes (Calderone et al., 1998). These results indicate that ANP and NO can attenuate the effects of norepinephrine on the growth of cardiac myocytes via a cGMP-stimulated inhibition of norepinephrine stimulated Ca2+ influx, and raise the possibility that endogenous ANP supressively regulates the development of cardiac myocyte hypertrophy. In addition, Mori et al, showed volume overload resulted in exaggerated cardiac hypertrophy in atrial natriuretic peptide knockout mouse, which was not prevented by normalization of blood pressure (Mori et al., 2004). Therefore, the findings suggest that ANP plays an important physiologic role as a local regulator of ventricular remodelling (Calderone et al., 1998; Mori et al., 2004; Brandt et al., 1995) (Figure 2, Table 1).

ANP has also been reported as an antigrowth factor of endothelial cells (Itoh et al., 1992); endothelial proliferation represents a key event in angiogenesis and tumor progression (Felmeden et al., 1997). ANP seems to attenuate the expression of vascular endothelial growth factor (VEGF), a protein implicated in the stimulation of normal angiogenesis, but also in angiogenesis that underlies tumor metastasis (Pedram et al., 1997).

It has been demonstrated that VEGF also induces vascular permeability (Pedram et al., 2002). Such increases in endothelial cell leak and formation of intercellular gaps in vascular endothelium is regarded as one of the initial conditions contributing to the development of an atheromatus atheromatous plaque (Raines and Ross, 1995).

Table 1. Causes of raised levels of brain natriuretic peptide in plasma

S/No.	Biological effects of natriuretic peptides
	Atrial natriuretic peptide
1	Blood pressure downregulation
2	Increase in glomerular filtration
3	Endogenous antagonism of the renin angiotensin-aldosterone and the antidiuretic hormone
4	Natriureric and diuretic effects: regulation of water and salt homeostasis Maintanance of plasma volume
5	Reduction of vasopressin and corticotrophin
6	Suppression of salt appetite and inhibition of water intake
7	Lipolytic activity
	Urodilatin
1	Increase of urine flow, filtration rate and renal vascular resistance
2	Regulation of Na+ and water reabsorption through actions at distal segments of the nephrons / Dose-dependent increase at urinary cGMP and Na+ excretion
	Brain Natriuretic Peptide
1	Increase of renal plasma flow, glomelural filtration rate and urine flow rate
2	Inhibition of sodium reabsorption through anti-aldosterone properties
3	Natriuresis and diuresis
4	Reduction of norepinephrine spillover leading to inhibition of cardiac sympathetic nervous system activity
5	Reduction of blood pressure and ventricular preload
6	Antiproliferative and antifibrotic actions in the heart and vascular tissues: ventricular/vessel remodelling
	C-type natriuretic peptide
1	Stimulation of long bone growth with the chondrocyte being its major target
2	Inhibition of vascular smooth muscle proliferation and endothelial cell migration/anti-atherogenic properties
3	Weak vasorelaxation
	Dendroaspis
1	Involvement in the regulation of blood volume and renal function
2	Stimulation of guanylate cyclase in cultured aortic myocytes and in bovine aortic endothelial cells

Moreover, inflammatory mediators, such as TNF<alpha> (Kiemer et al., 2002), can induce respective vascular changes. ANP was shown to abrogate such changes in vascular permeability associated with stress fiber formation and actin polymerization induced by either TNF-a (Pedram et al., 2002; Mounier et al., 2002) or VEGF (Pedram et al., 2002). Although the underlying mechanisms have not been elucidated yet, further data indicate the potency of ANP to protect from endothelial morphology change and increase in permeability occurring upon exposure to oxidants (Murohara et al., 1999; Lofton et al., 1991) or thrombin (Baron et al., 1989). It might be of special importance that ANP does not only counteract the inflammatory, permeability-increasing actions of mediators, such as TNF<alpha> (Lofton et al., 1991) and VEGF (Pedram et al., 2002), but that it also reduces the production of these factors (Pedram et al., 1997; Schwartz, 1997; Tsukagoshi et al., 2001; Morita et al., 2003). This strongly points to a double safeguarding function of ANP against the excessive activation of endothelial cells by these mediators.

ANP exerts a specific lipolytic effect on human isolated fat cells through NPR-A activation. The presence of NPR-A receptor in human adipose was confirmed by the binding studies performed on human fat cell membranes with the use of (125I) ANP as a radioligand and various peptide competitors (Sengenes et al., 2000). ANP activates hormone sensitive lipase in human fat cell in

vitro via phosphorylation of the enzyme through a cGMP-mediated mechanism (Sengenes et al., 2003). Subsequently, hormonesensitive lipase breaks down triglycerides into non-esterified fatty acids (NEFAs) and glycerol. Experimental studies have shown that pharmacological administration of human ANP is followed by a significant increase in plasma FFA and glycerol concentration that reflect adipose lipolysis (Galitzky et al., 2001).

The physiological relevance of the metabolic effect of

ANP has been assessed during exercise, a situation known to induce both cardiac ANP secretion and lipid mobilization. ANP induces this lipid mobilization independently of a reflex-activity of the sympathetic nervous system [99]. Besides, exercise-induced cardiac release of ANP can be potentiated by acute β-blocker treatment (Berlin et al., 1993). In this condition where β-blockage is efficient, exercice-induced subcutaneous abdominal tissue lipolysis is paradoxically enhanced (Moro et al., 2004). Therefore, the therapeutic management of obesity-associated hypertension, combining regular physical activity and β-blocker treatment, might be attractive to lower both blood pressure and body weight. In addition, the lipolytic effect of natriuretic peptides is completely independent from the major antilipolytic hormone, insulin. Insulin treatment on human fat cells has no effect on ANP-induced lypolytic response (Sengenes et al., 2000; Moro et al., 2004; Moro et al., 2005).

Although the natriuretic peptides and their receptors are found in many immune cells (mainly in macrophages and dendritic cells), the significance of these peptides in the immune system is only now emerging. It seems that ANP elicits antiinflammatory effect by reducing production of proinflammatory cytokines (TNF-a and IL-12) while enhancing production of IL-10 (Kiemer et al., 2000; Pedram et al., 1997; Schwartz, 1997; Tsukagoshi et al., 2001; Morita et al., 2003; Holliday et al., 1995). However, ANP has been demonstrated to increase neutrophil migration *in vitro* (Elferink et al., 1995). Excessive neutrophil infiltration after ischemia can lead to further tissue damage, thus lending a cardioprotective function to blocking ANP signaling after ischemia. Yet, NPR-A knockout mice also exhibit decreased eosinophil accumulation in the lungs after allergic challenge with ovalbumin (Mohapatra et al., 2004), suggesting that ANP signaling may play a role in asthma.

Urodilatin

An alternative processing of proANP by an unknown protease in the kidney generates a 32-residue peptide called urodilatin (URO). URO and the “renal urodilatin system” were identified after the observation that immunoassayable ANP in urine may not be identical to the circulating cardiac hormone ANP (Schulz-Knappe Baron et al., 1988). Therefore, URO is a natriuretic peptide isolated from human urine belonging to the family of A-type natriuretic peptides.

Actions

URO is synthesized in kidney tubular cells and secreted luminally. After secretion from epithelial cells of the distal and connecting tubules, URO interacts at distal segments of the nephron with luminally located NPR-A receptors whereby it regulates Na+ and water reabsorption. Thus, the physiological function of the renal URO system can be described as a paracrine intrarenal regulator for Na+ and water homeostasis, considering this peptide as a real diuretic-natriuretic regulatory peptide. In fact, many investigators studying the pharmacokinetics and pharmacodynamics of URO in healthy men found that URO exerted natriuretic and diuretic effects and thus increased urine flow, filtration rate and renal and systemic vascular resistance (Dorner et al., 1998; Bestle et al., 1999). Carstens et al. studied the pharmacokinetics and pharmacodynamics of URO in 12 healthy men in a randomized, double-blind, crossover study. The kinetics of URO were characterized by a large apparent volume of distribution, a high total body clearance and a short plasma half-life of 5,57 min. Mean blood pressure was lowered (Carstens et al., 1998). However, the regulation upon which the URO secretion depends is still not clear.

Bestle et al. investigated the cardiovascular, endocrine and renal effects of intravenus infusion of URO in a randomized, double-blind study in healthy men. An increase in both plasma and urinary cGMP followed the infusion of URO (Bestle et al., 1999). The renin-angiotensin–aldosterone system was found to be suppressed at 5, 10 and 20 ng kg^{-1} min^{-1} and activated by URO 40 ng Kg^{-1} min^{-1}.

In order to compare URO with other NPs, Saxenhofer et al studied the outcome of the i.v. bolus injection o URO and ANP. Dose-dependent increase in urinary cGMP and Na^{+} excretion was observed, with URO being more potent than ANP (Saxenhofer et al., 1990).

Brain natriuretic peptide (BNP)

Brain natriuretic peptide is an amino 32- amino acid hormone that was named so because it was primarily detected in porcine brain (Lang et al., 1992; White, 2005; Zakynthinos et al., 2008). Subsequent studies found that BNP is constituvely released from ventricular myocytes as a preprohormone of 134 amino acids in response to ventricular stress, volume and pressure loading and increased neurohormonal stimuli (Grepin et al., 1994; Thuerauf et al., 1994; Lee et al., 2005). This preprohormone undergoes cleavages which yield primarily a 108- amino acid proBNP hormone and secondly a 76 amino-acid N-terminal fragment (NT-proBNP), that is the inactive byproduct, and a 32 amino-acid hormone (BNP) that is the active component (Figure 4). Both BNP and NT-proBNP circulate in the blood (Lee et al., 2005) and are

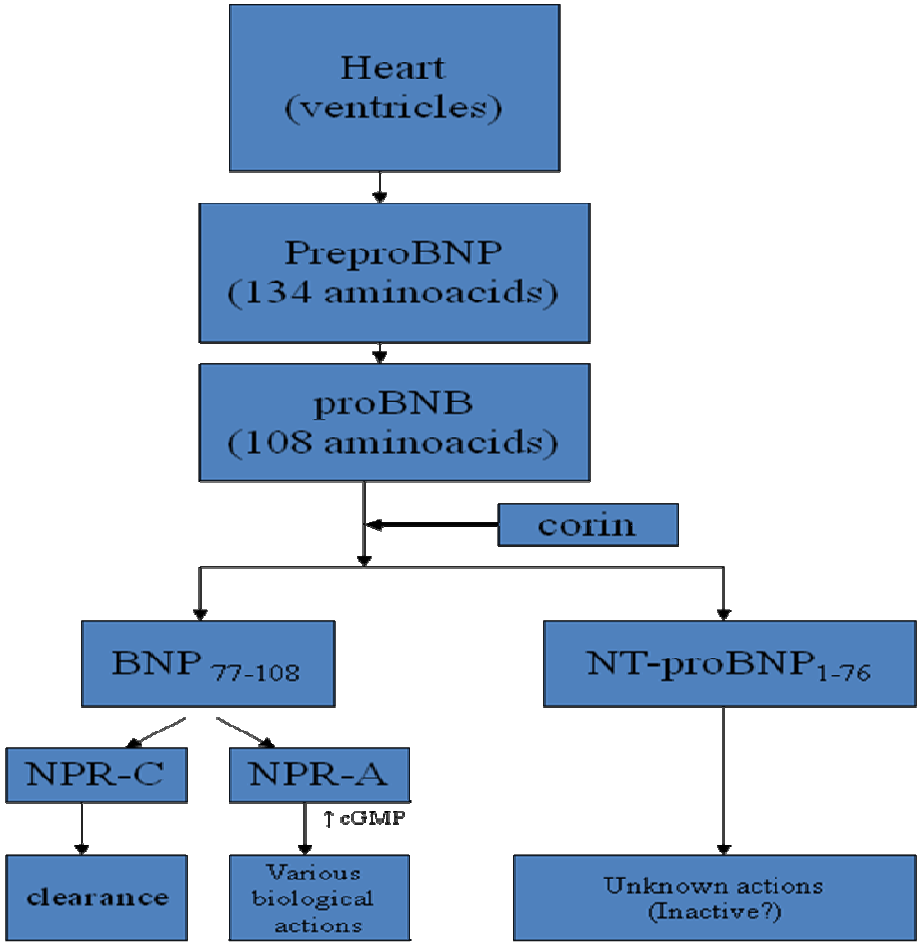

Figure 4. Schematic represantation of the production of BNP from inactive prohormone proBNP1-108 to the biological active form of BNP 1-32 and to probably inactive form of NTproBNP1-76 after corin activation .Clearance of BNP via NPR-C.

are secreted through the coronary sinus (Richards et al., 1993).

Although BNP is stored with ANP in atrial granules, BNP is not stored in granules in the ventricles (Potter et al., 2005). The circulating active BNP is characterized by a ring structure closed by a disulfide bond between two cysteine residues, an aminoterminal tail of nine amino acids, and a carboxylterminal tail of six aminoacids (Valli et al., 1999). The ring structure must be intact to ensure natriuretic peptide binding to natriuretic peptide receptors A and C (Figure 2). Besides BNP clearance through receptor binding to NPRC, renal excretion, and enzymatic degradation by NEP contribute to the elimination of circulating elimination of circulating BNP (Richards et al., 1993; Valli et al., 1999; Pemberton et al., 2000). Renal clearance is the dominant mechanism for eliminating NT-proBNP. NT-proBNP has a longer biologic half-time of approximately 120 min whereas the half-life of BNP is only 20 min (Pemberton et al., 2000; Hunt Grepin et al., 1997). Levels of BNP and NT-proBNP surge at birth, plateauing on days 3 - 4. This is followed by a steady fall to reach a constant level in infancy (Mir Grepin et al., 2002). This is due to the loss of placenta that has a role in clearance of natriuretic peptides (Mir Pemberton et al., 2003), kidney maturation, a rise in systemic vascular resistance and a fall in pulmonary pressures (Afif El-Khuffash and Molloy, 2007).

