Thirty years of the heart as an endocrine organ: physiological role and clinical utility of cardiac natriuretic hormones

Aldo Clerico, Alberto Giannoni, Simona Vittorini and Claudio Passino

Am J Physiol Heart Circ Physiol 301:H12-H20, 2011. First published 6 May 2011;
doi:10.1152/ajpheart.00226.2011

Am J Physiol Heart Circ Physiol 301: H12–H20, 2011.
First published May 6, 2011; doi:10.1152/ajpheart.00226.2011.

Thirty years of the heart as an endocrine organ: physiological role and clinical utility of cardiac natriuretic hormones

Aldo Clerico, Alberto Giannoni, Simona Vittorini, and Claudio Passino

Scuola Superiore Sant'Anna, Fondazione del Consiglio Nazionale delle Ricerche e della Regione Toscana, Gabriele Monasterio, Pisa, Italy

Submitted 7 March 2011; accepted in final form 4 May 2011

Clerico A, Giannoni A, Vittorini S, Passino C. Thirty years of the heart as an endocrine organ: physiological role and clinical utility of cardiac natriuretic hormones. *Am J Physiol Heart Circ Physiol* 301: H12–H20, 2011. First published May 6, 2011; doi:10.1152/ajpheart.00226.2011.—Thirty years ago, De Bold et al. (20) reported that atrial extracts contain some biologically active peptides, which promote a rapid and massive diuresis and natriuresis when injected in rats. It is now clear that the heart also exerts an endocrine function and in this way plays a key role in the regulation of cardiovascular and renal systems. The aim of this review is to discuss some recent insights and still-debated findings regarding the cardiac natriuretic hormones (CNHs) produced and secreted by cardiomyocytes (i.e., atrial natriuretic peptide and B-type natriuretic peptide). The functional status of the CNH system depends not only on the production/secretion of CNHs by cardiomyocytes but also on both the peripheral activation of circulating inactive precursor of natriuretic hormones and the transduction of the hormone signal by specific receptors. In this review, we will discuss the data supporting the hypothesis that the production and secretion of CNHs is the result of a complex integration among mechanical, chemical, hemodynamic, humoral, ischemic, and inflammatory inputs. The cross talk among endocrine function, adipose tissue, and sex steroid hormones will be discussed more in detail, considering the clinically relevant relationships linking together cardiovascular risk, sex, and body fat development and distribution. Finally, we will review the pathophysiological role and the clinical relevance of both peripheral maturation of the precursor of B-type natriuretic peptides and hormone signal transduction.

B-type natriuretic peptide; sex steroids; adipokines; heart failure; cardiovascular risk

THIRTY YEARS AGO, De Bold et al. (20) reported that atrial extracts contain some biological active peptides, which promote a rapid and massive diuresis and natriuresis when injected in rats. Several endogenous peptide hormones with natriuretic and vasodilator activity have been identified in the human blood and peripheral tissues (3, 30, 69, 85, 86). Atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and their related peptides are predominantly produced by atrial and ventricular cardiomyocytes. The term "cardiac natriuretic hormones" (CNHs) will be used in this review to indicate these two families of natriuretic peptides. Another natriuretic peptide, named C-type natriuretic peptide (CNP), is predominantly produced by the endothelial cells, including those of cardiac vessels. Finally, urodilatin is an NH_2-terminal (NT) 4-amino acid (aa) extented form of ANP, which is produced by the same ANP gene and secreted into the urine by renal tubular cells (16, 34, 69).

From the original observations made 30 years ago, the advances in this particular research field have determined a complete revision about the role of the heart. It is now clear that the heart also exerts an endocrine function and in this way plays a key role in the regulation of cardiovascular and renal function. The aim of this review is to discuss in details some recent insights and still-debated findings regarding the CNH system. The activity of CNH system not only depends on the production/secretion of CNHs by cardiomyocytes but is also related both to the peripheral activation of circulating inactive precursor of natriuretic hormones (such as proBNP) and to the transduction of the hormone signal by specific receptors. In the first part of the review, we will discuss the data supporting the hypothesis that the production and secretion of CNHs is the result of a complex integration among mechanical, chemical, hemodynamic, humoral, ischemic, and inflammatory inputs. The cross talk between endocrine function, adipose tissue, and sex steroid hormones will be discussed more in detail, considering the clinically relevant relationship linking together cardiovascular risk, sex, and body fat development and distribution. In the second part of this review, we will discuss the recent evidence regarding the influence on the biological effects of the CNHs exerted by both the peripheral maturation of proBNP and the alteration in the hormone transduction process.

Address for reprint requests and other correspondence: A. Clerico, Laboratory of Cardiovascular Endocrinology and Cell Biology, Fondazione CNR-Regione Toscana G. Monasterio, Scuola Superiore Sant'Anna, Via Trieste 41, 56126 Pisa, Italy (e-mail: clerico@ifc.cnr.it).

The Regulation of Gene Expression and Production/Secretion of ANP and BNP in Cardiomyocytes

CNHs are synthesized by cardiomyocytes as prohormones (i.e., proANP and proBNP), which are then split into two fragments at the time of secretion: the longer fragment includes the inactive NT peptide (i.e., NT-proANP and NT-proBNP), whereas the shorter one (i.e., COOH-terminus fragment) represents the active hormone (i.e., ANP and BNP) (34). Studies on structure-activity relationships have underscored the importance of the ring structure of CNHs, related to a disulfide cysteine bridge, which is necessary for the binding to the specific receptors. For this reason, only ANP and BNP, presenting the disulfide bridge in the peptide chain, hold hormonal activity.

Atrial cardiomyocytes store prohormones (proANP and proBNP) in secretory granules (16, 34, 69). In particular, human BNP is synthesized as a 134-aa precursor protein (preproBNP) and is subsequently processed during secretion to form the 108-aa peptide, proBNP. The propeptide hormones of cardiac natriuretic peptides can be enzymatically cleaved by proprotein convertases produced in the cardiomyocytes, such as corin and furin (24, 34, 43, 49). Indeed, the precursor proBNP is processed to form the 76-aa NT peptide (i.e., NT-proBNP), and then the biologically active 32-aa COOH-terminal peptide (i.e., BNP).

Although the distension of atrial and ventricular cardiomyocytes is generally considered the main mechanical stimulus for the production/secretion of ANP and BNP (57), endothelin-1, α-adrenergic agonists, and angiotensin II are also powerful stimulators of production and/or release of CNHs by cardiomyocytes (34, 52, 67) (Fig. 1 and Table 1). Furthermore, several studies reported that arginine vasopressin (97), glucocorticoids (21, 64, 65), thyroid hormones (4, 33), female sex steroids (15, 60), some growth factors (27, 39), and some cytokines (e.g., TNF-α, interleukin-1, and interleukin-6) (19, 60, 90) stimulate CNH production/secretion (Table 1). On the contrary, nitric oxide (NO) exerts a direct inhibitory effect on the production/secretion of CNHs (37, 48, 107) (Table 1) and also counteracts their relaxant action on cardiac vessels by desensitizing the big conductance calcium-activated potassium channels of vascular smooth muscle (56).

It is generally believed that ANP is predominantly produced in the atria, whereas BNP is predominantly produced in the ventricles (16). Indeed, the specific atrial granules of cardiomyocytes predominantly contain proANP (67). Experimental animal models and clinical studies in patients with cardiovascular diseases have demonstrated that CNH synthesis and secretion may be differently regulated in atrial versus ventricular cardiomyocytes and probably during neonatal versus adult life (34, 59, 67, 69). Ventricular cardiomyocytes do not usually display secretory granules at electron microscopy in the normal heart (44, 47), whereas granules, similar to the atrial ones, have been observed in samples of ventricular myocardium collected during surgery or endocardial biopsies in patients with cardiac disease (34, 63).

