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The heart, an endocrine gland: natriuretic peptides
Le cœur, une glande endocrine : peptides natriurétiques

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Abstract
The natriuretic peptide family consists of three biologically active peptides: atrial natriuretic peptide (ANP), brain (or B-type) natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). ANP and BNP, secreted by the heart, act as cardiac hormones, whereas CNP is an endothelial peptide. The aim of this manuscript is to review the production, action mechanisms, effects and clinical applications of natriuretic peptides.

Résumé
La famille des peptide natriurétiques inclut 3 peptides biologiquement actifs : le peptide atrial natriurétique (ANP), le peptide natriurétique cérébral (BNP), and le peptide natriurétique de type 2 (CNP). ANP et BNP, sécrétés par le cœur, agissent en tant qu'hormones cardiaques, alors que le CNP est un peptide endothélial. L'objectif de cette courte revue est de détailler la synthèse, les mécanismes d'action, les effets et les applications cliniques des peptides natriurétiques.

Keywords: natriuretic peptide, ANP, BNP, heart failure, clearance receptor, achondroplasia
Mots-clés : peptides natriurétiques ANP, BNP, insuffisance cardiaque, récepteur de clearance, achondroplasie

MAIN TEXT

Introduction

The natriuretic peptide (NPs) family consists of three biologically active peptides: atrial natriuretic peptide (ANP), brain (or B-type) natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). ANP and BNP, secreted by the heart, act as cardiac hormones, whereas CNP is an endothelial peptide (1, 2).

Maturation and receptors

The human ANP precursor proANP is proteolytically processed by an enzyme named corin, resulting in secretion of bioactive α-ANP and other peptides such as β-ANP in the circulation. Similarly, proBNP is processed to BNP1-32 and N-terminal proBNP (NT-proBNP) within ventricles. ProANP, β-ANP, uncleaved proBNP, mature BNP 1-32 and NT-proBNP are increased in patients with heart failure.

Both ANP and BNP preferentially bind to natriuretic peptide receptor-A (NPR-A or guanylyl cyclase-A) and exert similar effects through increase in intracellular cyclic guanosine monophosphate (cGMP).

CNP rather binds to NPR-B. The 3 peptides are cleared up after binding to NPR-C clearance receptors coupled to adenylcyclase and phospholipase C allowing lysosomal degradation by neutral endopeptidase such as neprilysin (Fig 1). Blood levels of NPs depend on the ratio "active NRP-A receptor"/"clearance NPR-C receptor" (3,4).

Physiological effects

ANP exerts systemic diuretic, natriuretic, and vasodilatory effects counteracting the renin-angiotensin-aldosterone system (RAAS), the corticotrope and vasopressin axes, and the sympathetic nervous system (Fig 2). These effects contribute to maintain water-salt balance and regulate blood pressure. Besides, ANP displays pleiotropic effects such as pro-angiogenetic, anti-inflammatory, anti-atherosclerotic, anti-fibrotic and anti-mitogenic effects through autocrine and paracrine mechanisms that are independent of blood pressure regulation. NPs also show metabolic effects and increase lipolysis, thermogenesis (through browning of adipose tissue), beta cell proliferation and muscle sensitivity to insulin (3). NPR-C receptors are abundant on adipocytes they may regulate, acting as a link between blood pressure and metabolic syndrome. Insulin can limit lipolysis through the upregulation of NPR-C (4). A dysregulation of NPs called "natriuretic handicap" is associated to metabolic syndrome and heart failure, participating to its initiation and progression (5-7). In addition, CNP acts on chondrocytes and activate the receptor of Fibroblast Growth Factor 3 (FGFR3), which is mutated in achondroplasia, a rare form of nanism. (8)

Applications

Different applications of NPs have been developed or are under development.

Markers of heart failure

BNP and NTproBNP are useful markers of heart failure, except in case of end-stage renal failure, where they increase because of a lack of catabolism.

Treatment of heart failure

Novel pharmacological therapies have been developed with the following rational: enhancing NPs bioavailability through exogenous NP administration and inhibition of neprilysin, its catabolic enzyme. In patients with heart failure, the combination of an angiotensin receptor blocker and of neprilysin inhibitors reduces cardiovascular death and hospital admission for heart failure, leading this drug in

current recommendations for heart failure treatment (9). Note that angioedema may be induced by association of this treatment with inhibitors of conversion enzyme or neprilysin such as racecadotril, an antidiarrheic drug.

Improvement of metabolic syndrome

Even if the causal link between the natriuretic handicap and the development of obesity and type 2 diabetes is not completely understood, targeting the NPs pathway may improve the metabolic syndrome (10,11). Nevertheless, natriuretic peptides are not currently marketed in this indication.