There are two available established methods for measuring BNP levels in clinical practice. In the first one, BNP is measured immediately after ethylenediamine tetra-acetic acid-anticoagulated whole blood sample acquisition with well-validated immunoassay (Triage; Biosite; San Diego, CA) not needing laboratory personnel. In the other way BNP is measured by Elisa in biochemistry laboratory (Maisel et al., 2002; Kaditis et al., 2006).

The human BNP gene is only 8 kb upstream of the ANP gene on chromosome 1p36.2. It consists of 3 exons and 2 introns.

Actions

Numerous studies found that the biological actions of BNP include kidneys, vascular vessels, endocrine and heart (Figure 2, Table 1). BNP increases glomelural filtration rate, renal plasma flow, urine flow rate, inhibits distal sodium reabsorption through antialdosterone properties and finally, causes natriuresis and diuresis (Richards et al., 1993; Li and Wang, 2000; Jensen et al., 1998).

BNP seems to have antiproliferative and antifibrotic actions in the heart and vascular tissues. Early studies indicated that BNP inhibits the proliferation of cardiac fibroblasts in culture, observation that was validated *in vivo* when mice lacking BNP were shown to display pressure-sensitive ventricular fibrosis (Ta Mura et al., 2000). In another study, mice with targeted disruption of BNP developed multifocal fibrotic lesions in the cardiac ventricle in the absence of systemic hypertension or ventricular hypertrophy. This observation together with the lusitropic effects of BNP infusion suggest that BNP acts as a cardiomyocyte-derived antifibrotic factor *in vivo* that may function as local regulator of ventricular remodelling (Ta Kone, 2001). The mechanism involved in the BNP-dependent regulation of fibroblasts is controversial (Takahashi et al., 2003; Kapoun et al., 2004). Evidence suggests that the cardiac fibrosis involves matrix metalloproteinases (MMPs); yet, it is observed that both ANP and BNP regulate MMP levels (Kapoun et al., 2004; Wang et al., 2003). In addition, BNP inhibits cardiac sympathetic nervous system activity (which is also involved in cardiac fibrosis) by reducing norepinephrine spillover, in low dose (Westerlind et al., 2004; Maisel, 2003).

In vessels BNP causes dilation (Clarkson et al., 1996; Van der et al., 1999; Van der et al., 2002) leading to blood pressure reduction and ventricular preload release. Consequently, the recombinant human BNP attenuates pulmonary capillary wedge pressure (PCWP) and mean pulmonary artery pressure in rest and during exercise (Zakynthinos et al., 2008; Valli et al., 1999; Clarkson et al., 1996).

C-type natriuretic peptide (CNP)

C-type natriuretic peptide, besides BNP, was also identified in porcine brain (Paul et al., 1987), where is the most highly expressed natriuretic peptide (Vesely et al., 20050. It is expressed in endothelial cells, chondrocytes and in the urogenital tract (Suga et al., 1992; Hagiwara et al., 1994). It is nearly nonexistent in cardiac tissue and it is not stored in granules (Hagiwara et al., 1994).

The gene encoding CNP is localized to human chromosome 2 between 2q24 and the 2q terminus (Nakayama, 2005) and contains two exons separated by an intron. Human proCNP contains 103 residues and is processed by furin to 53-amino acid peptide *in vitro* (Wu et al., 2003). In some tissues CNP-53 is cleaved to CNP-22 by an unknown extracellular enzyme (Tawaragi et al., 1990). The CNP-22 is thought to be the biological active peptide, although their tissue expression differs (Mattingly et al., 1994). CNP-22 is more abundant in human plasma (Stingo et al., 1992) and cerebral spinal fluid (Togashi et al., 1992), whereas CNP-53 is the major form in endothelial cells and in the brain. It looks alike ANP in its amino acid sequence, except for the Carboxy-terminal tail of ANP (Tawaragi et al., 1991). It binds preferentially to natriuretic receptor-B (NPR-B) (Figure 1 and 2).

Actions

CNP is thought to act through a paracrine mechanism (Ahluwalia et al., 2004). It seems to play a role in cardiovascular physiology. It has been noted that CNP reduces pulmonary hypertension. However, CNP plasma concentration increases minimally, if at all, in patients with congestive heart failure (Kalra et al., 2003). Although it suppresses aldosterone release (Igaki et al., 1998), unlike to the other natriuretic peptides, it has no significant natriuretic or diuretic effects (Hunt et al., 1994).

CNP induces vasorelaxation *in vivo*. It may also enhance the vasodilatory effects of ANP and BNP (Ahluwalia et al., 2004). It inhibits vascular smooth muscle proliferation and endothelial cell migration (de Lemos et al., 2003). Yet, CNP is likely to exert a potent anti-atherogenic influence on blood vessel walls similar to that of nitric oxide and prostacyclin (Ahluwalia and Hobbs, 2005).

Like other NPs, CNP also inhibits hypetrophy of cardiac myocytes and growth of fibroblasts (Tokudome et al., 2004) (Figure 2, Table 1); it prevents the remodelling following myocardial infarction (Soeki et al., 2005).

However, the most obvious physiological effect of CNP is to stimulate long bone growth (Figure 2, Table 1). It regulates many types of bone cells, with the chondrocyte being its major target. In a mouse osteoclast model, 1, 25-dihydroxyvitamin D3 stimulated CNP expression, cGMP and osteoclast bone resorptive activity. In osteoblasts, CNP increased the levels of differentiation markers like alkaline phosphatase and increased the mineralization of nodules (Hagiwara et al., 1996). In chondrocytes, CNP increased cGMP concentrations while in fetal mouse tibia cultures, CNP induced endochondrial ossification (Yasoda et al., 1998). Inactivating mutations in the genes coding for CNP (Chusho et al., 2001) or NPR-B (Berlin et al., 1993; Tsuji and Kunieda, 2005), cause dwarfism and early death in mice, whereas superphysiological levels of CNP cause skeletal overgrowth. No growth abnormalities are observed in any of these mutant animals at birth, suggesting that CNP only stimulates postpartum bone growth. Multiple putative loss of functional mutations in the gene encoding NPR-B were recently identified in human patients with the autosomal recessive disease, acromesomelic dysplasia, type Maroteaux (Bartels et al., 2004).

CNP expression may be stimulated or suppressed by several factors. Thus, it was found that CNP expression was stimulated *in vitro* by TNF-a [160], transforming growth factor-β (TGF-β) (Suga et al., 1992) and IL-1 (Koller et al., 1991; Suga et al., 1992), shear stress exerted on the endothelium wall (Ahluwalia and Hobbs, 2005) and suppressed by insulin.

Dendroaspis natriuretic peptide (DNP)

Dendroaspis natriuretic peptide (DNP) was isolated from the venom of Dendroaspis angusticeps, a green mamba snake (Schweitz et al., 1992). It contains a 17-amino acid disulfide ring structure similar to that in atrial, brain, and C-type natriuretic peptides. This sequence forms a loop structure that is considered to play an important role to the biological activity of the natriuretic peptides. No sequence homology was observed in the N- terminal parts of the molecules.

Schirger et al. demonstrated, for the first time, the presence of DNP-like peptide in normal human plasma and atrial myocardium and increased DNP-like immuno-reactivity (DNP-LI) in human CHF (Schrirger et al., 1999).

The gene for DNP has not yet been identified in the human genome (Margulies and Burnett, 2006).

Actions

When DNP was injected in rat strips, which had been precontracted with KCL, a rapid relaxation was observed (Schweitz et al., 1992). As a vasorelaxant, DNP was about as potent as ANP and much more potent than CNP. Thus, it is assumed that the vasorelaxing action of this peptide is mediated by NPR-A receptors. Yet, DNP stimulated guanylate cyclase in cultured aortic myocytes and in bovine aortic endothelial cells and it obstructed the binding of 125I-ANP to aortic myocytes, which are indirect indications for DNP action through NPR-A.

Finally, experimental studies showed that when recombinant DNP is administered exogenously in animals, it is involved in the regulation of blood volume and renal function (Lisy et al., 1999; Lisy et al., 2001).

Osteocrin/musclin

Two groups of investigators identified a peptide with limited similarities to natriuretic peptides. One group identified it primarily in muscle and named it musclin (Chusho et al., 2001), whereas the other group identified it primarily in bone (Thomas et al., 2003) and thus named it osteocrin.

Actions

Transgenic expression of osteocrin, under the bone specific collagen type I promoter, resulted in mice with elongated bones and marked kyphosis, which is similar to the phenotype of mice transgenically overexpressing CNP or lacking NPR-C (Suda et al., 1998). These data suggested that osteocrin increases local CNP levels in the growth plate by blocking binding to NPR-C.

Later on, Thomas et al verified that osteocrin binds with high affinity to NPR-C, but not to NPR-A or NPR-B, in a manner that is competitive with ANP. When NPR-A and NPR-C were expressed in the same cells, osteocrin increased ANP-dependent cGMP elevations, presumably by blocking NPR-C mediated ANP degradation (Thomas et al., 2004).

DIAGNOSTIC APPLICATIONS OF NATRIURETIC PEPTIDES

BNP increase in cardiac and non-cardiac diseases

Among NPs, only BNP is easily measured in plasma serum or blood (Zakynthinos et al., 2008). The fact that BNP levels had been found significantly elevated up to 200- and 300- fold in patients with CHF, led the in-vestigators to assess BNP initially in many cardiovascular diseases including CHF, and later in other diseases with no primary cardiovascular origin, as well (Mukoyama et al., 1991).

BNP in heart failure

As the diagnosis of heart failure is difficult, with both overdianosis and underdiagnosis occurring commonly in practice, BNP has been proposed as a significant test for assisting diagnosis.

Plasma BNP is closely correlated with left ventricular end-diastolic pressure, PCWP and diastolic pulmonary artery pressure in CHF (Haug et al., 1993; Kazanegra et al., 2001; Maeda et al., 1998). Yet, an inverse relationship between log BNP plasma levels and left ventricular ejection fraction (LVEF) was noted in an early prospective study (Davis et al., 2007). Since the alteration of BNP concentration is a result of a dynamic process, serial monitoring is superior to a single value of BNP (Li and Wang, 2000).

Karmpaliotis et al, tested the utility of BNP for dis-criminating Acute Respiratory Distress Syndrome (ARDS) versus cardiogenic pulmonary edema (CPE). Eighty ICU patients with acute hypoxemic respiratory failure and bilateral pulmonary infiltrates were enrolled. Median BNP was 325 pg/ml in acute lung injury/ARDS patients vs 1200 pg/ml in CPE patients. A cut point < 200 pg/ml provided specificity of 91% for ARDS while a cut point of >1200 pg/ml had a specificity of 92% for CPE. Therefore, BNP appears useful in excluding CPE and identifycing patients with a high probability of ARDS. Yet, high BNP levels were associated with mortality in patients with both ARDS and CPE. However, the correlation between BNP and pulmonary capillary wedge pressure was modest in this

(Mukoyama et al., 1991).

Regarding NT-proBNP, levels >450 pg/mL for patients <50 years of age and >900 pg/mL for patients >50 years of age are sensitive and specific for CHF (The Criteria Committee of the New York Heart Association, 1979). If the value is <300 mg/mL, heart failure is highly unlikely with a negative predictive value of 99% (The Criteria Committee of the New York Heart Association, 1979). However, in the middle ranges, the predictive accuracy is less (grey zone), resulting in over or under- diagnosis in the less typical patients (Jaffe et al., 2006).

Plasma BNP levels are elevated not only in systolic but in diastolic heart failure, as well. BNP levels are closely correlated to the severity of diastolic dysfunction, provided the systolic function is preserved (Maisel et al., 2003; Lubien et al., 2002). Plasma levels were found to correlate with echocardiographic markers of diastolic left ventricular function (Lubien et al., 2002). However, BNP was unable to accurately differentiate preserved systolic left ventricular function among heart failure patients, although plasma levels were lower in diastolic compared with systolic heart failure, due to significant values' overlap (Maisel et al., 2003).

The underlying cause of the cardiac failure may modify the relationship between plasma levels and severity in some cases, but not to an extent that would impact on clinical judgment (Sullivan et al., 2005), that is BNP levels may be more markedly elevated in obstructive, as compared to nonobstructive hypertrophic cardiomyopathy (Yoshibayashi et al., 1993).

The routine use of plasma BNP decreased hospitalization rates and length of stay in the hospital compared with 'usual care' and decreased the costs of treatment without having any significant impact on 30-day mortality rate (Morrison et al., 2002). Moreover, it seems that plasma BNP measurement in acute settings is a better indicator of heart failure severity compared with clinical assessment alone (Maisel et al., 2004). It is plausible that plasma BNP levels may complement the information obtained from patient history, physical examination, and chest radiography in the emergency.

However, the utility of plasma BNP seems limited when used to identify asymptomatic individuals with preclinical heart failure. Sensitivity of plasma BNP for detecting asymptomatic left ventricular systolic dysfunction (mild or median systolic impairment) was modest in two large community-based investigations (Vasan et al., 2002; Redfield et al., 2004). Nevertheless, plasma BNP provided improved discrimination, when it was used to screen for asymptomatic individuals with severe left ventricular systolic dysfunction (Left Ventricular Ejection Fraction, LVEF <30%) (McDonagh et al., 2003).