According to these findings, under physiological conditions, ventricular myocardium produces only a limited amount of BNP; conversely, several pathophysiological mechanisms, such as ventricular hypertrophy, inflammation, and fibrosis, stimulate BNP production and release from ventricular cardiomyocytes (19, 60, 69, 77, 102). Furthermore, myocardial ischemia and perhaps hypoxia per se can induce the synthesis/secretion of BNP and its related peptides by ventricular cells, even when isolated and cultured (8, 12, 33, 89, 94) (Fig. 1). Mammalian cells respond to low oxygen with an increased expression of several hypoxia-inducible genes. The master regulator of this cellular adaptation to hypoxia is the hypoxia-inducible factor, which is a heterodimeric transcription factor. Some studies indicate that low oxygen conditions induce the expression of hypoxia-inducible factor-1a, which in turn acti-

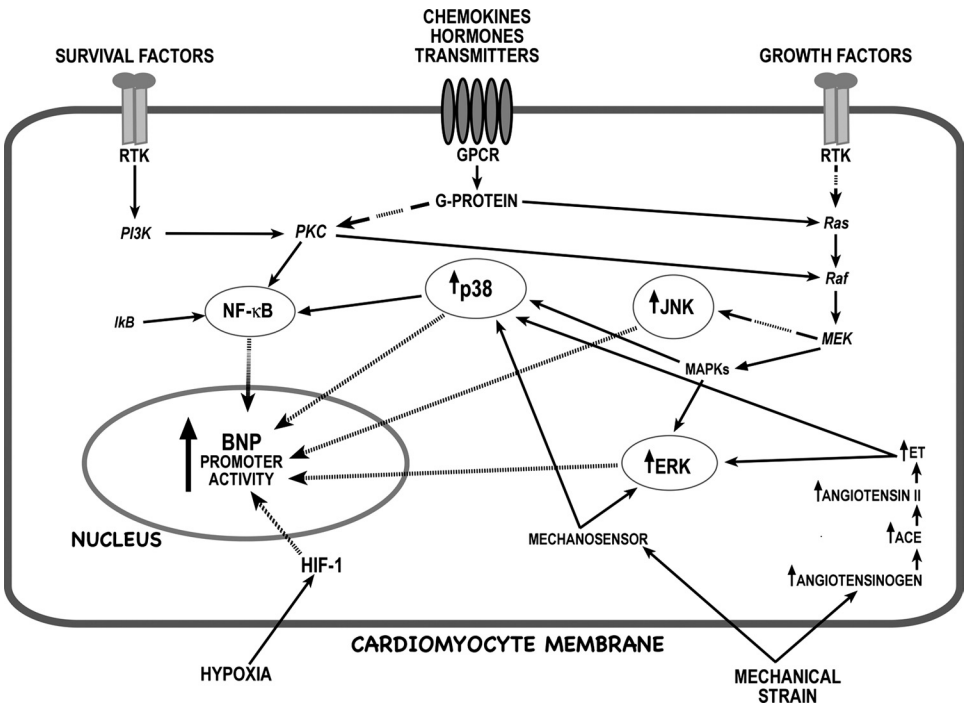

Fig. 1. Highly schematic representation of brain natriuretic peptide (BNP) gene regulation in the cardiomyocyte. BNP production by cardiomyocytes may be affected by a huge number of neurohormones, cytokines, and survival and growth factors, as well as by mechanical strain and hypoxia. The stimulation (or inhibition) of the MAPK activity and the transcriptor factor NF-κB may play a relevant role in many of these regulatory pathways (according to Refs 8, 13, 19, 34, 57, 60, 67, 91, 93, and 104). As indicated, low oxygen conditions (hypoxia) can activate both atrial natriuretic peptide and BNP transcription throughout an alternative pathway by inducing the expression of hypoxia-inducible factor (HIF)-1α (Refs. 13, 104). GPCR, G protein-coupled receptor; PKC, protein kinase C; PI3K, posphoinositide 3-kinase; RTK, receptor of tyrosine kinase; ACE, angiotensin-converting enzyme; ET, endothelin.

Table 1. *Biological factors suggested to stimulate or inhibit the production/secretion of CNHs in vivo or in cell culture of cardiomyocytes*

Suggested Factors	Suggested Mean Intracellular Signaling Mechanism	References
Stimulating		
Mechanical strain	Transcription factor NF-κB activated by p38 MAPK	57
Angiotensin II	Transcription factor NF-κB activated by p38 MAPK	34, 52, 67
Endothelin-1	Transcription factor NF-κB activated by p38 MAPK	34, 52, 67
α-Adrenergic agents	Transcription factor NF-κB activated by p38 MAPK	16, 34, 52, 67
Arginine vasopressin	Ca^{2+} influx and PKC	97
Cytokines (including IL-1, IL-6, TNF-α)	Transcription factor NF-κB activated by p38 MAPK	19, 60
Growth factors (such as bFGF)	MAPK	27, 39
Prostaglandins (such as $PGF_{2\alpha}$ and PGD_2)	PLC, IP_3, PKC, and MLCK pathway	5, 54
Lipolysaccharide	Transcription factor NF-κB activated by p38 MAPK	19
Chromogranin B	Transcription factor NF-κB and IP_3/Ca^{2+} influx	41
Thyroid hormones	Thyroid hormone regulatory element	4, 21, 32, 65, 66, 69
Corticosteroids	Glucocorticoid responsive element	21, 65, 66, 69
Estrogens	Not yet determined	51, 61
Inhibiting		
Androgens	Not yet determined	9, 42, 76
Nitric oxide	Transcription factor JMJ	37, 48, 107

CNH, cardiac natriuretic hormone; MAPK, mitogen-activated protein kinase; PKC, protein kinase C; IL, interleukin; TNF, tumor necrosis factor; bFGF, basic fibroblastic growth factor; PG, prostaglandin; PLC, phospholipase C; IP_3, inositol 1,4,5-trisphosphate; MLCK, myosin light chain kinase; JMJ, jumonji domain-containing protein.

vates both ANP and BNP transcription (13, 104). These data may explain the increased BNP levels observed in patients with ischemic heart diseases and preserved ventricular function (16, 35, 69).

Studies using culture of cardiomyocytes (especially from rodents) have demonstrated that several factors (including calcium, catecholamines, endothelins, angiotensin II, and some cytokines) can regulate the expression of ANP and BNP genes throughout the same transcriptional factors, including p38 mitogen-activated protein kinase (MAPK) (19, 34, 41, 50, 52, 56, 60, 91), as indicated in Fig. 1. A still unresolved question is the role of insulin on the regulation of production/secretion of CNHs by cardiomyocytes. Some studies (2, 6, 18) indicated that insulin has a potent acute anti-inflammatory effect, which is mediated by the inhibition of transcription factor NF-κB. According to these studies (2, 6, 18), an inhibitory role of insulin on the production/secretion of CNHs may be hypothesized. However, to our knowledge, only the study by Tokudome et al. (92) was performed with the specific aim to examine the direct effects of insulin on the secretion/production of CNHs from cardiomyocytes. This study reported that insulin increased ANP secretion and gene expression in cultures of rat cardiomyocytes, whereas glucose had no effect (92). These conflicting results suggest that further studies are necessary to clarify the complex biochemical pathways and molecular mechanisms responsible for CNH production in cardiomyocytes (34).