Susceptibility to cardiovascular risk

Several polymorphisms of genes involved in the NPs system (BNP, corin…) are associated to a higher risk of cardiovascular diseases (12).

Achondroplasia treatment

In addition, CNP prevents bone shortness in achondroplasia by correcting the defect of synthesis of the extracellular matrix through inhibition of MAPK pathway of FGFR-3 signaling. Clinically, it is now an option in the treatment of human dyschondroplasia (13, 14).

Natriuretic peptides and Inhibitors of sodium-glucose transporter

The most famous effects of natriuretic peptides are their beneficial effects on cardiac insufficiency, which was a major step in the improvement of the prognosis of heart failure. Very recently, a second drug family, the gliflozins, has also shown a significant improvement in patients with heart failure, with or without reduced ejection fraction, and with or without diabetes (15-17). Gliflozins act as inhibitors of sodium-glucose transporter. Therefore, the question was to understand whether there was a link between the efficacy of these 2 treatments on heart failure to determine if their association could potentiate their specific effects or not. Different studies summarized in Table 1 show that atrial natriuretic peptides decrease in most patients treated with inhibitors of sodium-glucose transporter (18-22). A retrospective study including 244 patients with heart failure and ejection fraction ≤40% found a significant lower cardiac mortality rate in the sacubitril/valsartan+dapagliflozin group compared to the sacubitril/valsartan monotherapy group after 2.5 years of treatment (23). This suggests that the association of the 2 drugs is beneficial in heart failure. Nevertheless, a control group

only treated with gliflozin was not present in this retrospective study. It seems that an effect on natriuretic peptides explains only part of the benefit of gliflozins on heart failure events (24)

Conclusion

In conclusion, NPs is a family of peptides that exert protective cardiovascular effects through renal (natriuresis, diuresis), vascular (vasodilator) and hormonal (inhibition or RAAS, cortisol, vasopressin) mechanisms, therefore regulating salt and body-fluid balance. In addition, Nps have favorable metabolic effects, increasing lipolysis and insulin sensitivity, with anti-inflammatory properties. Therefore, NPs constitute a link between metabolic syndrome and cardiovascular complications with numerous present and future clinical applications. The most known is its use in cardiac insufficiency, which was the first step in the improvement of the prognosis of heart failure.

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LEGENDS OF FIGURES AND TABLES

Fig 1: Schematic representation of maturation and receptors of natriuretic peptides

Abbreviations: atrial natriuretic peptide: ANP**;** brain natriuretic peptide: BNP; C-type natriuretic peptide: CNP; cyclic adenosine monophosphate: cAMP; cyclic guanosine monophosphate:cGMP; Natriuretic peptide receptors type A, B or C: NPR-A, B or C; Proprotein Convertase Subtilisin/Kexin

Type 6: PCSK6; pro brain natriuretic peptide: proBNP**;** N-terminal brain natriuretic peptide: NT-proBNP.

Fig2: Physiologic effects of natriuretic peptides. Abbreviations: adrenocorticotrophin hormone: ACTH; arginin-vasopression: AVP; atrial natriuretic peptide: ANP**;** brain natriuretic peptide: BNP; corticotrophin releasing hormone: CRH

Table1: Main studies of natriuretic peptides in patients treated with inhibitors of sodium-glucose transporter. Abbreviations**:** angiotensin II: ATII**;** atrial natriuretic peptide: ANP**;** brain natriuretic peptide: BNP; ejection fraction: EF**;** Canagliflozin Cardiovascular Assessment Study: CANVAS; heart failure: HF**;** inhibitor of sodium-glucose co-transporter-2: iSGLT2**;** inhibitor of dipeptidyl peptidase-4: *i*DPPP4**;** pro brain natriuretic peptide: proBNP**;** N-terminal brain natriuretic peptide: NT-proBNP**;** renal angiotensin aldosterone system: RAAS**;** type2 diabetes: T2D**;** weeks : wks