BNP concentrations may decrease in patients with decompansated heart failure after aggressive treatment with diuretics, vasodilators, angiotensin converting enzyme (ACE) inhibitors, angiotensin-receptor blockers and aldosterone antagonists (Maisel et al., 2004; Vasan et al., 2002). When evaluating treatment regimens, a decreasing BNP level in a patient being treated for CHF appears to indicate improvement in the patient's condition, while a rising level may demonstrate the need for more aggressive or different treatment strategies (Peacock and Freda, 2003). However, the change in response to therapy is less than anticipated regarding the short half-lives for BNP and NT-proBNP (20 and 120 min, respectively) and often less than the biological variability, suggesting that the natriuretic peptide system itself may need some time to autoregulate (Zakynthinos et al., 2008; Miller et al., 2005).

BNP in other cardiovascular diseases than left heart failure

Plasma BNP has been reported to be of potential use in a number of other clinical settings antedating or associated with heart failure. Therefore, plasma BNP may perform better when used to screen for a wide array of cardiovascular disorders (White, 2005).

BNP has a recognized role in cardiac ischemia. In patients with chronic stable angina, the BNP level was correlated with the size of the ischemic area (Tateishi et al., 2000; Kyriakides et al., 2000). In patients with unstable angina BNP level was higher than that in patients with stable angina or in healthy patients (Kikuta et al., 1996). An elevated BNP level 48 h after myocardial infarction appears to be a strong predictor of death or the reoccurrence of heart failure within 1 year (Kikuta et al., 1996).

In patients with chronic right ventricular overload due to primary or thromboembolic pulmonary hypertension, BNP level has been shown to increase depending on the extent of right ventricular dysfunction (Nagaya et al., 1998). Acute right ventricular overload following pulmonary embolism can also lead to BNP release (Kucher and Goldhaber, 2003), and the degree of BNP elevation is predictive of the occurrence of right ventricular failure in this setting. Cutoff levels of 50 pg/ml for BNP (Adachi et al., 1997) and 500 pg/ml for NT-proBNP had a negative predictive value of 97% for adverse clinical events in acute pulmonary embolism (Incalzi et al., 2002).

Chronic obstructive pulmonary disease is often difficult to differentiate with CHF in the emergency department (Incalzi et al., 2002); yet, CHF is underdiagnosed in patients with COPD as they can coexist in the same patient (Gan et al., 2000). In 42 patients with an acute COPD exacerbation, including 11 with previous although not current CHF, BNP levels were low (54 ± 71 pg/ml) (Davis et al., 2007). On the other hand, 54 other patients with previous COPD but current decompensated CHF had higher BNP levels (734 ± 764 pg/ml).

Plasma BNP seems to increase during sleep in adult patients with obstructive sleep apnoea, probably due to intermittent right or/and left heart dysfunction on apneas.

Kita et al. (1998) recorded increasing BNP levels in the second half of sleep time (2:00 - 6:00 am) that was correlated with average apnoea duration. Recently, we found that children with apnoea-hypopnea index (AHI) ≥5/h had a four-times higher risk for nocturnal increase in BNP (log-transformed morning to evening BNP ratio) >0.15 compared to subjects with AHI<5/h (Kaditis et al., 2006).

BNP elevation has been also reported in many other cardiac conditions including valvular heart disease and its repair (Tharaux et al., 1994). The presence of symptoms due to aortic stenosis is associated with higher BNP and NT-pro BNP levels (Gerber et al., 20030.

Infectious, inflammatory and metabolic insults to the heart can also induce an increase in BNP. Elevation has been reported due to diverse aetiologies including Chagas Disease (Ribeiro et al., 2002), Kawasaki Disease (Kawamura and Wago, 20020, viral myocarditis (Nakao, 1992), Duchenne muscular dystrophy and its carrier state (Adachi et al., 1997) and myocardial cytotoxicity during chemotherapy (Hayakawa et al., 2001).

Finally, a recent investigation from the Framingham Heart Study reported that increased plasma BNP predicted a wide range of cardiovascular events, including heart failure, atrial fibrillation, stroke, transient ischemic attack, and death (Wang et al., 2004). In another report, plasma BNP was used to screen for the presence vs. absence of a spectrum of cardiovascular conditions ranging from arrhythmias and ventricular hypertrophy to congenital heart disease. When used for such screening purposes, the sensitivity and specificity of plasma BNP were 90% and 96%, respectively (Nakamura et al., 2002).

BNP in sepsis and other non-cardiovascular critical diseases

BNP elevation in patients with sepsis can be considerably high, even though a cardiac disorder is not obvious. A small retrospective analysis revealed that BNP levels in patients with sepsis and preserved systolic left ventricular function can be as high as that in patients admitted to the hospital because of CHF, due to severely impaired systolic left ventricular function. Six of eight patients with sepsis and five of eight patients with CHF presented a BNP level of > 1.000 pg/mL (Maeder et al., 2005). Accordingly, BNP does not correlate with left-sided filling pressures in sepsis (Tung et al., 2004) as opposed to previous studies in patients with CHF, demonstrating a close relationship between BNP levels and left-sided filling pressures (Haug et al., 1993; Kazanegra et al., 2001; Maeda et al., 1998).

Charpentier et al found higher levels of BNP in septic patients with impaired than in those with preserved systolic ventricular function at days 1 - 4 during their ICU stay. In addition, on days 2 and 3, BNP levels were higher in non-survivors compared to survivors. A BNP cutoff of > 190 pg/ml could differentiate survivors from non-survivors with a sensitivity of 70% and a specificity of 67% (Maeder et al., 2006). Similarly, Post et al found that plasma BNP concentration on day 5 may be used as a prognostic marker to identify patients with an elevated risk for an adverse outcome (Post et al., 2008).

As for NTproBNP levels, one case series demonstrated elevations of > 35.000 pg/mL in septic patients (Chua and Kang-Hoe, 2004). Roch at al evaluated NT-pro-BNP in 39 patients with septic shock who receiving mechanical ventilation and found higher median maximal NT-pro-BNP levels in nonsurvivors compared to survivors (Maeder et al., 2006).

Yet, Kotanidou at al, found raised levels of plasma NT-pro BNP in non cardiac, mixed, critically ill mechanically ventilated patients; nonsurvivors had consistently higher levels than survivors. Yet, elevated admission NT-pro-BNP levels represented an independent predictor for poor ICU outcome (Kotanidou et al., 2009).

Despite BNP increase in sepsis, other non-cardiovascular critical diseases perform high BNP levels, as well. Liver cirrhosis may be associated with mildly elevated BNP and NT-proBNP levels probably due to cirrhotic cardiomyopathy (Henriksen et al., 2003).

Brain disorders or brain injury affect BNP levels in the critical care settings: Plasma NT-proBNP levels are elevated in acute stroke and predict poststroke mortality (Makikallio et al., 2005). Release of BNP from the brain, or more probably from the heart, in subarachnoid haemorrhage is associated with more brain oedema, cerebral vasospasm, and poorer outcome (McGirt et al., 2004) and is a possible cause of cerebral salt wasting.

Hyperthyroidism increases while hypothyroidism decreases BNP and NTproBNP levels (Liang et al., 2003).

Finally, anaemia independently predicts elevated BNP levels (Wold Knudsen et al., 2005) (Table 2).

BNP in various populations

Despite diseases with high plasma BNP levels, there are also physiological factors associated with increased values. These factors include increasing age, female sex, and impaired renal function (McCullough et al., 2003) (Table 2).

The increase of BNP levels seen with advancing age is to be expected on the basis of a physiological decline in cardiac function (McLean et al., 2003). Consistent with the increase associated with female gender, hormone replacement causes an elevation of BNP (Maffei et al., 2001). Exercise has little effect on BNP, but BNP increases that occur following extreme exertion may reflect mild myocardial damage (Ohba et al., 2001). However, the ventricular Enlargement, which is consistent with elite training, does not appear to increase BNP (Almeida et al., 2002).

NPs are elevated in chronic renal failure patients. BNP was higher in those receiving haemodialysis, but the level

Table 2. Causes of raised and lowered levels of naturetic pepetides.

Situations	Causes
Raised levels of brain natriuretic peptide in plasma	1) Left ventricular dysfunction (systolic or diastolic); 2)Hypertension (ventricular hypertrophy); 3) Myocardial infarction; 4) Angina (unstable and stable); 5) Myocarditis; 6) Chagas disease; 7) Kawasaki disease; 8) Primary pulmonary hypertension; 9) Pulmonary embolism; 10) Chronic obstructive pulmonary disease associated with pulmonary hypertension; 11) Acute respiratory distress syndrome; 12) Congenital heart diseases with pulmonary hypertension; 13) Arrhythmias; 14) Subarachnoid haemorrhage, transient ischemic attack, stroke; 15) Increasing age; 16) Renal failure; 17) Sepsis, septic shock; 18) Liver cirrhosis; 19) Hyperthyroidism; 20) Anaemia; 21) Valvular Heart disease; 22) Chronic renal failure; 23) Immunosuppressive treatment after liver tansplantation; 24) Therapy with β-blockade; 25) Obstructive sleep apnea syndrome.
Brain natriuretic peptide levels lower than expected values	1) Obesity (Body mass index > 30 kg/m^2) (increased clearance in adipose tissue); 2) Acute pulmonary oedema (lag in increase); 3) Acute mitral regurgitation; 4) Mitral stenosis/atrial myxoma (preserved left ventricular function); 5) Hypothyroidism
Raised levels of αtrial natriuretic peptide in plasma	1) Congestive heart failure; 2) Chronic renal failure; 3) Myocardial infarction; 4) Pulmonary hypertension; 5) Cirrhosis; 6) Subarachnoid hemorrhage
Levels of of ANP lower than expected values	1) ANP decrease significantly during hemodialysis treatment but increase again during the interdialytic interval

decreased in proportion to volume reduction following the procedure. Forfia et al reported fourfold greater BNP levels in patients with impaired renal function (creatinine clearance < 60 ml/min) compared to patients with normal renal function, despite similar PCWP values, cardiac index, and LVEF.

Mekontso-Dessap et al studied the value of BNP during weaning process in one hundred and two patients in a medical intensive care unit of a university hospital. They found that baseline plasma BNP levels before the first weaning attempt are higher in patients with subsequent weaning failure and correlates to weaning duration; therefore, high BNP level could predict weaning failure (Mekontso-Dessap et al., 2006).

Dernellis and Panaretou, (2006) evaluated the predictive value of BNP for assessment of cardiac risk in 1590 pateints before non-cardiac surgery. They found that BNP is an independent predictor of postoperative cardiac events. Levels of BNP>189pg/ml identified patients at highest risk. Specifically, an elevated pre-operative plasma BNP level is a strong and independent predictor of postoperative atrial fibrillation (AF). Therefore, this finding may have important implications for identifying patients at higher risk of postop AF who could receive prophylactic antiarrhythmic or b-blocker therapy (Wazni et al., 2004).

Plasma BNP levels in heart failure patients may also vary according to their body mass index. Obese patients with heart failure tend to have lower plasma natriuretic peptide levels, whereas patients with lower body mass index (including but not limited to those with cardiac cachexia) have higher levels (Mehra et al., 2004) (Table 2).

THERAPEUTIC APPLICATIONS OF NATRIURETIC PEPTIDES

Acute renal failure

Acute Renal Failure (ARF) develops in 2 - 5% of all patients admitted to tertiary care hospitals (Woolf et al., 1989) and has a very poor prognosis, with mortality, remaining in the 40 - 80% range in oliguric ARF (Woolf et

al., 1989; Hou et al., 1983).

Atrial natriuretic peptide

In animals, the infusion of ANP led to an improvement in renal failure that did not last much and depended on whether ANP was given intravenously or directly upon into the renal artery (Shaw et al., 1987; Neumayer et al., 1989). However, in humans, ANP is considered more harmful than helpful with respect to the treatment of ARF. Its usefulness is hampered by its very short duration of action and by the hypotension that it develops (Shaw et al., 1987; Neumayer et al., 1989). ANP has also been investigated in humans with chronic renal failure to determine whether it could prevent radiocontrast-induced nephropathy and ARF. Unfortunately, no beneficial effects were identified (Kurnik et al., 1998).

Vessel dilator

Although not yet fully investigated, vessel dilator seems to present promising beneficial effects in the treatment of ARF. It was found that vessel dilator decreased creatinine and mortality rate when it was infused in animals with ARF [236]. Vessel dilator (0.3 μg/kg per min via intraperitoneal pump) decreased serum creatinine from 8.2 ± 0.5 - 0.98 ± 0.12 mg/dl in ARF animals (where ARF was established for 2 days after vascular clamping, before vessel dilator was given). Moreover, mortality decreased to 14% with vessel dilator (compared to 88% without vessel dilator) at day 6 of ARF (Clark et al., 2000).

Long-acting natriuretic, kaliuretic peptides and brain natriuretic peptide

Neither of them has been investigated for their potential effects in acute or chronic renal failure.

Congestive heart failure - Myocardial infarction

NPs, as already mentioned, have actions of diuresis, natriuresis, vasodilation, and suppression of aldosterone and exert a significant role in regulating blood pressure and blood volume. Therefore, NPs have been tested in various cardiovascular diseases including CHF which is the leading cause of hospital admissions in persons 65 years of age or older.

Atrial natriuretic peptide

The actions of ANP have led to efforts to use this peptide hormone in the treatment of various cardiovascular disorders such as hypertension, CHF and myocardial infarction (Hayashi et al., 2001). However, the peptide nature of ANP and its rapid elimination from the circulation limited its suitability as a drug. More promising is the development of long-acting ANP analogues and inhibitors of ANP degradation.