The Cross Talk Between the Cardiac Endocrine Function and Adipose Tissue System

Since some adipokines (such as leptin, resistin, and visfatin) are able to activate the transcription factor NF-κB (1, 55, 84, 93, 101), it may be hypothesized that these adipokines also have a stimulatory action on ANP and BNP throughout this metabolic pathway. However, Mascareno et al. (64) reported that leptin has antihypertrophic action in vivo in mice, rather than a hyperthrophic effect, as expected by the studies in the culture of ventricular cardiomyocytes. This effect is indeed mediated in vivo by CNHs, since leptin was found to increase the expression of the ANP gene by the activation of nuclear factor of activated T-cell domain of ANP gene promoter (64). On the contrary, Yuan et al. (107) reported that intravenous infusion of leptin reduces ANP plasma levels via an NO-dependent mechanism in rats. Therefore, these studies point out that CNH production/secretion by cardiomyocytes can be differently regulated by the same biological factor (such as leptin) throughout multiple metabolic pathways activated, or inhibited, according to different pathophysiological conditions.

On the other hand, recent findings indicated that CNHs have a role in the regulation of fat tissue function and growth (17) and also exert potent lipolytic effects in human fat cells (52). Furthermore, ANP can increase the production of adiponectin (95), a polypeptide involved in glucose and free fatty acid metabolism (so to be protective in diabetes and metabolic syndrome), whereas the release of leptin is inhibited in culture of human adipocytes (28, 68).

The above-mentioned studies indicate that there is a cross talk between the cardiac endocrine function and adipose tissue. From a pathophysiological point of view, further studies on the interrelationship between CNHs and adipokines may allow new insights on the link between metabolic disorders (such as diabetes mellitus, metabolic syndrome, and obesity), body fat distribution, and increased cardiovascular risk (7, 15). Indeed, a still unexplained finding is the lower CNH levels found in obese compared with lean health subjects and patients with heart failure (HF) (15). Although the increased expression of clearance natriuretic peptide receptor (i.e., NPR-C) in fat tissue can, at least in part, explain this finding (see *Resistance to the Biological Effects of CNHs*), the increased production of some adipokines may be a good explanation for a link relating the increased visceral fat tissue to reduced circulating levels of CNHs. A good candidate should be a biological substance (or more substances) showing inhibitory properties on the production/secretion of CNHs and released by fat tissue.

The Cross Talk Between Cardiac Natriuretic and Sex Steroid Hormones

According to the hypothesis that CNHs share complex interactions with the neurohormonal system, the interest on the interrelationships between cardiac endocrine and gonadal functions progressively increased throughout the first 10 years of this century. Cardiovascular risk is significantly lower in healthy premenopausal women compared with men, a difference abolished after menopause, suggesting an important role for female sex steroid estrogens on pathophysiological mechanisms related to cardiovascular diseases (15, 51). On the other hand, CNHs exert some cardioprotective actions, including *1*) decrease in blood pressure; *2*) increase in natriuresis and diuresis; and *3*) inhibition of both the sympathetic nervous system and the release or action of several hormones, including aldosterone, angiotensin II, endothelins, renin, and vasopressin (16). Kuroski de Bold (51) hypothesized that the lower cardiovascular risk of healthy fertile women compared with men is, at least in part, due to the stimulatory effect of sex female steroid hormones on cardiac endocrine function, in this way virtually opening the search for some pathophysiological mechanisms linking together sex, endocrine function, and cardiovascular risk.

There are only few experimental studies in animal models specifically designed to investigate the influence of sex steroid hormones on cardiac endocrine function (15). These studies have some important limitations: rodents rather than primates, and castrated rather than fertile animals, have been studied. As a consequence, the results of these studies should be applied with extreme caution to healthy fertile men and women. Experimental studies in animals have pointed out that female sex steroids increase ANP gene expression in a dose-dependent manner and that both estradiol and progesterone are necessary to maintain suitable levels of ANP gene expression in rat cardiomyocytes (15). Furthermore, hormone replacement therapy with female steroid hormones shows a stimulatory action on the production/secretion of CNHs in postmenopausal women (46, 61).

As far as the effects of androgens on the production/secretion of CNHs are concerned, the currently available data are still conflicting. Results of experimental studies with atrial cultured myocytes of newborn rats suggested that testosterone stimulates the synthesis and secretion of both ventricular and atrial ANP (65, 66). On the contrary, in another study, performed in castrated male rats, plasma ANP concentration and atrial stores were found to be increased and testosterone replacement was associated with a decrease in plasma ANP concentration, but not in atrial stores (42). In a clinical study, androgen receptor blockade and, to a lesser extent, androgen suppression were found to increase NT-proBNP plasma value in men with prostate cancer (23).

More recently, two large population-based studies have attempted to clarify the role of male sex steroid hormones on the regulation of cardiac endocrine function in humans. The Dallas Heart Study, observed by Chang et al. (9), reported no association between estrogen status and NT-proBNP levels, whereas a strong inverse association was found between measures of free testosterone and NT-proBNP in young women (age range, 35–49 yr). Saenger et al. (76) reported an inverse association of NT-proBNP with serum testosterone, a direct association with sex hormone-binding globulin, and no significant association with circulating levels of estradiol in a large population of girls and boys (age range, from 2 mo up to 18 yr).

The above-mentioned data suggest that female and male sex steroid hormones together contribute to the regulation of production/secretion of CNHs: estrogens may have a stimulatory, whereas androgens a inhibitory, action (15). The interrelationships between CNHs and steroid hormones may be schematically represented by three distinct retroactive mechanisms. In normal cycling women, natriuretic peptides may share an inhibitory action on steroidogenesis, follicular development, granulosa cell maturation, and ovulation, whereas estrogens have a stimulatory effect on the production/secretion of ANP and BNP production/secretion by cardiomyocytes. Conversely, in adult men, natriuretic peptides may share a stimulatory effect on testis steroidogenesis, whereas androgens may have an inhibitory effect on ANP and BNP production/secretion by cardiomyocytes. Adrenal corticosteroids (including glucocorticosteroids and mineralcorticosteroids) show both direct and indirect stimulating actions on cardiac endocrine function, whereas CNHs inhibit the production of corticosteroids by adrenal gland both directly throughout the specific natriuretic peptide receptors on zona fasciculata and glomerulosa cells of adrenal gland and indirectly by inhibiting the action of renin-angiotensin system. However, although fascinating, this hypothesis needs further evidence. In particular, it should be elucidated whether sex steroids are actually able to affect (increase or decrease) the production/secretion of BNP in mammalian cardiomyocytes both in cell cultures and in vivo (15).

Plasma proBNP May Be a Circulating Precursor of Active BNP Hormone

Cardiac endocrine function has attracted the attention of clinicians when the pivotal role of CNHs in the pathophysiology of HF was established (10, 11, 16, 36, 69). Furthermore, the introduction of the assay of B-type-related natriuretic peptides in clinical practice has resulted in a significant accuracy improvement of the diagnostic and prognostic stratification workup in patients with cardiac diseases (14, 22, 25, 26, 29, 45, 70).

A deficient response of cardiac endocrine function was proposed to explain the altered electrolyte and fluid homeostasis occurring in chronic HF (16). This phenomenon, defined as the "endocrine paradox" of the heart (33, 36), is characterized by extremely high-circulating levels of hormones with powerful diuretic/natriuretic and vasodilator activity in patients with congestive HF, showing signs of fluid retention and vasoconstriction. Some recent findings suggest that the posttranslational processing of ventricular proBNP is not efficient in HF patients. As a consequence, the great part of BNPs, assayed in these patients, is devoid of biological activity (11, 34, 58).