Fig1

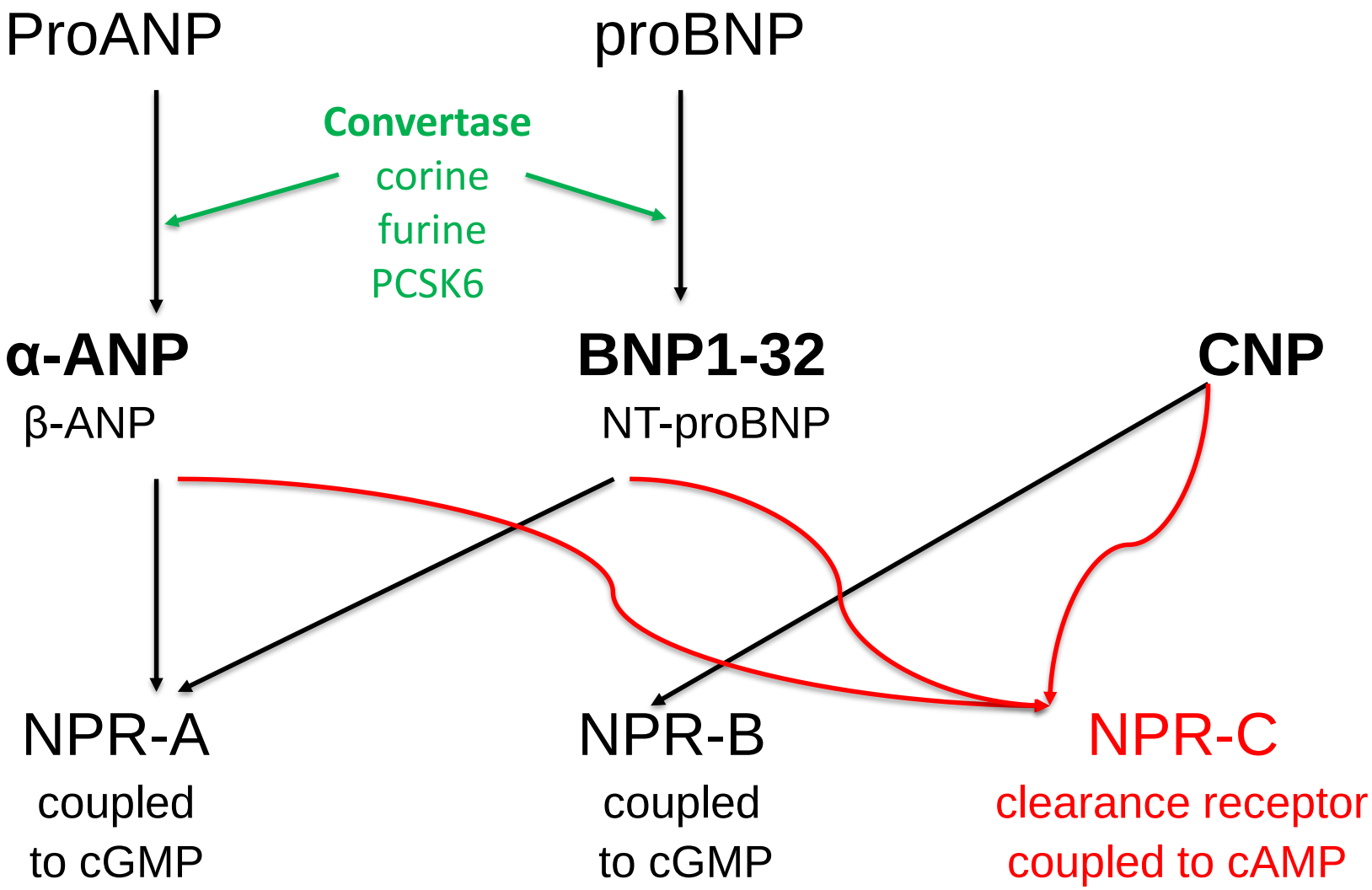
ProANP
proBNP
Convertase
corine
furine
PCSK6
α-ANP
β-ANP
BNP1-32
NT-proBNP
CNP
NPR-A
coupled
to cGMP
NPR-B
coupled
to cGMP
NPR-C
clearance receptor
coupled to cAMP