Synthetic atrial natriuretic peptide is clinically known as anaritide (Vesely, 2006). Initially, a dose of 50 μg of anaritide was given bolus and was followed by a 45 min maintenance infusion at 6.25 micrograms/min. It was shown that i.v. infusion of αnaritide in healthy men resulted in increase in glomelural filtration rate (GFR), a decrease in systemic blood pressure and induced natriuresis and diuresis (Weidmann et al., 1986). In patients with CHF the i.v. infusion of ANP resulted also in suppression of aldosterone and decrease in systemic blood pressure and PCWP. However renal response was attenuated compared to normals (Giles et al., 1991). There are several explanations for this resistance to anaritide such as the downregulation of NP receptors in the kidney, reduced production or increased degradation of cGMP or enhanced activity of functional antagonists.

The efficacy of anaritide was evaluated in a 6-year prospective open-label registry of 3777 patients with acute HF (51% Killip class III or IV) who were treated with a median dose of 0,085 $kg^{-1}min^{-1}$ (median duration 65 h). It was reported that 82% of patients improved clinically (Suwa et al., 2005).

Finally, ANP may prove a significant adjunctive therapy to acute myocardial infarction. Investigators comparing the effects of ANP to nitroglycerin on left ventricular remodeling after a first anterior acute myocardial infarction noted that the improvement of LVEF was greater in the ANP group; yet, left ventricular enlargement was prevented only by ANP infusion and not by nitroglycerin administration (Kuga et al., 2003).

Moreover, ANP infusion showed to prevent not only left ventricular remodelling but also arrhythmias in patients with a first acute myocardial infarction (Kuga et al., 2003).

Urodilatin

The effect of Urodilatin has been evaluated in CHF. Mitrovic et al. (2005) investigated the influence of URO infusion in patients with decompensated CHF. Twenty-four patients were included in the study. A significant reduction in PCWP, right arterial pressure (RAP) and N-terminal pro-BNP was observed, compared to the baseline. The SIRIUS-II (Safety and efficacy of an Intravenous placebo controlled Randomized Infusion of Ularitide in a prospective double-blind Study in patients with symptomatic decompensated CHF) trial evaluated URO in 221 HF patients with dyspnea at rest or with minimal exertion. Patients were randomized to placebo or URO continuous infusion at 7.5, 15, 30 ng Kg^{-1} min^{-1} for 24 h. Forty percent of patients in each of the URO-treated groups showed improvement. On the contrary, only 25%

of patients in the placebo group showed improvement. The decrease in PCWP was 11 mmHg in patients treated with URO 30 ng Kg^{-1} min^{-1} versus 4 mm Hg in the placebo group. Mean systolic BP decreased by up to 15 mmHg without change in heart rate (URO 15 or 30 ng Kg^{-1} min^{-1}). Serum creatinine increased to a similar extent in the placebo group and two of the URO-treated groups (7.5 and 30 ng Kg^{-1} min^{-1}). Death occurred in 7 placebo-treated and 5 URO-treated patients, indicating a probable role of URO in CHF therapy.

Vessel dilator

The effects of vessel dilator in CHF have significant similarities with ANP and URO (Vesely et al., 1998).

Vessel dilator increased 5-hold both urinary flow and sodium excretion; yet, it decreased systemic vascular resistance and systemic blood pressure which resulted in improvement in both afterload and preload and improved cardiac output by 34% and cardiac index by 35% in CHF (Vesely et al., 1994).

It seems that vessel dilator may prove as the natriuretic peptide with the most significant natriuretic and diuretic effects of all ANPs. Interestingly, no side effects with the administration of vessel dilator were observed [59-61].

Long-acting natriuretic peptide

The administration of Long-acting NP in humans with CHF enhanced urine flow fourfold. Additionally, sodium excretion was increased fourfold in the first 20 min of its infusion (in contrast to healthy individuals that did not affect sodium excretion). Moreover, it increased the urinary excretion of K+ and the fractional excretion (FE) of K+ and doubled FENA (Vesely et al., 1994).

Brain natriuretic peptide

BNP, and especially its synthetic analogue Nesiritide, is the most investigated among all NPs. Nesiritide, a purified preparation of human BNP, is manufactured from *Escherichia coli* using recombinant DNA techonology (Keating and Goa, 2003). Nesiritide exhibits similar physiologic actions as endogenous BNP (Keating and Goa, 2003). The distribution half–life and the mean terminal elimination half-life of nesiritide are 2 and 18 min respectively; its clearance is achieved through 3 mechanisms that include binding to the NPR-C, degradation by neutral endopeptidase and renal filtration, as endogenous BNP (Keating and Goa, 2003) (Figure 1).

Nesiritide has been shown to cause vasodilation accompanied with increases in natriuresis and diuresis, as well as suppression of aldosterone and endothelin in patients with acute HF. Nesiritide has also shown to cause decrease in PCWP, an increase in cardiac output (Heart Failure Society of America (HFSA), 2006), a reduction in LV filling pressure and an improvement in heamodynamic function, and finally a significant improvevement of the clinical status in patients with decompansated CHF (Fonarow, 2003). Nesiritide, as an intravenous therapy for acute decompansated HF, is in use in the United States since 2001.

Unfortunately, the spread use of nesiritide has recently become under scrutiny due to the observed risk of renal dysfunction and mortality in patients undergoing BNP treatment (Aaranson et al., 2007). The reason for this type of side-effects could be a relatively increased dose of BNP used. The production and secretion of ANP and BNP are very tightly regulated in our body; as previously mentioned, increased levels of natriuretic peptides compensate for decompnsated heart failure. In CHF, further increase of natriuretic peptide levels, by exogenous administration, may overcome the dominant effects of vasodilative and antidiuretic hormones. A continuous infusion of relatively excessive amount of BNP could probably lead to the deterioration of renal failure and the decrease in the blood pressure due to intravascular volume lessening. Therefore, the side effects of nesiritide may be due to an inappropriate use (Aaranson et al., 2007).

Finally, further prospective studies are necessary to answer the controversy about the safety of this drug. The results of FUSION trial will probably enlighten whether the worsening of renal function is in fact a signal for adverse outcome (Yancy et al., 2007).

C-type natriuretic peptide

Recent evidence indicates that it can prevent cardiac remodeling after myocardial infarction in rats (Soeki et al., 2005). Yet, CNP is likely to exert a potent antiatherogenic influence on blood vessel walls, since CNP seems to prevent smooth muscle proliferation, leukocyte recruitment and platelet aggregation (Ahluwalia and Hobbs, 2005). However the therapeutic uses of CNP in cardiovascular disease have not yet been extensively explored.

Cancer

Recently, the natriuretic peptides have been evaluated in cancer cells (Vesely et al., 2003; Saba et al., 2005). Pancreatic adenocarcinoma was the first cancer studied both *in vitro* and *in vivo*. Vessel dilator, LANP, kaliuretic peptide and ANP not only decreased the number of human pancreatic adenocarcinoma cells in culture by 65, 47, 37 and 34% respectively, but inhibited adenocarcinoma cells proliferation for the 3 consecutive days, as well (Vesely et al., 2003). *In vivo*, the effects of peptide hormones as anticancer agents were even more impressive. Vessel dilator, when was infused for 14 days, stopped completely the growth of human pancreatic

adenocarcinomas in athymic mice accompanied by a decrease in tumour volume (Vesely et al., 2004). Immunocytochemical evaluation after the removal of the human pancreatic adenocarcinomas revealed that all ANP peptides (vessel dilator, LANP, kaliuretic peptide and ANP) were localized to the nucleus and cytoplasm of the cancer cells and to the endothelium of the capillaries growing in these tumours. Therefore, probably, they directly inhibited DNA synthesis (Saba et al., 2005).

Growth-promoting peptides, such as the extracellular-signal regulated kinase (ERK)-1 have been shown to move from the plasma membrane to the nucleus causing proliferation; recently, it was shown that a slightly modified kaliuretic peptide could decrease the activation of ERK-1. Therefore, these peptide hormones may inhibit the growth of cancer cells not only by directly inhibitng DNA synthesis in the nucleus of the cancer cell, but by decreasing the activation of growth-promoting substances, that promote the cancer cells growth, as well (Mohapatra et al., 2004). Yet, as already mentioned in the actions of ANP, ANP has been reported to attenuate the expression of VEGF, which has been extensively implicated in tumor angiogenesis.

Vessel dilator, kaliuretic peptide and ANP caused a similar significant decrease in the number of breast adenocarcinoma and small cell lung cancer. However, BNP and CNP had no significant effects in any of these cancer cells, not only at the usual concentration of 1 µmol/lt, but even when concentration was 10-fold increased (Saba et al., 2005; Vesely et al., 2005).

Finally, it seems that NPs, except BNP and CNP, have anticancer effects; till now vessel dilator has been proven to possess the strongest anticancer properties (Saba et al., 2005; Vesely et al., 2004; Vesely et al., 2005).

Conclusion

It seems that NPs play important roles in the regulation of cardiovascular, renal, and skeletal homeostasis. Accordingly, dysregulation of the NP signaling systems appears to contribute to the pathophysiology of clinical disorders. As BNP plasma levels are highly increased mainly in HF, measurement of plasma concentrations heve been used to diagnose, assess severity and prognose the development of various cardiovascular diseases. Anaritide and nesiritide are being used, last years, in the management of acute heart failure. Despite significant advances in our knowledge in the field of NPs, much work remains to be done in refining current treatment strategies, in minimizing side effects, and in identifying opportunities in drug discovery.

LEARNING POINTS

1. Natriuretic peptides (mainly, atrial natriuretic peptide-ANP, B type natriuretic peptide-BNP and C type natriuretic peptide-CNP) are protean compounds with currently significant diagnostic applications (BNP) and probably noteworthy future treatment options in congestive heart failure, cancer, etc.
2. ANPs and BNP peptides bind to Natriuretic Peptide Receptor A (NPR-A) and CNP to NPR-B, in order to exert their biological effects. All NPs bind to a third receptor, NPR-C, which acts to clear them from the circulation.
3. Activation of NPR-A mediates natriuresis and inhibition of rennin-aldosterone system, as well as vasorelaxant, antifibrotic, anti-hypertrophic and anti-inflammatory effects. NPR-B activation is mainly responsible for long bone growth.
4. Among NPs, only BNP is easily measured in plasma, serum or blood. A plasma BNP cutoff value less than 100 pg/ml is a widely cited threshold with high diagnostic accuracy for distinguishing acute heart failure from other causes of shortness of breath. BNP levels below 100 pg/ml indicate that heart failure is unlikely; levels in the range of 100–500 pg/ml suggest an intermediate probability of heart failure (grey zone) while values exceeding 500 pg/ml are consistent with a high likelihood of heart failure.
5. BNP elevation in patients with sepsis and preserved systolic left ventricular function can be considerably high, exceeding 500 pg/ml, reaching the levels of acute heart failure.

REFERENCES

Aaranson KD, Sackner-Bernstein JD (2006) Risk of death associated with nesiritide in patients with acutely decompensated heart failure. JAMA; 296:1465-1466.

Adachi K, Kawai H, Saito M, Naruo T, Kimura C, Mine H (1997). Plasma levels of brain natriuretic peptide as an index for evaluation of cardiac function in female gene carriers of Duchenne muscular dystrophy. Int. Med. 36:497-500.

Afif El-Khuffash Eleanor J Molloy (2007). Are B-type natriuretic peptide (BNP) and Nterminal- pro-BNP useful in neonates? Arch. Dis. Child. Fetal Neonatal Ed., 92: 320-324.

Ahluwalia A, Hobbs AJ (2005). Endothelium-derived C-type natriuretic peptide: more than just a hyperpolarizing factor. Trends Pharmacol. Sci., 26:162-167.

Ahluwalia A, MacAllister RJ, Hobbs AJ (2004). Vascular actions of natriuretic peptides. Cyclic GMP-dependent and –independent mechanisms. Basic Res. Cardiol. 9:83-89.

Almeida SS, Azevedo A, Castro A, Frioes F, Freitas J, Ferreira A (2002). B-type natriuretic peptide is related to left ventricular mass in hypertensive patients but not in athletes. Cardiology 98:113–115.

Anand-Srivastava MB, Trachte GJ. (1993). Atrial natriuretic factor receptors and signal transduction mechanisms Pharmacol. Rev., 45:455-497.

Antunes-Rodrigues J, Mc Cann SM, Rogers LC, Samson WK (1985). Atrial natiuretic factor inhibits dehydration-and angiotensin II-induced water intake in the conscious, unrestrained rat. Proc. Natl. Acad. Sci., 82:8720.

Baron DA, Lofton CE, Newman WH, Currie MG (1989). Atriopeptin inhibition of thrombin-mediated changes in the morphology and permeability of endothelial monolayers. Proc. Natl. Acad. Sci. USA., 86:3394-3398.