In addition to bioactive $BNP_{1–32}$, a huge numbers of circulating proBNP-derived fragments can be identified by chromatographic procedures in human plasma, including the intact and glycosylated forms of precursor proBNP and NT-truncated BNP form 3–32 (34, 43, 58, 80–83). When compared with inactive peptides proBNP and NT-proBNP, the active peptide BNP has a shorter plasma half-life (~15–20 min vs. 1 or 2 h) and consequently lower plasma concentration (Table 2).

Table 2. *Biochemical and physiological characteristics of BNP, NT-proBNP, and proBNP peptides*

	BNP	NT-proBNP	proBNP
Molecular mass, Da	3,462	8,457*	11,900*
Amino acids	32	76	108
Biological function	active hormone	inactive	prohormone
Half-life, min	15–20	>60	>60
Glycosylation	not glycosylated	Highly glycosylated in vivo	Highly glycosylated in vivo

*Molecular mass of NH_2-terminal (NT)-pro-brain natriuretic peptide (proBNP) and proBNP depends on the degree of glycosylation of the peptide. Reported are the molecular masses of nonglycosylated peptides.

Recent studies demonstrated that the intact or glycosylated forms of proBNP constitute a significant portion of immunoreactive B-type-related peptides circulating in plasma of patients with HF (34, 58, 80–83). According to these findings, it is theoretically conceivable that the active hormone (i.e., BNP) may be produced even in vivo from the circulating intact precursor proBNP through enzymatic cleavage by some plasma proteases (24, 43, 49). Indeed, a very recent study demonstrated that the processing of human proBNP to active BNP can occur in the circulation by means of in vivo in a rat model (81). The above-mentioned studies (11, 34, 43, 58) open a new and more complex scenario regarding the circulating BNPs: the intact precursor proBNP might be actually considered a circulating prohormone. This hypothesis assumes that the peripheral processing of circulating proBNP would be submitted to regulatory rules, possibly altered with HF progression.

Resistance to the Biological Effects of CNHs

All natriuretic peptides share a direct diuretic, natriuretic, and vasodilator effect as well as an inhibitory action on the inflammatory processes of both myocardium and smooth muscle cells (19, 40, 62), thus exerting a protective effect on endothelial dysfunction and vascular remodeling (71, 79, 98). These effects are mediated by two different guanylate cyclase-coupled receptors, NPR-A (more specific for ANP and BNP) and NPR-B (more specific for CNP), whereas a third specific receptor NPR-C, not coupled to a guanylate cyclase, has essentially a clearance function for all natriuretic peptides (16).

A blunted natriuretic response after pharmacological doses of ANP and BNP has been observed in experimental models and in patients with chronic HF, suggesting a resistance to the biological effects of CNHs, principally natriuresis (10, 73, 100). As discussed in detail previously (11, 16), resistance to the biological action of CNHs can be attributed at least to three different causes/mechanisms, acting at prereceptor, receptor, and postreceptor levels, respectively (Table 3).

As concerns the prereceptor level, recent studies suggest that in patients with HF, there is an insufficient posttranslation maturation of the biosynthetic precursors of BNP system (i.e., proBNP). An insufficient maturation of proBNP can be caused by an altered processing that may occur before (i.e., within the cardiomyocyte) or after (i.e., in the bloodstream) the secretion of the prohormone (33, 36). Circulating proBNP can be processed in vivo in the human blood by a soluble form of protease corin. Indeed, corin is present in human blood (24), and so this enzyme can process the circulating intact precursors of natriuretic hormones (49). Furthermore, plasma corin levels have been found to be significantly lower in HF patients than in healthy controls with a reduction in the plasma enzyme levels paralleled by the severity of the disease (24). An altered processing of proBNP might represent a possible future therapeutical target, i.e., by developing drugs able to induce the cleavage of the prohormone into the active BNP. Furthermore, the measurement of circulating corin levels may be used as a diagnostic and/or prognostic biomarker of HF (24).

Considering the possible causes of resistance at the receptor level (Table 3), it is theoretically conceivable that an increased expression of the NPR-C in some peripheral tissues can increase the peripheral clearance of CNHs throughout this specific way, thus reducing their circulating levels. It is well known that obese individuals have reduced levels in circulating BNP compared with lean subjects (15, 78). The finding that NPR-C is overexpressed in adipocytes of obese individuals allowed an explanation for these reduced CNH levels in obese subjects (15, 78). Moreover, some gene polymorphisms of specific natriuretic peptide receptors have associated with some cardiovascular diseases, including systemic arterial hypertension (72, 74, 96, 106), cardiomyopathy (103), and stroke (75). However, the true clinical impact of these studies is still debated, considering that the most frequent cardiovascular diseases are polygenic disorders (99).

Finally, at the postreceptor level, an increased activity of the cGMP phosphodiesterase (PDE) V, which metabolizes cGMP, may contribute to increase the resistance to the natriuretic peptide action. The CNHs and NO systems are activated in congestive HF, resulting in an increased synthesis of cGMP, which serves as a second messenger for both humoral systems (88). In severe chronic experimental HF, glomerular cGMP accumulation decreases in response to both ANP and sodium nitroprusside, whereas cGMP- and cGMP-PDE activities are enhanced (88). In vivo, cGMP PDE V inhibition was reported to markedly potentiate the natriuretic response to acute volume expansion, an effect that was attenuated by the administration of a monoclonal antibody directed against ANP (105). Forfia et al. (31) demonstrated that the inhibition of PDE V by sildenafil

Table 3. *Classification of possible mechanisms of resistance to biological effects of CNH*

Prereceptor level
A) Presence of inactive peptides in plasma
B) Increase in inactivation/degradation of active peptides
1) Upregulation of NPR-C
2) Increased activity of proteases
C) Decreased renal filtration
Receptor level
A) Downregulation of NPR-A and NPR-B in target tissues
B) Altered CNH receptor binding or desensitization
Postreceptor level (activated counterregulatory mechanisms)
Altered intracellular signaling
1) Decreased cGMP cellular accumulation (decreased production or increased degradation)
2) Altered intracellular pathways downstream cGMP

NPR-A, NPR-B, and NPR-C, natriuretic peptide receptor typres A, B, and C, respectively.

had minimal effects on cardiovascular hemodynamics in healthy dogs; conversely, when sildenafil was administered to HF animals, it exerted similar hemodynamic effects as synthetic BNP, and the combination of BNP and sildenafil was additive in reducing pulmonary pressures. These findings demonstrated that an increased PDE V activity is involved in the pathophysiology of HF, suggesting a novel possible pharmacological target.

Conclusions and Prospective Remarks

A huge number of experimental and clinical studies, published in the first decade of this century, have added further support to the hypothesis that that human heart is a relevant component of a complex network including endocrine, nervous, and immune systems. In particular, novel research fields have been intensively developed with the aim to elucidate the complex interrelationships between cardiac endocrine function, sex steroid hormones, and adipokine systems (15). However, some issues need to be further investigated.

Although fascinating, the hypothesis that gonadal function regulates both body fat distribution and cardiac endocrine function needs further evidence (15). In particular, it is still lacking the conclusive demonstration that sex steroids (especially androgens) are able to actually affect (increase or decrease) the production/secretion of CNHs from mammalian (including human) cardiomyocytes both in cell cultures and in vivo.