Bartels CF, Bukulmez H, Padayatti P (2004).Mutations in the transmembrane natriuretic peptide receptor NPR-B impair skeletal

growth and cause acromesomelic dysplasia, type Maroteaux. Am. J. Hum. Genet., 75:27-34.
Bennett BD, Bennett GL, Vitangcol RV, Jewett JR, Burnier J, Henzel W, Lowe DG (1991). Extracellular domain-IgG fusion proteins for three human natriuretic peptide receptors. Hormone pharmacology and application to solid phase screening of synthetic peptide antisera. J. Biol. Chem., 266:23060-7.
Berlin I, Lechat P, Deray G (1993). Beta-adrenoceptor blockade potentiates acute exercise-induced release of atrial natriuretic peptide by increasing atrial diameter in normotensive healthy subjects. Eur. J. Clin. Pharmacol., 44:127-133.
Bestle MH, Olsen NV, Christensen P, Jensen BV, Bie P (1999). Cardiovascular, endocrine, and renal effects of urodilatin in normal humans. Am. J. Physiol., 276:684-695.
Blackburn RE, Samson WK, Fulton RJ, Stricker EM, Verbalis JG (1995). Central oxytocin and ANP receptors mediate osmotic inhibition of salt appetite in rats. Am. J. Physiol., 269:245-251.
Brandt RR, Heublein DM, Mattingly MT, Pittelkow MR, Burnett JC (1995). Jr. Presence and secretion of atrial natriuretic peptide from cultured human aortic endothelial cells. Am. J. Physiol., 268:921-925.
Burrell LM, Lambert HJ, Baylis PH (1991). Effect of atrial natriuretic peptide on thirst and arginine vasopressin release in humans. Am. J. Physiol., 260:475-478.
Calderone A, Thaik CM, Takahashi N, Chang DL, Colucci WS (1998). Nitric oxide, atrial natriuretic peptide, and cyclic GMP inhibit the growth-promoting effects of norepinephrine in cardiac myocytes and fibroblasts. J. Clin. Invest., 101:812-818.
Candace YW, Lee John C (2007). Burnett Jr. Natriuretic peptides and therapeutic Applications. Heart Fail Rev., 12:131-142.
Cao L, Wu J, Gardner DG. (1995). Atrial natriuretic peptide suppresses the transcription of its guanylyl cyclase-linked receptor. J. Biol. Chem., 270:24891–24897.
Carstens J, Jensen KT, Pedersen EB (1998). Metabolism and action of urodilatin infusion in healthy volunteers.Clin. Pharmacol. Ther., 64:73-86.
Chang MS, Lowe DG, Lewis M, Hellmiss R, Chen E, Goeddel DV. Differential activation by atrial and brain natriuretic peptides of two different receptor guanylate cyclases. Nature 1989;34:68–72.
Chartier L, Schiffrin EL (1986). Atrial natriuretic peptide inhibits the stimulation of aldosterone secretion by ACTH *in vitro* and *in vivo*. Proc. Soc. Exp. Biol. Med., 182:132-136.
Chinkers M, Singh S, Garbers DL (1991). Adenine nucleotides are required for activation of rat atrial natriuretic peptide receptor/guanylyl cyclase expressed in a baculovirus system. J. Biol. Chem., 266:4088-4093.
Chrisman TD, Schulz S, Potter LR, Garbers DL (1993).Seminal plasma factors that cause large elevations in cellular cyclic GMP are C-type natriuretic peptides. J. Biol. Chem., 268:3698-3703.
Chua G, Kang-Hoe L (2004). Marked elevations in N-terminal brain natriuretic peptide levels in septic shock. Crit. Care, 8:248-250.
Chun TH, Itoh H, Ogawa Y, Tamura N, Takaya K, Igaki T, Yamashita J, Doi K, Inoue M, Masatsugu K, Korenaga R, Ando J, Nakao K (1997). Shear stress augments expression of C-type natriuretic peptide and adrenomedullin. Hypertension, 29:1296–1302.
Chusho H, Tamura N, Ogawa Y, Yasoda A, Suda M, Miyazawa T, Nakamura K, Nakao K, Kurihara T, Komatsu Y, Itoh H, Tanaka K, Saito Y, Katsuki M (2001).Dwarfism and early death in mice lacking C-type natriuretic peptide. Proc Natl Acad Sci USA. 98: 4016-4021.
Clark LC, Farghaly H, Saba SR, Vesely DL (2000). Amelioration with vessel dilator of acute tubular necrosis and renal failure established for two days. Am. J. Physiol., 278:1555-1564.
Clarkson PB, Wheeldon NM, MacFadyen RJ, Pringle SD, MacDonald TM (1996). Effects of brain natriuretic peptide on exercise hemodynamics and neurohormones in isolated diastolic heart failure. Circulation, 93:2037- 2042.
Clinical trials update from the European Society of Cardiology meeting (2005). CARE-HF extension study, ESSENTIAL, CIBIS-III, S-ICD, ISSUE-2, STRIDE- 2, SOFA, IMAGINE, PREAMI, SIRIUS-II and ACTIVE. SIRIUS-II (Safety and efficacy of an Intravenous placebo controlled Randomised Infusion of Ularitide in a prospective double-blind Study in patients with symptomatic decompensated chronic heart failure). Eur. J. Heart Fail., 7:1070-1075.
Davis M, Espiner E, Richards G, Billings J, Town I, Neill A (1994). Plasma brain natriuretic peptide in assessment of acute dyspnoea. Lancet, 343:440–444.
de Bold AJ, Borenstein HB, Veress AT, Sonnenberg H (1981). A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. Life Sci., 28:89-994.
de Lemos JA, McGuire DK, Drazner MH (2003). B-type natriuretic peptide in cardiovascular disease. Lancet, 362:316-322.
Dernellis J, Panaretou M (2006). Assessment of cardiac risk before non-cardiac surgery:brain natriuretic peptide in 1590 patients. Heart, 92:1645-1650.
Dietz JR, Scott DY, Landon CS, Nazian SJ (2001). Evidence supporting a physiological role for proANP-(1-30) in the regulation of renal excretion Am. J. Physiol. Regul. Integr. Comp. Physiol., 280:R1510-7.
Dorner GT, Selenko N, Kral T, Schmetterer L, Eichler HG, Wolzt M (1998). Hemodynamic effects of continuous urodilatin infusion: a dose-finding study. Clin. Pharmacol.Ther., 64: 322-330.
Duda T, Goraczniak RM, Sitaramayya A, Sharma RK (1993). Cloning and expression of an ATP-regulated human retina C-type natriuretic factor receptor guanylate cyclase. Biochem., 32:1391-1395.
Elferink JG, De Koster BM (1995). Atrial natriuretic factor stimulates migration by human neutrophils. Eur. J. Pharmacol., 288:335-340.
Felmeden DC, Blann AD, Lip GY (2003). Angiogenesis: basic pathophysiology and implications for disease. Eur. Heart J., 24:586-603.
Fethiere J, Graihle R, Larose L, Babinski K, Ong H, De Lean A (1993). Distribution and regulation of natriuretic factor-RIC receptor subtypes in mammalian cell lines. Mol. Cell Biochem., 124:11-16
Fonarow GC (2003) B-type natriuretic peptide: spectrum of application. Nesiritide (recombinant BNP) for heart failure. Heart Fail. Rev., 8:321–325.
Fuller F, Porter JG, Arfsten AE, Miller J, Schilling JW, Scarborough RM, Lewicki JA, Schenk DB. (1988). Atrial natriuretic peptide clearance receptor. Complete sequence and functional expression of cDNA clones. J. Biol. Chem., 263: 9395-9401.
Galitzky J, Sengene`s C, Thalamas C (2001). The lipid-mobilizing effect of atrial natriuretic peptide is unrelated to sympathetic nervous system activation or obesity in young men. Lipid Res., 42:536-544.
Gan SC, Beaver SK, Houck PM (2000).Treatment of acute myocardial infarction and 30-day mortality among women and men. N. Engl. J. Med., 343:08–15.
Gerber IL, Stewart RA, Legget ME, West TM, French RL, Sutton TM (2003). Increased plasma natriuretic peptide levels reflect symptom onset in aortic stenosis. Circulation, 107:1884–1890.
Giles TD, Quiroz AC, Roffidal LE, Marder H, Sander GE (1991). Prolonged hemodynamic benefits from a high-dose bolus injection of human atrial natriuretic factor in congestive heart failure. Clin. Pharmacol. Ther., 50:557– 563.
Grepin C, Dagnino L, Robitaille L, Haberstroh L, Antakly T, Nemer M (1994). A hormone-encoding gene identifies a pathway for cardiac but not skeletal muscle gene transcription. Mol. Cell Biol., 14:3115-129.
Gunning ME, Brady HR, Otuechere G, Brenner BM, Ziedel ML (1992). Atrial natriuretic peptide(31-67) inhibits Na+ transport in rabbit inner medullary collecting duct cells. Role of prostaglandin E2. J. Clin. Invest., 89:1411-147.
Hagiwara H, Inoue A, Yamaguchi A, Yokose S, Furuya M, Tanaka S, Hirose S (1996). cGMP produced in response to ANP and CNP regulates proliferation and differentiation of osteoblastic cells. Am. J. Physiol., 270:1311–1318.
Hagiwara H, Sakaguchi H, Itakura M, Yoshimoto T, Furuya M, Tanaka S, Hirose S (1994). Autocrine regulation of rat chondrocyte proliferation by natriuretic peptide C and its receptor, natriuretic peptide receptor-B. J. Biol. Chem., 269:10729– 10733.
Haug C, Metzele A, Kochs M, Hombach V, Grunert A (199). Plasma brain natriuretic peptide and atrial natriuretic peptide concentrations correlate with left ventricular end-diastolic pressure. Clin. Cardiol., 16:553-557.
Hayakawa H, Komada Y, Hirayama M, Hori H, Ito M, Sakurai M (2001). Plasma levels of natriuretic peptides in relation to doxorubicin-induced cardiotoxicity and cardiac function in children with cancer. Med. Pediatr. Oncol., 37: 04–09.
Hayashi M, Tsutamoto T, Wada A, Maeda K, Mabuchi N, Tsutsui T

(2001). Intravenous atrial natriuretic peptide prevents left ventricular remodeling in patients with first anterior acute myocardial infarction. J. Am. Coll. Cardiol., 37:1820-1826.
Heart Failure Society of America, HFSA (2006). Comprehensive heart failure practice guidelines: Section 12: Evaluation and management of patients with acute decompensated heart failure. J. Card. Fail., 12:86–103.
Henriksen JH, Gotze JP, Fuglsang S (2003). Increased circulating pro-brain natriuretic peptide (proBNP) and brain natriuretic peptide (BNP) in patients with cirrhosis: Relation to cardiovascular dysfunction and severity of disease. Gut, 52:1511–1517.
Herman JP, Dolgas CM, Rucker D, Langub Jr MC (1996). Localization of natriuretic peptide-activated guanylate cyclase mRNAs in the rat brain. J. Comp. Neurol., 369:65-87
Hirsch JR, Skutta N, Schlatter E (2003).Signaling and distribution of NPR-Bi, the human splice form of the natriuretic peptide receptor B. Am. J. Physiol. Renal Physiol., 285:F370-F374.
Holliday LS, Dean AD, Greenwald JE, Glucks SL (1995). C-type natriuretic peptide increases bone resorption in 1,25-dihydroxyvitamin D3-stimulated mouse bone marrow cultures. J. Biol. Chem., 270:18983-18989.
Hou SH, Bushinsky DA, Wish JB, Cohen JJ, Harrington JT (1983). Hospital-acquired renal insufficiency: A prospective study. Am. J. Med., 74:243–248.
Hunt PJ, Richards AM, Espiner EA, Nicholls MG, Yandle TG (1994). Bioactivity and metabolism of C-type natriuretic peptide in normal man. J. Clin. Endocrinol. Metab., 78:1428–1435.
Hunt PJ, Richards AM, Nicholls MG (1997). Immunoreactive amino-terminal probrain natriuretic peptide (NT-PROBNP): a new marker of cardiac impairment. Clin. Endocrinol., (Oxf) 47:287-296.
Igaki T, Itoh H, Suga SI, Hama N, Ogawa Y, Komatsu Y (1998). Effects of intravenously administered C-type natriuretic peptide in humans: comparison with atrial natriuretic peptide. Hypertens. Res., 1:07–13.
Incalzi RA, Fuso L, Serra M (2002).Exacerbated chronic obstructive pulmonary disease: A frequently unrecognized condition . J Intern Med., 252:48–55.
Itoh H, Nakao K, Katsuura G, Morii N, Shiono S, Sakamoto M, Sugawara A, Yamada T, Saito Y, Matsushita A (1986). Centrally infused atrial natriuretic polypeptide attenuates exaggerated salt appetite in spontaneously hypertensive rats. Circ. Res., 59:342-347.
Itoh H, Pratt RE, Ohno M, Dzau VJ (1992). Atrial natriuretic polypeptide as a novel antigrowth factor of endothelial cells. Hypertension, 19:758-761.
Jaffe AJ, Babuin L (2006). Apple FS. Biomarkers in Acute Cardiac Disease. The Present and the Future. J. Am. Coll. Cardiol. 48:1-11.
Jaubert J, Jaubert F, Martin N, Washburn LL, Lee BK, Eicher EM, Guenet JL (1999). Three new allelic mouse mutations that cause skeletal overgrowth involve the natriuretic peptide receptor C gene (Npr3). Proc Natl Acad Sci. 96:10278- 83.
Jensen KT, Carstens J, Pedersen EB (1998). Effect of BNP on renal hemodynamics tubular function and vasoactive hormones in humans. Am. J. Physiol., 274:63- 72.
John SW, Krege JH, Oliver PM, Hagaman JR, Hodgin JB, Pang SC, Flynn TG, Smithies O (1995).Genetic decreases in atrial natriuretic peptide and salt-sensitive hypertension. Science, 267:679-681.
Kaditis A, Alexopoulos E, Hatzi F, Kostadima E, Kiaffas M, Zakynthinos E, Gourgoulianis K (2006). Overnight change in brain natriuretic peptide levels in children with sleep-disordered breathing. Chest, 130:1377-1384.
Kalra PR, Clague JR, Bolger AP, Anker SD, Poole-Wilson PA, Struthers AD (2003). Myocardial production of C-type natriuretic peptide in chronic heart failure. Circulation, 107:571-573.
Kampaliotis D, Kirtane AJ, Ruisi CP, Polonsky T, Malhotra A,Talmor D, Kosmidou T (2007). Chest, 131:964-971.
Kapoun AM, Liang F, O'Young G, Damm DL, Quon D, White RT, Munson K, Lam A, Schreiner GF, Protter AA (2004). B-type natriuretic peptide exerts broad functional opposition to transforming growth factor in primary human cardiac fibroblasts: fibrosis, myofibroblast conversion, proliferation, and inflammation. Circ. Res., 94:453-461.
Kawamura T, Wago M (2002). Brain natriuretic peptide can be a useful biochemical marker for myocarditis in patients with Kawasaki disease. Cardiol Young 12:153–158.
Kazanegra R, Cheng V, Garcia A (2001). A rapid test for B-type natriuretic peptide correlates with falling wedge pressures in patients treated for decompensated heart failure: a pilot study. J. Card. Fail., 7: 21-29.
Keating GM, Goa KL (2003). Nesiritide: a review of its use in acute decompensated heart failure. Drugs, 63:47-70.
Kiemer AK, Hartung T, Vollmar AM (2000). cGMP-mediated inhibition of TNF-alpha production by the atrial natriuretic peptide in murine macrophages. J. Immunol., 165:175-181.
Kiemer AK, Weber NC, Fürst R, Bildner N, Kulhanek-Heinze S, Vollmar AM (2002). Inhibition of p38 MAPK activation via induction of MKP-1: atrial natriuretic peptide reduces TNF-alpha-induced actin polymerization and endothelial permeability. Circ. Res., 90:874-881.
Kikuta K, Yasue H, Yoshimura M, Morita E, Sumida H, Kato H, Kugiyama K, Ogawa H, Okumura K, Ogawa Y (1996). Increased plasma levels of B-type natriuretic peptide in patients with unstable angina. Am. Heart J., 132:101-107.
Kita H, Ohi M, Chin K (1998).The nocturnal secretion of cardiac natriuretic peptides during obstructive sleep apnoea and its response to therapy with nasal continuous positive airway pressure . J. Sleep Res., 7:199-207 .
Koller KJ, Lowe DG, Bennett GL, Minamino N, Kangawa K, Matsuo H, Goeddel DV (1991). Selective activation of the B natriuretic peptide receptor by C-type natriuretic peptide (CNP). Science, 252:120-123.
Kone BC (2001). Molecular biology of natriuretic peptides and nitric oxide synthases. Cardiovascol. Res., 51:429-441.
Kotanidou A, Karsaliakos P, Tzanela M, Mavrou I, Kopterides P, Papadomichelakis E, Theodorakopoulou M, Botoula E, Tsangaris I, Lignos M, Ikonomidis I, Ilias I, Armaganidis A, Orfanos SE, Dimopoulou I (2009). Prognostic importance of increased plasma amino-terminal pro-brain natriuretic peptide levels in a large non-cardiac, general intensive care unit population. Shock, 31:342-347.
Kucher N, Goldhaber SZ (2003). Cardiac biomarkers for risk stratification of patients with acute pulmonary embolism. Circulation, 108: 2191-2194.
Kuga H, Ogawa K, Oida A, Taguchi I, Nakatsugawa M, Hoshi T, (2003). Administration of atrial natriuretic peptide attenuates reperfusion phenomena and preserves left ventricular regional wall motion after direct coronary angioplasty for acute myocardial infarction, Circ. J. 67: 443-448.
Kuhn M. ((2003).Structure, Regulation, and function of mammalian membrane guanylyl cyclase receptors, with a focus on guanylyl cyclase-A. Circ. Res., 93:700-709.
Kuno T, Andresen JW, Kamisaki Y, Waldman SA, Chang LY, Saheki S, Leitman DC, Nakane M, Murad F (1986). Co-purification of an atrial natriuretic factor receptor and particulate guanylate cyclase from rat lung. J. Biol. Chem., 261:5817-23.
Kurnik BR, Allgren RL, Genter FC, Solomon RJ, Bates ER, Weisberg LS (1998). Prospective study of atrial natriuretic peptide for the prevention of radiocontrastinduced nephropathy. Am. J. Kidney Dis., 31:674-680.
Kyriakides ZS, Markianos M, Michalis L, Antoniadis A, Nikolaou NI, Kremastinos DT (2000). Brain natriuretic peptide increases acutely and much more prominently than atrial natriuretic peptide during coronary angioplasty. Clin. Cardiol., 23:285-288.
Lafontan M, Moro C, Sengenes C, Galitzky J, Crampes F, Berlan M (2005). An unsuspected Metabolic Role for Atrial Natriuretic Peptides. The Control of Lipolysis, Lipid Mobilization, and Systemic Nonesterified Fatty Acids Levels in Humans. Arterioscler. Thromb. Vasc. Biol., 25:2032.
Lang CC, Choy AJ, Struthers AD (1992). Atrial and brain natriuretic peptides: a dual natriuretic peptide system potentially involved in circulatory homeostasis. Clin. Sci., 83:519-527.
Lee D, Vasan R (2005). Novel markers for heart failure diagnosis and prognosis. Novel markers for heart failure diagnosis and prognosis. Curr. Opin. Cardiol., 20:201-210.
Levin E, Gardner D, Samson W (1998). Natriuretic peptides. N. Engl. J. Med., 339:321-328.
Li N, Wang J (2005). Brain natriuretic peptide and optimal management of heart failure. JZUS 6:877-884.
Liang F, Webb P, Marimuthu A (2003). Triiodothyronine increases brain

natriuretic peptide (BNP) gene transcription and amplifies endothelin-dependent BNP gene transcription and hypertrophy in neonatal rat ventricular myocytes. J. Biol. Chem., 278:15073–15083.
Lincoln TM, Cornwell TL (1993). Intracellular cyclic GMP receptor proteins. FASEB J., 7:328-38.
Lisy O, Jougasaki M, Heublein DM (1999). Renal actions of synthetic dendroaspis natriuretic peptide. Kidney Int., 56:502–508.
Lisy O, Lainchbury JG, Leskinen H, Burnett JC Jr (2001). Therapeutic actions of a new synthetic vasoactive and natriuretic peptide, dendroaspis natriuretic peptide, in experimental severe congestive heart failure. Hypertension, 37:1089–1094.
Lofton CE, Baron DA, Heffner JE, Currie MG, Newman WH (1991). Atrial natriuretic peptide inhibits oxidant-induced increases in endothelial permeability. J. Mol. Cell. Cardiol., 23:919-927.
Lopez MJ, Wong SK, Kishimoto I, Dubois S, Mach V, Friesen J, Garbers DL, Beuve A (1995). Salt-resistant hypertension in mice lacking the guanylyl cyclase-A receptor for atrial natriuretic peptide. Nature, 378: 65-658.
Lowe DG, Chang MS, Hellmiss R, Chen E, Singh S, Garbers DL, Goeddel DV (1989). Human atrial natriuretic peptide receptor defines a new paradigm for second messenger signal transduction. EMBO. J., 8:1377-1384.
Lubien E, DeMaria A, Krishnaswamy P, Clopton P, Koon J, Kazanegra R, Gardetto N, Wanner E, Maisel AS (2002). Utility of B-natriuretic peptide in detecting diastolic dysfunction: Comparison with Doppler velocity recordings. Circulation, 105:595-601.
Maeda K, Tsutamoto T, Wada A (1998). Plasma brain natriuretic peptide as a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction. Am Heart. J., 35:825– 832 .
Maeder M, Ammann P, Kiowski W (2005).B-type natriuretic peptide in patients with sepsis and preserved left ventricular ejection fraction. Eur. J. Heart Fail., 7:1164–1167 .
Maeder M, Fehr Th, Rickli H, Ammann P (2006). Diagnostic and prognostic impact of cardiac troponins and natriuretic peptides. Chest, 129:1349-1366.
Maffei S, Del Ry S, Prontera C, Clerico A (2001). Increase in circulating levels of cardiac natriuretic peptides after hormone replacement therapy in postmenopausal women. Clin. Sci., (Colch) 101:447-453.
Maisel A, Hollander JE, Guss D (2004).Primary results of the Rapid Emergency Department Heart Failure Outpatient Trial (REDHOT): a multicenter study of Btype natriuretic peptide levels, emergency department decision making, and outcomes in patients presenting with shortness of breath. J. Am. Coll. Cardiol., 44:1328-1333.
Maisel A, Krishnaswamy P, Nowak R, McCord J, Hollander J, Duc P (2002). Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N. Engl. J. Med., 347: 161-167.
Maisel AS (2003). Nesiritide: A new therapy for the treatment of heart failure. Cardiovasc. Toxicol., 3:37-42.
Maisel AS, McCord J, Nowak RM, Hollander JE, Wu AH, Duc P (2003). Breathing Not Properly Multinational Study Investigators. Bedside B-type natriuretic peptide in the emergency diagnosis of heart failure with reduced or preserved ejection fraction. Results from the Breathing Not Properly Multinational Study. J. Am. Col. Cardiol., 41:2010-2017 .
Makikallio AM, Makikallio TH, Korpelainen JT (2005). Natriuretic peptides and mortality after stroke. Stroke, 36:1016-1020.
Marala RB, Sitaramayya A, Sharma RK (1991). Dual regulation of atrial natriuretic factor-dependent guanylate cyclase activity by ATP. EBS Lett., 281:73-76.
Margulies KB, Burnett JC Jr (2006). Visualizing the basis for paracrine natriuretic peptide signaling in human heart. Circ. Res., 99:113–115.
Martin DR, Pevahouse JB, Trigg DJ, Vesely DL, Buerkert JE (1990). Three peptides from the ANF prohormone NH(2)-terminus are natriuretic and/or kaliuretic. Am. J. Physiol., 258:1401-1408.
Martin FL, Chen HH, Cataliotti A, Burnett JC (2008). Jr. B-type natriuretic peptide: beyond a diagnostic. Heart Fail. Clin., 4:449-54.
Matsukawa N, Grzesik WJ, Takahashi N, Pandey KN, Pang S, Yamauchi M, Smithies O (1999). The natriuretic peptide clearance receptor locally modulates the physiological effects of the natriuretic peptide system. Proc. Natl. Acad. Sci. 96:7403-7408.
Mattingly MT, Brandt RR, Heublein DM (1994). Presence of C-type natriuretic peptide in human kidney and urine. Kidney Int. 46:744-747.
McCullough PA, Duc P, Omland T (2003). B-type natriuretic peptide and renal function in the diagnosis of heart failure: an analysis from the Breathing Not Properly Multinational Study. Am. J. Kidney Dis., 41:571-579.
McDonagh TA, Robb SD, Murdoch DR (1998).Biochemical detection of left ventricular systolic dysfunction. Lancet, 351:09-13.
McGirt MJ, Blessing R, Nimjee SM (2004).Correlation of serum brain natriuretic peptide with hyponatremia and delayed ischemic neurological deficits after subarachnoid hemorrhage. Neurosurgery, 54:1369-1373.
McGregor CG, Edwards WD, Schaff HV, Burnett Jr. JC (1993).Natriuretic peptide system in human heart failure Circ. Res .71:1004-1009.
McLean AS, Huang SJ, Nalos M, Tang B, Stewart DE (2003). The confounding effects of age, gender, serum creatinine, and electrolyt concentrations on plasma B-type natriuretic peptide concentrations in critically ill patients. Crit. Care Med., 31:2611-2618.
Mehra MR, Uber PA, Park MH (2004). Obesity and suppressed B-type natriuretic peptide levels in heart failure. J. Am. Coll. Cardiol., 43:1590- 1595.
Mekontso-Dessap A, de Prost N, Girou E, Braconnier F, Lemaire F, Brun-Buisson C, Brochard L (2006). B-type natriuretic peptide and weaning from mechanical ventilation. Intensive Care Med., 32:529-536.
Miller WL, Hartman KA, Burritt MF, Borgeson DD, Burnett JC Jr, Jaffe AS (2005). Biomarker responses during and after treatment with nesiritide infusion in patients with decompensated chronic heart failure. Clin. Chem., 51:569-577.
Mir TS, Laux R, Hellwege HH (2003).Plasma concentrations of aminoterminal pro brain natriuretic peptide in healthy neonates: marked and rapid increase after birth . Pediatrics, 112:896-899.
Mir TS, Marohn S, Laer S (2002). Plasma Concentrations of N-terminal pro-brain natriuretic peptide in control children from neonatal to adolescent period and in children with congestive heart failure. Pediatrics, 110:176.
Misono KS (2002).Natriuretic peptide receptor: structure and signalling Mol Cell Biochem 230: 49-60.
Mitrovic V, Luss H, Nitsche K, Forssmann K, Maronde E, Fricke K (2005). Effects of the renal natriuretic peptide urodilatin (ularitide) in patients with decompensated chronic heart failure: a double-blind, placebo-controlled, ascending-dose trial. Am. Heart J., 150:1239.
Mohapatra SS, Lockey RF, Vesely DL, Gower Jr WR (2004). Natriuretic peptides and genesis of asthma: an emerging paradigm? J. Allergy Clin. Immunol., 114:520-526.
Mori T, Chen YF, Feng JA, Hayashi T, Oparil S, Perry GJ (2004). Volume overload results in exaggerated cardiac hypertrophy in the atrial natriuretic peptide knockout mouse. Cardiovasc. Res., 61:771-779.
Morishita Y, Sano T, Ando K, Saitoh Y, Kase H, Yamada K, Matsuda Y (1991). Microbial polysaccharide, HS-142-1, competitively and selectively inhibits ANP binding to its guanylyl cyclase-containing receptor. Biochem. Biophys. Res. Commun., 176: 949-957.
Morita R, Ukyo N, Furuya M, Uchiyama T, Hori T (2003). Atrial natriuretic peptide polarizes human dendritic cells toward a Th2-promoting phenotype through its receptor guanylyl cyclase-coupled receptor A. J. Immunol., 170:5869-5875.
Moro C, Berlan M (2006). Cardiovascular and metabolic effects of natriuretic peptides. Fundam. Clin. Pharmacol. 20:41-49.
Moro C, Crampes F, Sengenes C (2004). Atrial natriuretic peptide contributes to physiological control of lipid mobilization in humans. FASEB J., 18:908-910.
Moro C, Galitzky J, Sengenes C, Crampes F, Lafontan M, Berlan M (2004). Functional and pharmacological characterization of the natriuretic peptide-dependent lipolytic pathway in human fat cells. J Pharmacol. Exp. Ther., 308:984-992.
Moro C, Polak J, Richterova B, Sengenes C, Pelikanova T, Galitzky J, Stich V, Lafontan M, Berlan M (2005). Differential regulation of atrial natriuretic peptide- and adrenergic receptor-dependent lipolytic pathways in human adipose tissue. Metabolism, 54:122-131.
Morrison L, Harrison A, Krishnaswamy P, Kazanegra R, Clopton P, Maisel A (2002). Utility of a rapid B-natriuretic peptide assay in differentiating congestive heart failure From lung disease in patients