Obesity is associated with ectopic lipid deposition even in the heart, which may directly exert a lipotoxic effect on the myocardium by locally secreting several cytokines and adipokines (38). These substances may affect both the endocrine and the contractile function of the cardiomyocytes through a paracrine effect (38). However, the specific role of adipokines in the CNH production/secretion process needs to be further investigated.

These studies will hopefully shed light on the complex, but clinically relevant, interrelationships between cardiovascular risk, sex, and body fat mass and distribution (7, 15, 51).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES

1. **Adya R, Tan BK, Chen J, Randeva HS.** Nuclear factor-kappaB induction by visfatin in human vascular endothelial cells: its role in MMP-2/9 production and activation. *Diabetes Care* 31: 758–760, 2008.
2. **Aljada A, Ghanim H, Mohanty P, Kapur N, Dandona P.** Insulin inhibits the pro-inflammatory transcription factor early growth response gene-1 (Egr)-1 expression in mononuclear cells (MNC) and reduces plasma tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1) concentrations. *J Clin Endocrinol Metab* 87: 1419–1422, 2002.
3. **Arden KC, Viars CS, Weiss S, Argentin S, Nemer M.** Isolation and identification of rat brain natriuretic peptides in cardiac atrium. *Biochem Biophys Res Commun* 163: 226–232, 1989.
4. **Argentin S, Drouin J, Nemer M.** Thyroid hormone stimulates rat pro-natriodilatin mRNA levels in primary cardiocyte cultures. *Biochem Biophys Res Commun* 146: 1336–1341, 1987.
5. **Bai G, Gao S, Shah A, Yuan K, Park WH, Kim SH.** Regulation of ANP secretion from isolated atria by prostaglandins and cyclooxygenase-2. *Peptides* 30: 1720–1728, 2009.
6. **Bi Y, Sun WP, Chen X, Li M, Liang H, Cai MY, Zhu YH, He XY, Xu F, Weng JP.** Effect of early insulin therapy on nuclear factor kappaB and cytokine gene expressions in the liver and skeletal muscle of high-fat diet, streptozotocin-treated diabetic rats. *Acta Diabetol* 45: 167–178, 2008.
7. **Canoy D.** Coronary heart disease and body fat distribution. *Curr Atheroscler Rep* 12: 125–133, 2010.
8. **Casals G, Ros J, Sionis A, Davidson MM, Morales-Ruiz M, Jiménez W.** Hypoxia induces B-type natriuretic peptide release in cell lines derived from human cardiomyocytes. *Am J Physiol Heart Circ Physiol* 297: H550–H555, 2009.
9. **Chang AY, Abdullah SM, Jain T, Stanek HG, Das SR, McGuire DK, Auchus RJ, de Lemos JA.** Associations among androgens, estrogens, and natriuretic peptides in young women: observations from the Dallas Heart Study. *J Am Coll Cardiol* 49: 109–116, 2007.
10. **Charloux A, Piquard F, Doutreleau S, Brandenberger G, Geny B.** Mechanisms of renal hyporesponsiveness to ANP in heart failure. *Eur J Clin Invest* 33: 769–778, 2003.
11. **Chen HH.** Heart failure. A state of brain natriuretic peptide deficiency or resistance or both! *J Am Coll Cardiol* 49: 1089–1091, 2007.
12. **Chiu CZ, Wang BW, Chung TH, Shyu KG.** Angiotensin II and the ERK pathway mediate the induction of myocardin by hypoxia in cultured rat neonatal cardiomyocytes. *Clin Sci (Lond)* 119: 273–282, 2010.
13. **Chun YS, Hyun JY, Kwak YG, Kim IS, Kim CH, Choi E, Kim MS, Park JW.** Hypoxic activation of the atrial natriuretic peptide gene promoter through direct and indirect actions of hypoxia-inducible factor-1. *Biochem J* 370: 149–157, 2003.
14. **Clerico A, Fontana M, Ripoli A, Emdin M.** Clinical relevance of BNP measurement in the follow-up of patients with chronic heart failure. *Adv Clin Chem* 48: 163–179, 2009.
15. **Clerico A, Fontana M, Vittorini S, Emdin M.** The search for a pathophysiological link between gender, cardiac endocrine function, body mass regulation and cardiac mortality: proposal for a working hypothesis. *Clin Chim Acta* 405: 1–7, 2009.
16. **Clerico A, Recchia FA, Passino C, Emdin M.** Cardiac endocrine function is an essential component of the homeostatic regulation network: physiological and clinical implications. *Am J Physiol Heart Circ Physiol* 290: H17–H29, 2006.
17. **Costello-Boerrigter LC, Burnett JC Jr.** A new role for the natriuretic peptides: metabolic regulators of the adipocyte. *J Am Coll Cardiol* 53: 2078–2079, 2009.
18. **Dandona P, Aljada A, Mohanty P, Ghanim H, Hamouda W, Assian E, Ahmad S.** Insulin inhibits intranuclear nuclear factor kappaB and stimulates IkappaB in mononuclear cells in obese subjects: evidence for an anti-inflammatory effect? *J Clin Endocrinol Metab* 86: 3257–3265, 2001.
19. **De Bold AJ.** Natriuretic peptides gene expression and secretion in inflammation. *J Investig Med* 57: 29–32, 2009.
20. **De Bold AJ, Borenstein HB, Veress AT, Sonnenberg H.** A rapid and important natriuretic response to intravenous injection of atrial myocardial extracts in rats. *Life Sci* 28: 89–94, 1981.
21. **Deschepper CF, Nguyen KP, Lapointe MC, Zahs KR, Gardner DG.** Production and differential endocrine regulation of atrial natriuretic peptide in neuron-enriched primary cultures. *Endocrinology* 128: 5–12, 1991.
22. **Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Strömberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K; ESC Committee for Practice Guidelines (CPG).** ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur J Heart Fail* 10: 933–989, 2008.
23. **Dockery F, Bulpitt CJ, Agarwal S, Vernon C, Nihoyannopoulos P, Kemp M, Hooper J, Rajkumar C.** Anti-androgens increase N-terminal pro-BNP levels in men with prostate cancer. *Clin Endocrinol (Oxf)* 68: 59–65, 2008.
24. **Dong N, Chen S, Yang J, He L, Liu P, Zheng D, Li L, Zhou Y, Ruan C, Plow E, Wu Q.** Plasma soluble corin in patients with heart failure. *Circ Heart Fail* 3: 207–211, 2010.
25. **Doust JA, Glasziou PP, Pietrzak E, Dobson AJ.** A systematic review of the diagnostic accuracy of natriuretic peptides for heart failure. *Arch Intern Med* 164: 1978–1984, 2004.