presenting with dyspnea. J. Am. Coll. Cardiol., 39:202-209.
Mounier N, Arrigo AP (2002). Actin cytoskeleton and small heat shock proteins: how do they interact? Cell Stress Chaperones 7:167-176.
Mueller C, Scholer A, Laule-Kilian K (2004). Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. N Engl J. Med. 350:647- 654.
Mukoyama M, Nakao K, Hosoda K, Suga S, Saito Y, Ogawa Y, Shirakami G, Jougasaki M, Obata K, Yasue H, Kambayashi Y, Inouye K, Imura H (1991). Brain natriuretic peptide as a novel cardiac hormone in humans. Evidence for an exquisite dual natriuretic peptide system, atrial natriuretic peptide and brain natriuretic peptide. J Clin Invest 87:1402–1412.
Murohara T, Kugiyama K, Ota Y, Doi H, Ogata N, Ohgushi M, Yasue H (1999). Effects of atrial and brain natriuretic peptides on lysophosphatidylcholine-mediated endothelial dysfunction. J Cardiovasc Pharmacol 34:870-878.
Nagase M, Katafuchi T, Hirose S, Fujita T (1997).Tissue distribution and localization of natriuretic peptide receptor subtypes in stroke-prone spontaneously hypertensive rats. J. Hypertens. 15:1235-1243.
Nagaya N, Nishikimi T, Okano Y (1998). Plasma brain natriuretic peptide levels increase in proportion to the extent of right ventricular dysfunction in pulmonary hypertension. J. Am. Coll. Cardiol., 31:202–208.
Nakamura M, Endo H, Nasu M (2002). Value of plasma B type natriuretic peptide measurement for heart disease screening in a Japanese population. Heart. 87:131-135.
Nakao K (1992). Natriuretic peptide family. Nippon Naibunpi Gakkai Zasshi 68:134–142.
Nakayama T (2005). The genetic contribution of the natriuretic peptide system to cardiovascular diseases. Endocr. J., 52:11–21.
Neumayer HH, Blossei N, Seherr-Thohs U, Wagner K (1990). Amelioration of postischaemic acute renal failure in conscious dogs by human atrial natriuretic peptide. Nephrol. Dial Transplant, 5:32–38.
Ogawa H, Qiu Y, Ogata CM, Misono KS (2004). Crystal structure of hormone-bound atrial natriuretic peptide receptor extracellular domain:rotation mechanism for transmembrane signal transduction. J. Biol. Chem. 279:28625-28631.
Ohba H, Takada H, Musha H, Nagashima J, Mori N, Awaya T (2001). Effects of prolonged strenuous exercise on plasma levels of atrial natriuretic peptide and brain natriuretic peptide in healthy men. Am Heart J., 141:751-758.
Paul AK, Marala RB, Jaiswal RK, Sharma RK (1987). Coexistence of guanylate cyclise and atrial natriuretic factor receptor in a 180-kD protein. Science, 235: 1224-1226.
Peacock WF, Freda BJ (2003). Heart failure part I. Emerg. Med. Rep. 3: 89-92.
Pedram A, Razand M, Levin ER (2002). Deciphering vascular endothelial cell growth factor/vascular permeability factor signaling to vascular permeability. Inhibition by atrial natriuretic peptide. J. Biol. Chem. 277:44385-44398.
Pedram A, Razandi M, Hu RM, Levin ER (1997). Vasoactive peptides modulate vascular endothelial cell growth factor production and endothelial cell proliferation and invasion. J. Biol. Chem., 272:17097-17103.
Pemberton CJ, Johnson ML, Yandle TG, Espiner EA (2000). Deconvolution analysis of cardiac natriuretic peptides during acute volume overload. Hypertension, 36:355-359.
Pfister R, Schneider CA (2009). ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: application of natriuretic peptides. Eur. Heart J., 30:382-383.
Pirrachio R, Deyne N, Lukaszewicz A, Mebazaa A, Cholley B, Mateo J, Megarbane, Launay J, Peynet J, Baud F, Payen D (2008). Impaired plasma B-type natriuretic peptide clearance in human septic shock. Crit. Care Med., 36:2542-2546.
Poirier H, Labrecque J, Deschenes J, DeLean A. (2002). Allotopic antagonism of the non-peptide atrial natriuretic peptide (ANP) antagonist HS-142-1 on natriuretic peptide receptor NPR-A. Biochemistry, 362:231-237.
Porter JG, Arfsten A, Fuller F, Miller JA, Gregory LC, Lewicki JA (1990). Isolation and functional expression of the human atrial natriuretic peptide clearance receptor cDNA. Biochem. Biophys. Res. Commun.,171:796.
Post F, Weilemann LS, Messow CM, Sinning C, Munzel T (2008). B-type natriuretic peptide as a marker for sepsis-induced myocardial depression in intensive care patients. Crit. Care Med., 36:3108-3109.
Potter KR, Abbey-Hosch S, Dickey DM (2005). Natriuretic Peptides, their receptors, and cyclic Guanosine Monophosphate-Dependent Signaling Functions. Endocrine Rev. 27:47-72.
Potter LR (1998). Phosphorylation-dependent regulation of the guanylyl cyclase-linked natriuretic peptide receptor B: dephosphorylation is a mechanism of desensitization. Biochemistry, 37:2422-2429.
Potter LR (2005). Domain analysis of human transmembrane guanylyl cyclise receptors: implications for regulation. Front Biosci.10:1205-1220.
Potter LR, Hunter T (2005). Phosphorylation of the kinase homology domain is essential for activation of the A-type natriuretic peptide receptor. Mol Cell Biochem ;124:11-16. Bryan PM, Potter LR (2002). The atrial natriuretic peptide receptor (NPR-A/GC-A) is dephosphorylated by distinct microcystin-sensitive and magnesium-dependent protein phosphatases. J. Biol. Chem., 277:16041-16047.
Rahmutula D, Nakayama T, Soma M, Kosuge K, Aoi N, Izumi Y, Kanmatsuse K, Ozawa Y. (2002). Structure and polymorphisms of the human natriuretic peptide receptor C gene. Endocrine, 17: 85-90.
Raines EW, Ross R (1995). Biology of atherosclerotic plaque formation: possible role of growth factors in lesion development and the potential impact of soy. J. Nutr., 125:624S-630S.
Redfield MM, Rodeheffer RJ, Jacobsen SJ (2004). Plasma brain natriuretic peptide to detect preclinical ventricular systolic or diastolic dysfunction: a communitybased study. Circulation, 109:3176-3181.
Rehemudula D, Nakayama T, Soma M, Takahashi Y, Uwabo J, Sato M, Izumi Y, Kanmatsuse K, Ozawa Y (1999).Structure of the B type human natriuretic peptide receptor gene and association of a novel microsatellite polymorphism with essential hypertension Circ. Res., 84:605-610.
Ribeiro AL, dos Reis AM, Barros MV, de Sousa MR, Rocha AL, Perez AA (2002). Brain natriuretic peptide and left ventricular dysfunction in Chagas' disease Lancet, 360:46-462.
Richards AM, Crozier IG, Holmes SJ, Espiner EA, Yandle TG, Frampton C (1993). Brain natriuretic peptide: natriuretic and endocrine effects in essential hypertension. J. Hypertens., 11:163-170.
Rodeheffer RJ, Tanaka I, Imada T (1986). Atrial pressure and secretion of atrial natriuretic factor into the human central circulation J. Am. Coll Cardiol., 18-626.
Rosenzweig A, Seidman CE (1991). Atrial natriuretic factor and related peptide hormones. Annu. Rev. Biochem., 60:229-55.
Saba SR, Garces AH, Clark LC (2005). Immunocytochemical localization of atrial natriuretic peptide, vessel dilator, long-acting natriuretic peptide, and kaliuretic peptide in human pancreatic adenocarcinomas. J. Histochem. Cytochem., 53:989-995.
Saito Y, Nakao K, Arai H (1989). Augmented expression of atrial natriuretic polypeptide gene in ventricle of human failing heart. J. Clin. Invest. 83:298-305.
Samson WK, Aguila MC, Martinovic J, Antunes-Rodrigues J, Norris M (1987). Hypothalamic action of atrial natriuretic factor to inhibit vasopressin secretion. Peptides, 8:449-454.
Sano T, Imura R, Morishita Y, Matsuda Y, Yamada K (1992). HS-142-1, a novel polysaccharide of microbial origin, specifically recognizes guanylyl cyclaselinked ANP receptor in rat glomeruli. Life Sci. 51:1445-14451.
Saxenhofer H, Raselli A, Weidmann P, Forssmann WG, Bub A, Ferrari P (1990). Urodilatin, a natriuretic factor from kidneys, can modify renal and cardiovascular function in men. Am. J. Physiol., 259:832-838.
Schrirger JA, Heublein DM, Chen HH, Lisy O, Jougasaki M, Wennberg PW, Burnett JC Jr (1999). Presence of Dendroaspis natriuretic peptide-like immunoreactivity in human plasma and its increase durong human heart failure. Mayo Clin. Proc., 74:126-130.
Schulz S, Singh S, Bellet RA, Singh G, Tubb DJ, Chin H, Garbers DL. (1989).The primary structure of a plasma membrane guanylate cyclase demonstrates diversity within this new receptor family. Cell. 58: 1155-1162.
Schulz-Knappe P, Forssmann K, Herbst F, Hock D, Pipkorn R, Forssmann WG (1988). Isolation and structural analysis of "urodilatin", a new peptide of the cardiodilatin-(ANP)-family, extracted from human urine. Klein Wochenschr. 66:752-759.

Schwartz SM (1997). Smooth muscle migration in atherosclerosis and restenosis. J. Clin. Invest., 100:87-89.
Schweitz H, Vigne P, Moinier D, Frelin C and Lazdunski. A (1992).new member of the natriuretic peptide family is present in the venom of the green mamba (dendroaspis angusticeps). The Journal of Biological Chem. 267:13928-13932.
Schweitz H, Vigne P, Moinier D, Frelin C, Lazdunski M (1992). A new member of the natriuretic peptide family is present in the venom of the green mamba (Dendroaspis angusticeps). J. Biol. Chem. 267:13928–13932.
Sengenes C, Berlan M, de Glisezinski I, Lafontan M, Galitzky J (2000). Natriuretic peptides: a new lipolytic pathway in human adipocytes. FASEB J. 14:1345- 1351.
Sengenes C, Bouloumie A, Hauner H (2003). Involvement of a cGMP-dependent pathway in the natriuretic peptide-mediated hormone-sensitive lipase phosphorylation in human adipocytes. J. Biol. Chem. 278:48617-48626.
Sengenes C, Moro C, Galitzky J, Berlan M, Lafontan M (2005). Natriuretic peptides: a new lipolytic pathway in human fat cells. Med. Sci., 21:61-65.
Shaw SG, Weidmann P, Hodler J, Zimmermann A, Paternostro A (1987). Atrial natriuretic peptide protects against ischemic renal failure in the rat. J. Clin. Invest. 80:1232–1237.
Soeki T, Kishimoto I, Okumura H, Tokudome T, Horio T, Mori K (2005). C-type natriuretic peptide, a novel antifibrotic and antihypertrophic agent, prevents cardiac remodeling after myocardial infarction. J. Am. Coll. Cardiol. 45:608-616.
Soeki T, Kishimoto I, Okumura H, Tokudome T, Horio T, Mori K, Kangawa K (2005). C-type natriuretic peptide, a novel antifibrotic and antihypertrophic agent, prevents cardiac remodeling after myocardial infarction. J. Am. Coll. Cardiol., 45:608-616.
Soualmia H, Barthelemy C, Masson F, Maistre G, Eurin J, Carayon A (1997). Angiotensin II-induced phosphoinositide production and atrial natriuretic peptide release in rat atrial tissue. J. Cardiovasc. Pharmacol., 29:605-611.
Steele MK, Gardner DG, Xie PL, Schultz HD (1991). Interactions between ANP and ANG II in regulating blood pressure and sympathetic outflow. Am. J. Physiol. 260:1145-1151.
Steinhelper ME, Cochrane KL, Field LJ (1990). Hypotension in transgenic mice expressing atrial natriuretic factor fusion genes. Hypertension, 16:301-310.
Stingo AJ, Clavell AL, Heublein DM, Wei CM, Pittelkow MR, Burnett Jr JC (1992). Presence of C-type natriuretic peptide in cultured human endothelial cells and plasma. Am. J. Physiol. 263:1318–1321.
Storrow A (2003). Advances in the diagnosis of CHF: new markers. Mod Adv Emerg Cardiac Care, 3:38- 48.
Suda M, Ogawa Y, Tanaka K, Tamura N, Yasoda A, Takigawa T, Uehira M, Nishimoto H, Itoh H, Saito Y, Shiota K, Nakao K (1998). Skeletal overgrowth in transgenic mice that overexpress brain natriuretic peptide. Proc. Natl. Acad. Sci. USA., 95:2337-2342.
Sudoh T, Minamino N, Kangawa K, Matsuo H (1990).C-type natriuretic peptide (CNP): a new member of natriuretic peptide family identified in porcine brain. Biochem. Biophys. Res. Commun., 168: 863-870.
Suga S, Itoh H, Komatsu Y, Ogawa Y, Hama N, Yoshimasa T, Nakao K (1993). Cytokine-induced C-type natriuretic peptide (CNP) secretion from vascular endothelial cells–evidence for CNP as a novel autocrine/paracrine regulator from endothelial cells. Endocrinology, 133:3038-3041.
Suga S, Nakao K, Hosoda K, Mukoyama M, Ogawa Y, Shirakami G, Arai H, Saito Y, Kambayashi Y, Inouye K, Imura H. (1992).Receptor selectivity of natriuretic peptide family, atrial natriuretic peptide, brain natriuretic peptide, and –type natriuretic peptide. Endocrinology, 130:229-239.
Suga S, Nakao K, Itoh H, Komatsu Y, Ogawa Y, Hama N, Imura H (1992). Endothelial production of C-type natriuretic peptide and its marked augmentation by transforming growth factor. Possible existence of “vascular natriuretic peptide system.” J. Clin. Invest., 90:1145-1149.
Sullivan DR, West M, Jeremy R (2005). Utility of Brain Natriuretic Peptide (BNP) Measurement in Cardiovascular Disease. Heart Lung Circ., 14:78-84.
Suwa M, Seino Y, Nomachi Y, Matsuki S, Funahashi K (2005). Multicenter prospective investigation on efficacy and safety of carperitide for acute heart failure in the ‘real world’ of therapy. Circ. J. Mar. 69:283-290.
Ta mura N, Ogawa Y, Chusho H, Nakamura K, Nakao K, Suda M (2000). Cardiac fibrosis in mice lacking brain natriuretic peptide. Proc. Natl. Acad. Sci. USA. 97:4239-4244.
Takahashi N, Saito Y, Kuwahara K, Harada M, Kishimoto I, Ogawa Y, Kawakami R, Nakagawa Y, Nakanishi M, Nakao K (2003). Angiotensin II-induced ventricular hypertrophy and extracellular signal-regulated kinase activation are suppressed in mice overexpressing brain natriuretic peptide in circulation. Hypertens. Res., 26: 847-853.
Takahashi Y, Nakayama T, Soma M, Izumi Y, Kanmatsuse K (1998). Organization of the human natriuretic peptide receptor A gene. Biochem. Biophys. Res. Commun., 246:736-739.
Tamura N, Garbers DL (2003). Regulation of the guanylyl cyclase-B receptor by alternarive splicing. J. Biol. Chem., 278:48880-48889.
Tateishi J, Masutani M, Ohyanagi M, Iwasaki T (2000). Transient increase in plasma brain (B-type) natriuretic peptide after percutaneous transluminal coronary angioplasty. Clin. Cardiol., 23:776-780.
Tawaragi Y, Fuchimura K, Nakazato H (1990). Gene and precursor structure of porcine C-type natriuretic peptide. Biochem. Biophys. Res Commun. 172:627–632.
Tawaragi Y, Fuchimura K, Tanaka S, Minamino N, Kangawa K, Matsuo H (1991). Gene and precursor structures of human C-type natriuretic peptide. Biochem. Biophys. Res. Commun., 175:645-651.
Tharaux PL, Dussaule JC, Hubert-Brierre J, Vahanian A, Acar J, Ardaillou R (1994). Plasma atrial and brain natriuretic peptides in mitral stenosis treated by valvulotomy. Clin. Sci., (Colch) 87:67-677.
The Criteria Committee of the New York Heart Association (1979). Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. Boston:Little, Brown,
Thomas G, Moffatt P, Salois P, Gaumond MH, Gingras R, Godin E, Miao D, Goltzman D, Lanctot C (2003). Osteocrin, a novel bonespecific secreted protein that modulates the osteoblast phenotype. J. Biol. Chem. 278: 50563–50571.
Thomas GP, Sellin K, Bessette M, Lafreniere F, Lanctot C, Moffatt P, Osteocrin (2004).a local mediator of the natriuretic system. Proc 26th Annual Meeting of the American Society for Bone and Mineral Research, Seattle, WA, (Presentation 1075).
Thuerauf DJ, Hanford DS, Glembotski CC (1994). Regulation of rat brain natriuretic peptide transcription. A potential role for GATArelated transcription factors in myocardial cell gene expression. J. Biol. Chem. 269: 17772–17775.
Togashi K, Kameya T, Kurosawa T, Hasegawa N, Kawakami M (1992). Concentrations and molecular forms of C-type natriuretic peptide in brain and cerebrospinal fluid. Clin. Chem., 38: 2136–2139.
Tokudome T, Horio T, Soeki T, Mori K, Kishimoto I, Suga S (2004). Inhibitory effect of C-type natriuretic peptide (CNP) on cultured cardiac myocyte hypertrophy: interference between CNP and endothelin-1 signaling pathways. Endocrinology, 145:2131–2140.
Tremblay J, Desjardins R, Hum D, Gutkowska J,Hamet P (2002). Biochemistry and physiology of the natriuretic peptide receptor guanylyl cyclases. Mol. Cell Biochem. 230:31-47.
Tsuji T, Kunieda T (2005). A loss-of-function mutation in natriuretic peptide receptor 2 (Npr2) gene is responsible for disproportionate dwarfism in cn/cn mouse. J. Biol. Chem. 280:14288–14292.
Tsukagoshi H, Shimizu Y, Kawata T (2001). Atrial natriuretic peptide inhibits tumor necrosis factor-alpha production by interferon-gamma-activated macrophages via suppression of p38 mitogen-activated protein kinase and nuclear factor-kappa B activation. Regul. Pept., 99:21-29.
Tung RH, Garcia C, Morss AM (2004).Utility of B-type natriuretic peptide for the evaluation of intensive care unit shock. Crit. Care Med. 32:1643-1647.
Valli N, Gobinet A, Bordenave L (1999). Review of 10 years of the clinical use of brain natriuretic peptide in cardiology. J Lab. Clin. Med. 134:437-444.
Van den Akker F (2001). Structural insights into the ligand binding domains of membrane bound guanylyl cyclases and natriuretic peptide receptors. J. Mol. Biol., 311:923-37.

Van der Zander K, Houben AJ, Kroon AA, de Leeuw PW (1999). Effects of brain natriuretic peptide on forearm vasculature: Comparison with atrial natriuretic peptide. Cardiovasc. Res., 44:595-600.
Van der Zander K, Houben AJ, Kroon AA, De Mey JG, Smits PA, de Leeuw PW (2002). Nitric oxide and potassium channels are involved in brain natriuretic peptide induced vasodilatation in man. J. Hypertens., 20:493-499.
Vanderheyden M, Bartunek J, Goethals M (2004). Brain and other natriuretic peptides; molecular aspects. E. J.Heart Failure, 6:261.
Vasan RS, Benjamin EJ, Larson MG (2002).Plasma natriuretic peptides for community screening for left ventricular hypertrophy and systolic dysfunction: the Framingham heart study. JAMA, 288:1252-1259.
Vesely BA, McAfee Q, Gower Jr WR, Vesely DL (2003). Four peptides decrease the number of human pancreatic adenocarcinoma cells. Eur J. Clin. Invest. 33:998–1005.
Vesely BA, Song S, Sanchez-Ramos J (2005). Four peptide hormones decrease the number of human breast adenocarcinoma cells. Eur. J. Clin. Invest. 35: 60–69.
Vesely BA, Song S, Sanchez-Ramos J, Fitz SR, Alli AA, Solivan SM, Gower WR, Vesely DL (2005). Five cardiac hormones decrease the number of human smallcell lung cancer cells. E. J. Clin. Invest. 35:388-398.
Vesely D(2006). Which of the cardiac natriuretic peptides is most effective for the treatment of congestive heart failure, renal failure and cancer? Clin. Exp. Pharmacol. Physiol. 33:169-176.
Vesely DL (1992). Atrial Natriuretic Hormones. Englewood Cliffs NJ: Prentice HallMisono KS, Fukumi H, Grammer RT, Inagami T (1984). Rat atrial natriuretic factor: complete amino acid sequence and disulfide linkage essential for biological activity. Biochem. Biophys. Res. Commun. 119:524-529.
Vesely DL (2005). Natriuretic hormones.In: Alpern RJ Hebert SC, editors. The Kidney: Physiology and Pathophysiology, 4th edn. San Diego, CA: Elsevier/Academic Press
Vesely DL, Clark LC, Garces AH, McAfee QW, Soto J, Gower Jr WR (2004). Novel therapeutic approach for cancer using four cardiovascular hormones. Eur. J. Clin. Invest., 34:674-682.
Vesely DL, Dietz JR, Parks JR, Baig M, McCormick MT, Cintron G (1998). Vessel dilator enhances sodium and water excretion and has beneficial hemodynamic effects in persons with congestive heart failure. Circulation. 98:323-329.
Vesely DL, Douglass MA, Dietz JR (1994). Three peptides from the atrial natriuretic factor prohormone amino terminus lower blood pressure and produce diuresis, natriuresis, and/or kaliuresis in humans.Circulation. 90:1129-1240.
Vesely DL, Douglass MA, Dietz JR, Giordano AT, McCormick MT, Rodriguez- Paz G (1994). Negative feedback of atrial natriuretic peptides. J. Clin. Endocrinol. Metab. 78:1128-34.
Vesely DL, Norris JS, Walters JM, Jespersen RR, Baeyens DA (1987). Atrial natriuretic prohormone peptides 1-30, 31-67, and 79-98 vasodilate theaorta. Biochem. Biophys. Res. Commun., 148:1540-8.
Wang D, Oparil S, Feng JA, Li P, Perry G, Chen LB, Dai M, John SW, Chen Y (2003). Effects of pressure overload on extracellular matrix expression in the heart of the atrial natriuretic peptide-null mouse. Hypertension. 42:88-95.
Wang TJ, Larson MG, Levy D (2004).Plasma natriuretic peptide levels and the risk of cardiovascular events and death. N Engl J Med. 350:655-663.
Wazni M, Martin D, Marrouche N, Latif A, Ziada K, Shaaraoui M (2004). Plasma B-type natriuretic peptide levels predict postoperative atrialm fibrillation in patients undergoing cardiac surgery. Circulation, 110:124-127.
Weidmann P, Hasler L, Gnadinger MP, Lang RE, Uehlinger DE, Shaw S (1986). Blood levels and renal effects of atrial natriuretic peptide in normal man. J. Clin. Invest. 77:734-742.
Westerlind A, Wahlander H, Lindstedt G (2004). Clinical signs of heart failure are associated with increased levels of natriuretic peptides A and B in children with congenital heart defects or cardiomyopathy. Acta Paediatr. 93:603-607.
White R (2005). The role of brain natriuretic peptide in systolic heart failure. Dimens. Crit. Care Nurs. 24:171-174.
Wilcox JN, Augustine A, Goeddel DV, LoweDG. (1991).Differential regional expression of three natriuretic peptide receptor genes within primate tissues. Mol. Cell. Biol. 11:3454-3462.
Wold Knudsen CW, Vik-Mo H, Omland T (2005). Blood haemoglobin is an independent predictor of B-type natriuretic peptide levels. Clin. Sci. (Lond) 109:69-74.
Wong SK, Ma CP, Foster DC, Chen AY, Garbers DL (1995). The guanylyl cyclase-A receptor transduces an atrial natriuretic peptide/ATP activation signal in the absence of other proteins. Biol., Chem. 270:30818-30822.
Woolf AS, Mansell MA, Hoffbrand BI, Cohen SL, Moult PJ (1989). The effect of lowdose intravenous 99–126 atrial natriuretic factor infusion in patients with chronic renal failure. Postgrad. Med. J. 65:362–366.
Wu C, Wu F, Pan J, Morser J, Wu Q (2003). Furin-mediated processing of Pro-C-type natriuretic peptide. J. Biol. Chem. 278:25847– 25852.
Yancy CW, Krum H, Massie BM, Silver MA, Stevenson LW, Cheng M, Kim SS, Evans R (2007). FUSION II Investigators The Second Follow-up Serial Infusions of Nesiritide (FUSION II) trial for advanced heart failure: study rationale and design. Am. Heart J.,153:478-84.
Yasoda A, Ogawa Y, Suda M, Tamura N, Mori K, Sakuma Y, Chusho H, Shiota K, Tanaka K, Nakao K (1998). Natriuretic peptide regulation of endochondral ossification. Evidence for possible roles of the C-type natriuretic peptide/ guanylyl cyclase-B pathway. J. Biol. Chem. 273:11695–11700.
Yoshibayashi M, Kamiya T, Saito Y, Matsuo H (1993). Increased plasma levels of brain natriuretic peptide in hypertrophic cardiomyopathy. N. Engl. J. Med. 329:433–434.
Zakynthinos E, Kiropoulos Th, Gourgoulianis K, Filippatos G (2008). Diagnostic and prognostic impact of brain natriuretic peptide (BNP) in cardiac and non-cardiac diseases. Heart Lung, 37:275-285.
Zeidel ML (1995). Regulation of collecting duct Na+ reabsorption by ANP 31-67. Clin. Exp. Pharmacol. Physiol. 22:121-124.