26. **Doust JA, Pietrzak E, Dobson A, Glasziou P.** How well does B-type natriuretic peptide predict death and cardiac events in patients with heart failure: systematic review. *BMJ* 330: 625, 2005.
27. **Eppenberger-Eberhardt M, Aigner S, Donath MY, Kurer V, Walther P, Zuppinger C, Schaub MC, Eppenberger HM.** GF-I and bFGF differentially influence atrial natriuretic factor and alpha-smooth muscle actin expression in cultured atrial compared to ventricular adult rat cardiomyocytes. *J Mol Cell Cardiol* 29: 2027–2039, 1997.
28. **Fain JN, Kanu A, Bahouth SW, Cowan GS, Lloyd Hiler M.** Inhibition of leptin release by atrial natriuretic peptide (ANP) in human adipocytes. *Biochem Pharmacol* 65: 1883–1888, 2003.
29. **Felker GM, Hasselblad V, Hernandez AF, O'Connor CM.** Biomarker-guided therapy in chronic heart failure: a meta-analysis of randomized controlled trials. *Am Heart J* 158: 422–430, 2009.
30. **Flynn TG, de Bold ML, de Bold AJ.** The amino acid sequence of an atrial peptide with potent diuretic and natriuretic properties. *Biochem Biophys Res Commun* 117: 859–865, 1983.
31. **Forfia PR, Lee M, Tunin RS, Mahmud M, Champion HC, Kass DA.** Acute phosphodiesterase 5 inhibition mimics hemodynamic effects of B-type natriuretic peptide and potentiates B-type natriuretic peptide effects in failing but not normal canine heart. *J Am Coll Cardiol* 49: 1079–1088, 2007.
32. **Gardner DG.** Natriuretic peptides: markers or modulators of cardiac hypertrophy? *Trends Endocrinol Metab* 14: 411–416, 2003.
33. **Goetze JP.** Biochemistry of pro-B-type natriuretic peptide-derived peptides: the endocrine heart revisited. *Clin Chem* 49: 1503–1510, 2004.
34. **Goetze JP.** Biosynthesis of cardiac natriuretic peptides. *Results Probl Cell Differ* 50: 97–112, 2010.
35. **Goetze JP, Gore A, Moller CH, Steinbruchel DA, Rehfeld JF, Nielsen LB.** Acute myocardial hypoxia increases BNP gene expression. *FASEB J* 18: 1929–1930, 2004.
36. **Goetze JP, Kastrup J, Rehfeld JF.** The paradox of increased natriuretic hormones in congestive heart failure patients: does the endocrine heart also fail in heart failure? *Eur Heart J* 24: 1471–1472, 2003.
37. **Gomes DA, Reis WL, Ventura RR, Giusti-Paiva A, Elias LL, Cunha FQ, Antunes-Rodrigues J.** The role of carbon monoxide and nitric oxide in hyperosmolality-induced atrial natriuretic peptide release by hypothalamus in vitro. *Brain Res* 1016: 33–39, 2004.
38. **Gualillo O, Gonzalez-Juanately JR, Lago F.** The emerging role of adipokines as mediators of cardiovascular function: physiologic and clinical perspectives. *Trends Cardiovasc Med* 17: 275–283, 2007.
39. **Harder BA, Schaub MC, Eppenberger HM, Eppenberger-Eberhardt M.** Influence of fibroblast growth factor (bFGF) and insulin-like growth factor (IGF-I) on cytoskeletal and contractile structures and on atrial natriuretic factor (ANF) expression in adult rat ventricular cardiomyocytes in culture. *J Clin Invest* 98: 1737–1744, 1996.
40. **Hardt SE, Sadoshima J.** Negative regulators of cardiac hypertrophy. *Cardiovasc Res* 63: 500–509, 2004.
41. **Heidrich FM, Zhang K, Estrada M, Huang Y, Giordano FJ, Ehrlich BE.** Chromogranin B regulates calcium signaling, nuclear factor kappaB activity, and brain natriuretic peptide production in cardiomyocytes. *Circ Res* 102: 1230–1238, 2008.
42. **Hwu CM, Tsai SC, Lau CP, Pu HF, Wang TL, Chiang ST, Wang PS.** Increased concentrations of atrial and plasma atrial natriuretic peptide in castrated male rats. *Life Sci* 52: 205–212, 1993.
43. **Ichiki T, Huntley BK, Heublein DM, Sandberg SM, McKie PM, Martin FL, Jougasaki M, Burnett JC Jr.** Corin is present in the normal human heart, kidney, and blood, with pro-B-type natriuretic peptide processing in the circulation. *Clin Chem* 57: 40–47, 2011.
44. **Jamieson JD, Palade GE.** Specific granules in atrial muscle cell. *J Cell Biol* 23: 151–162, 1964.
45. **Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, Konstam MA, Mancini DM, Rahko PS, Silver MA, Stevenson LW, Yancy CW.** 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* 119: 1977–2016, 2009.
46. **Kawano H, Nagayoshi Y, Soejima H, Tanaka Y, Hokamaki J, Miyamoto S, Miyazaki Y, Yamabe H, Ogawa H.** B-type natriuretic peptide after hormone therapy in postmenopausal women with chest pain and normal coronary angiogram. *Menopause* 15: 352–356, 2008.
47. **Kirsh B.** Electronmicroscopy of the atrium of the heart. I. Guinea pig. *Exp Med Surg* 14: 99–112, 1956.
48. **Klassen SS, Rabkin SW.** Nitric oxide induces gene expression of Jumonji and retinoblastoma 2 protein while reducing expression of atrial natriuretic peptide precursor type B in cardiomyocytes. *Folia Biol (Praha)* 54: 65–70, 2008.
49. **Knappe S, Wu F, Masikat MR, Morser J, Wu Q.** Functional analysis of the transmembrane domain and activation cleavage of human corin: design and characterization of a soluble corin. *J Biol Chem* 278: 52363–52370, 2003.
50. **Kudoh S, Akazawa H, Takano H, Zou Y, Toko H, Nagai T, Komuro I.** Stretch-modulation of second messengers: effects on cardiomyocyte ion transport. *Prog Biophys Mol Biol* 82: 57–66, 2003.
51. **Kuroski de Bold ML.** Estrogen, natriuretic peptides and the renin-angiotensin system. *Cardiovasc Res* 41: 524–531, 1999.
52. **Kuwahara K, Kinoshita H, Kuwabara Y, Nakagawa Y, Usami S, Minami T, Yamada Y, Fujiwara M, Nakao K.** Myocardin-related transcription factor A is a common mediator of mechanical stress- and neurohumoral stimulation-induced cardiac hypertrophic signaling leading to activation of brain natriuretic peptide gene expression. *Mol Cell Biol* 30: 4134–4148, 2010.
53. **Lafontan M, Moro C, Berlan M, Crampes F, Sengenes C, Galitzky J.** Control of lipolysis by natriuretic peptides and cyclic GMP. *Trends Endocrinol Metab* 19: 130–137, 2008.
54. **Lai J, Jin H, Yang R, Winer J, Li W, Yen R, King KL, Zeigler F, Ko A, Cheng J, Bunting S, Paoni NF.** Prostaglandin $F_{2\alpha}$ induces cardiac myocyte hypertrophy in vitro and cardiac growth in vivo. *Am J Physiol Heart Circ Physiol* 271: H2197–H2208, 1996.
55. **Lappas M, Permezel M, Rice GE.** Leptin and adiponectin stimulate the release of proinflammatory cytokines and prostaglandins from human placenta and maternal adipose tissue via nuclear factor-kappaB, peroxisomal proliferator-activated receptor-gamma and extracellularly regulated kinase 1/2. *Endocrinology* 146: 3334–3342, 2005.
56. **Liang CF, Au AL, Leung SW, Ng KF, Félétou M, Kwan YW, Man RY, Vanhoutte PM.** Endothelium-derived nitric oxide inhibits the relaxation of the porcine coronary artery to natriuretic peptides by desensitizing big conductance calcium-activated potassium channels of vascular smooth muscle. *Cell Physiol Biochem* 25: 443–450, 2010.
57. **Liang F, Gardner DG.** Mechanical strain activates BNP gene transcription through a p38/NF-kappa B-dependent mechanism. *J Clin Invest* 104: 1603–1612, 1999.
58. **Liang F, O'Rear J, Schellenberger U, Tai L, Tai L, Lasecki M, Schreiner GF, Apple FS, Maisel AS, Pollitt NS, Protter AA.** Evidence for functional heterogeneity of circulating B-type natriuretic peptide. *J Am Coll Cardiol* 49: 1071–1078, 2007.
59. **Luchner A, Stevens TL, Borgeson DD, Redfield M, Wei CM, Porter JG, Burnett JC Jr.** Differential atrial and ventricular expression of myocardial BNP during evolution of heart failure. *Am J Physiol Heart Circ Physiol* 274: H1684–H1689, 1998.
60. **Ma KK, Ogawa T, de Bold AJ.** Selective upregulation of cardiac brain natriuretic peptide at the transcriptional and translational levels by pro-inflammatory cytokines and by conditioned medium derived from mixed lymphocyte reactions via p38 MAP kinase. *J Mol Cell Cardiol* 36: 505–513, 2004.
61. **Maffei S, Del Ry S, Prontera C, Clerico A.** Increase in circulating levels of cardiac natriuretic peptides after hormone replacement therapy in postmenopausal women. *Clin Sci (Lond)* 101: 447–453, 2001.
62. **Magga J, Puhakka M, Hietakorpi S, Punnonen K, Uusimaa P, Risteli J, Vuolteenaho O, Ruskoaho H, Peuhkurinen K.** Atrial natriuretic peptide, B-type natriuretic peptide, and serum collagen markers after acute myocardial infarction. *J Appl Physiol* 96: 1306–1311, 2004.
63. **Marie JP, Guillemont H, Hatt PY.** Le degré de granulation des cardiocytes auriculaires. Etude planimétriques au cours de differents apports d'eau et de sodium chez le rat. *Pathol Biol (Paris)* 24: 549–554, 1976.
64. **Mascareno E, Beckles D, Dhar-Mascareno M, Siddiqui MA.** Enhanced hypertrophy in ob/ob mice due to an impairment in expression of atrial natriuretic peptide. *Vascul Pharmacol* 51: 198–204, 2009.
65. **Matsubara H, Hirata Y, Yoshimi H, Takata S, Takagi Y, Iida T, Yamane Y, Umeda Y, Nishikawa M, Inada M.** Effects of steroid and thyroid hormones on synthesis of atrial natriuretic peptide by cultured atrial myocytes of rat. *Biochem Biophys Res Commun* 145: 336–343, 1987.

66. **Matsubara H, Hirata Y, Yoshimi H, Takata S, Takagi Y, Yamane Y, Umeda Y, Nishikawa M, Inada M.** Ventricular myocytes from neonatal rats are more responsive to dexamethasone than atrial myocytes in synthesis of atrial natriuretic peptide. *Biochem Biophys Res Commun* 148: 1030–1038, 1987.
67. **McGrath MF, De Bold AJ.** Determinants of natriuretic peptide gene expression. *Peptides* 26: 933–943, 2005.
68. **Moro C, Klimcakova E, Lolmède K, Berlan M, Lafontan M, Stich V, Bouloumié A, Galitzky J, Arner P, Langin D.** Atrial natriuretic peptide inhibits the production of adipokines and cytokines linked to inflammation and insulin resistance in human subcutaneous adipose tissue. *Diabetologia* 50: 1038–1047, 2007.
69. **Nishikimi T, Kuwahara K, Nakao K.** Current biochemistry, molecular biology, and clinical relevance of natriuretic peptides. *J Cardiol* 57: 131–140, 2011.
70. **Porapakkham P, Porapakkham P, Zimmet H, Billah B, Krum H.** B-type natriuretic peptide-guided heart failure therapy: a meta-analysis. *Arch Intern Med* 170: 507–514, 2010.
71. **Qian JY, Haruno A, Asada Y, Nishida T, Saito Y, Matsuda T, Ueno H.** Local expression of C-type natriuretic peptide suppresses inflammation, eliminates shear stress-induced thrombosis, and prevents neointima formation through enhanced nitric oxide production in rabbit injured carotid arteries. *Circ Res* 91: 1063–1069, 2002.
72. **Rahmutula D, Nakayama T, Soma M, Sato M, Izumi Y, Kanmatsuse K, Ozawa Y.** Systematic screening of type B human natriuretic peptide receptor gene polymorphisms and association with essential hypertension. *J Hum Hypertens* 15: 471–474, 2001.
73. **Redfield MM, Edwards BS, McGoon MD, Heublein DM, Aarhus LL, Burnett JC Jr.** Failure of atrial natriuretic factor to increase with volume expansion in acute and chronic congestive heart failure in the dog. *Circulation* 80: 651–657, 1989.
74. **Rubattu S, Bigatti G, Evangelista A, Lanzani C, Stanzione R, Zagato L, Manunta P, Marchitti S, Venturelli V, Bianchi G, Volpe M, Stella P.** Association of atrial natriuretic peptide and type a natriuretic peptide receptor gene polymorphisms with left ventricular mass in human essential hypertension. *J Am Coll Cardiol* 48: 499–505, 2006.
75. **Rubattu S, Stanzione R, Di Angelantonio E, Zanda B, Evangelista A, Tarasi D, Gigante B, Pirisi A, Brunetti E, Volpe M.** Atrial natriuretic peptide gene polymorphisms and risk of ischemic stroke in humans. *Stroke* 35: 814–818, 2004.
76. **Saenger AK, Dalenberg DA, Bryant SC, Grebe SK, Jaffe AS.** Pediatric brain natriuretic peptide concentrations vary with age and sex and appear to be modulated by testosterone. *Clin Chem* 55: 1869–1875, 2009.
77. **Sakata Y, Yamamoto K, Masuyama T, Mano T, Nishikawa N, Kuzuya T, Miwa T, Hori M.** Ventricular production of natriuretic peptides and ventricular structural remodelling in hypertensive heart failure. *J Hypertens* 19: 1905–1959, 2001.
78. **Sarzani R, Salvi F, Dessi-Fulgeri P.** Renin-angiotensin system, natriuretic peptides, obesity, metabolic syndrome, and hypertension: an integrated view in humans. *J Hypertens* 26: 831–843, 2008.
79. **Scotland RS, Cohen M, Foster P, Lovell M, Mathur A, Ahluwalia A, Hobbs AJ.** C-type natriuretic peptide inhibits leukocyte recruitment and platelet-leukocyte interactions via suppression of P-selectin expression. *Proc Natl Acad Sci USA* 102: 14452–14457, 2005.
80. **Seferian KR, Tamm NN, Semenov AG, Mukharyamova KS, Tolstaya AA, Koshkina EV, Kara AN, Krasnoselsky MI, Apple FS, Esakova TV, Filatov VL, Katrukha AG.** The brain natriuretic peptide (BNP) precursor is the major immunoreactive form of BNP in patients with heart failure. *Clin Chem* 53: 866–873, 2007.
81. **Semenov AG, Seferian KR, Tamm NN, Artem'eva MM, Postnikov AB, Bereznikova AV, Kara AN, Medvedeva NA, Katrukha AG.** Human pro-B-type natriuretic peptide is processed in the circulation in a rat model. *Clin Chem.* 2011 Apr 7. [Epub ahead of print.].
82. **Shimizu H, Masuta K, Aono K, Asada H, Sasakura K, Tamaki M, Sugita K, Yamada K.** Molecular forms of human brain natriuretic peptide in plasma. *Clin Chim Acta* 316: 129–135, 2002.
83. **Shimizu H, Masuta K, Asada H, Sugita K, Sairenji T.** Characterization of molecular forms of probrain natriuretic peptide in human plasma. *Clin Chim Acta* 334: 233–239, 2003.
84. **Silswal N, Singh AK, Aruna B, Mukhopadhyay S, Ghosh S, Ehtesham NZ.** Human resistin stimulates the pro-inflammatory cytokines TNF-alpha and IL-12 in macrophages by NF-kappaB dependent pathway. *Biochem Biophys Res Commun* 334: 1092–1101, 2005.
85. **Sudoh T, Kangawa K, Minamino N, Matsuo H.** A new natriuretic peptide in porcine brain. *Nature* 332: 78–81, 1988.
86. **Sudoh T, Maekawa K, Kojima M, Minamino N, Kangawa K, Matsuo H.** Cloning and sequence analysis of cDNA encoding a precursor for human brain natriuretic peptide. *Biochem Biophys Res Commun* 159: 1427–1434, 1989.
87. **Sudoh T, Minamino N, Kangawa K, Matsuo H.** C-type natriuretic peptide (CNP): a new member of natriuretic peptide family identified in porcine brain. *Biochem Biophys Res Commun* 168: 863–870, 1990.
88. **Supaporn T, Sandberg SM, Borgeson DD, Heublein DM, Luchner A, Wei CM, Dousa TP, Burnett JC Jr.** Blunted cGMP response to agonists and enhanced glomerular cyclic 3′,5′-nucleotide phosphodiesterase activities in experimental congestive heart failure. *Kidney Int* 50: 1718–1725, 1996.
89. **Tan T, Scholz PM, Weiss HR.** Hypoxia inducible factor-1 improves the negative functional effects of natriuretic peptide and nitric oxide signaling in hypertrophic cardiac myocytes. *Life Sci* 80: 9–16, 2010.
90. **Tanaka T, Kanda T, Takahashi T, Saegusa S, Moriya J, Kurabayashi M.** Interleukin-6-induced reciprocal expression of SERCA and natriuretic peptides mRNA in cultured rat ventricular myocytes. *J Int Med Res* 32: 57–61, 2004.
91. **Thuerauf DJ, Arnold ND, Zechner D, Hanford DS, DeMartin KM, McDonough PM, Prywes R, Glembotski CC.** p38 Mitogen-activated protein kinase mediates the transcriptional induction of the atrial natriuretic factor gene through a serum response element. A potential role for the transcription factor ATF6. *J Biol Chem* 273: 20636–20643, 1998.
92. **Tokudome T, Horio T, Yoshihara F, Suga S, Kawano Y, Kohno M, Kangawa K.** Direct effects of high glucose and insulin on protein synthesis in cultured cardiac myocytes and DNA and collagen synthesis in cardiac fibroblasts. *Metabolism* 53: 710–715, 2004.
93. **Tong KM, Shieh DC, Chen CP, Tzeng CY, Wang SP, Huang KC, Chiu YC, Fong YC, Tang CH.** Leptin induces IL-8 expression via leptin receptor, IRS-1, PI3K, Akt cascade and promotion of NF-kappaB/p300 binding in human synovial fibroblasts. *Cell Signal* 20: 1478–1488, 2008.
94. **Toth M, Vuorinen KH, Vuolteenaho O, Hassinen IE, Uusimaa PA, Leppaluoto J, Ruskoaho H.** Hypoxia stimulates release of ANP and BNP from perfused rat ventricular myocardium. *Am J Physiol Heart Circ Physiol* 266: H1572–H1580, 1994.
95. **Tsukamoto O, Fujita M, Kato M, Yamazaki S, Asano Y, Ogai A, Okazaki H, Asai M, Nagamachi Y, Maeda N, Shintani Y, Minamino T, Asakura M, Kishimoto I, Funahashi T, Tomoike H, Kitakaze M.** Natriuretic peptides enhance the production of adiponectin in human adipocytes and in patients with chronic heart failure. *J Am Coll Cardiol* 53: 2070–2077, 2009.
96. **Usami S, Kishimoto I, Saito Y, Harada M, Kuwahara K, Nakagawa Y, Nakanishi M, Yasuno S, Kangawa K, Nakao K.** Association of CT dinucleotide repeat polymorphism in the 5′-flanking region of the guanylyl cyclase (GC)-A gene with essential hypertension in the Japanese. *Hypertens Res* 31: 89–96, 2008.
97. **Van der Bent V, Church DJ, Vallotton MB, Meda P, Kem DC, Capponi AM, Lang U.** $[Ca^{2+}]_i$ and protein kinase C in vasopressin-induced prostacyclin and ANP release in rat cardiomyocytes. *Am J Physiol Heart Circ Physiol* 266: H597–H605, 1994.
98. **Villar IC, Panayiotou CM, Sheraz A, Madhani M, Scotland RS, Nobles M, Kemp-Harper B, Ahluwalia A, Hobbs AJ.** Definitive role for natriuretic peptide receptor-C in mediating the vasorelaxant activity of C-type natriuretic peptide and endothelium-derived hyperpolarising factor. *Cardiovasc Res* 74: 515–525, 2007.
99. **Vittorini S, Clerico A.** Cardiovascular biomarkers: increasing impact of laboratory medicine in cardiology practice. *Clin Chem Lab Med* 46: 748–763, 2008.
100. **Volpe M, Tritto C, De Luca N, Mele AF, Lembo G, Rubattu S, Romano M, De Campora P, Enea I, Ricciardelli B.** Failure of atrial natriuretic peptide to increase with saline load in patients with dilated cardiomyopathy and mild heart failure. *J Clin Invest* 88: 1481–1489, 1993.
101. **Vuolteenaho K, Koskinen A, Kukkonen M, Nieminen R, Päivärinta U, Moilanen T.** Leptin enhances synthesis of proinflammatory mediators in human osteoarthritic cartilage—mediator role of NO in leptin-induced PGE2, IL-6, and IL-8 production. *Mediators Inflamm* 2009: 345838, 2009.

102. **Walther T, Klostermann K, Hering-Walther S, Schultheiss HP, Tschope C, Stepan H.** Fibrosis rather than blood pressure determines cardiac BNP expression in mice. *Regul Pept* 116: 95–100, 2003.
103. **Wang L, Lu L, Zhang F, Chen Q, Shen W.** Polymorphisms of beta-adrenoceptor and natriuretic peptide receptor genes influence the susceptibility to and the severity of idiopathic dilated cardiomyopathy in a Chinese cohort. *J Card Fail* 16: 36–44, 2010.
104. **Weidemann A, Klanke B, Wagner Volk T M, Willam C, Wiesener MS, Eckardt KU, Warnecke C.** Hypoxia, via stabilization of the hypoxia-inducible factor HIF-1alpha, is a direct and sufficient stimulus for brain-type natriuretic peptide induction. *Biochem J* 409: 233–242, 2008.
105. **Wilkins MR, Settle SL, Needleman P.** Augmentation of the natriuretic activity of exogenous and endogenous atriopeptin in rats by inhibition of guanosine 3′5′-cyclic monophosphate degradation. *J Clin Invest* 85: 1274–1279, 1990.
106. **Xue H, Wang S, Wang H, Sun K, Song X, Zhang W, Fu C, Han Y, Hui R.** Atrial natriuretic peptide gene promoter polymorphism is associated with left ventricular hypertrophy in hypertension. *Clin Sci (Lond)* 114: 131–137, 2008.
107. **Yuan K, Yu J, Shah A, Gao S, Kim SY, Kim SZ, Park BH, Kim SH.** Leptin reduces plasma ANP level via nitric oxide-dependent mechanism. *Am J Physiol Regul Integr Comp Physiol* 298: R1007–R1016, 2010.