Fig2

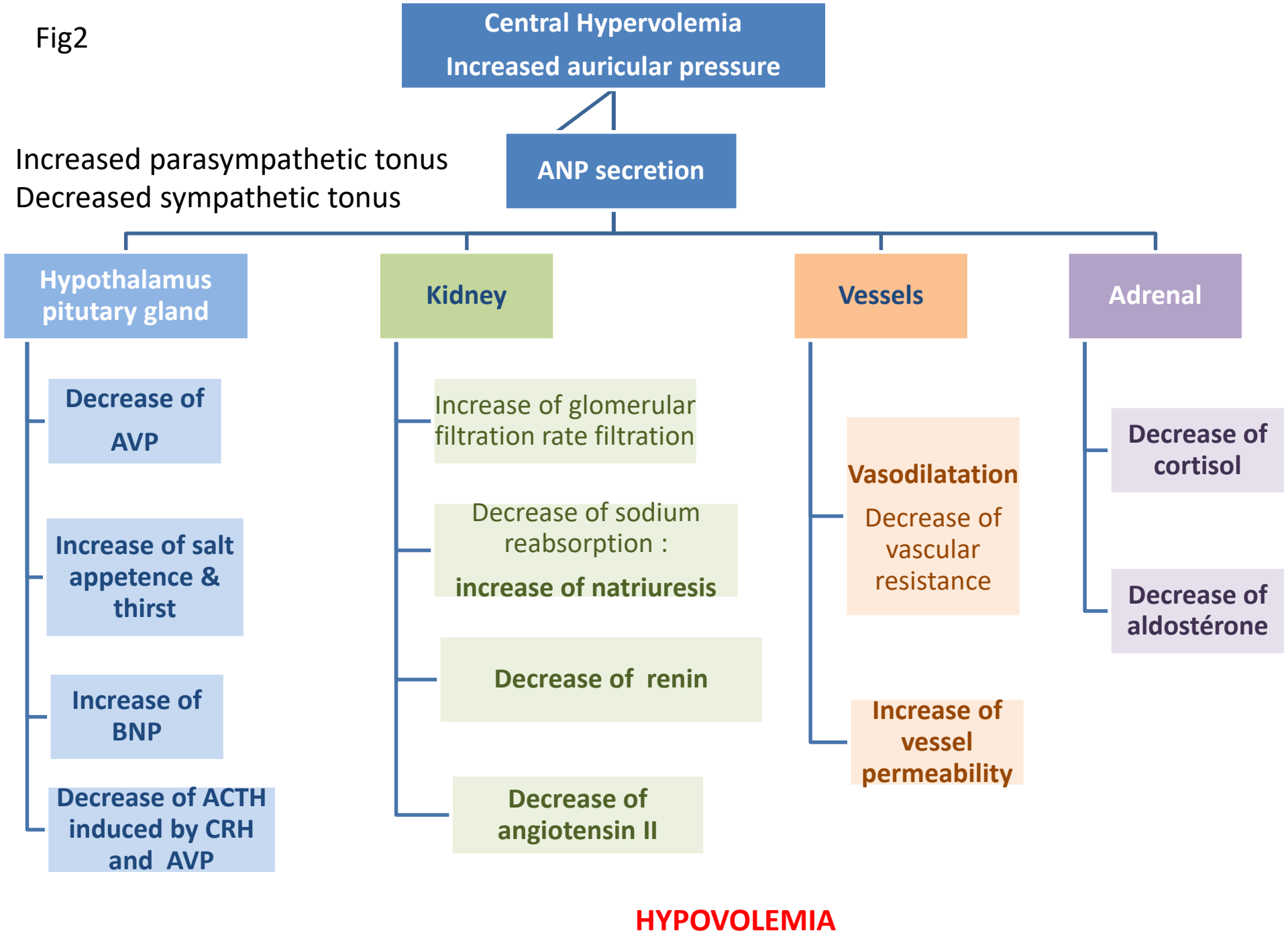
Central Hypervolemia
Increased auricular pressure
Increased parasympathetic tonus
Decreased sympathetic tonus
ANP secretion
Hypothalamus pitutary gland
Kidney
Vessels
Adrenal
Decrease of AVP
Increase of salt appetence & thirst
Increase of BNP
Decrease of ACTH induced by CRH and AVP
Increase of glomerular filtration rate filtration
Decrease of sodium reabsorption :
increase of natriuresis
Decrease of renin
Decrease of angiotensin II
Vasodilatation
Decrease of vascular resistance
Increase of vessel permeability
Decrease of cortisol
Decrease of aldostérone
HYPOVOLEMIA

Table 1

References	Sezai A et al 2019 (18)	Jannuzi J et al 2020 (19)	Feng X et al 2020 (20)	Matsubayashi H et al 2021 (21)	Ghanim H et al 2021 (22)
Study type	Paired before & one year after treatment	To measure NT-proBNP in CANVAS participants.	Randomized iSGLT2 (n= 18) *vs.* iDPP4 (n=19) *vs.* placebo (n=19)	Paired before and at 52 wks under iSGLT2,	prospective double blind randomized *vs.* placebo
	12 months	6 years	24 wks	then 2 wks after discontinuation	12 wks
Gliflozine type	Canagliflozin	Canagliflozin	Canagliflozin	Tofogliflozin	Dapagliflozin
Patients number & characteristics	35 with T2D and HF	4 330 with HF	56 uncontrolled T2D despite insulin	157 T2D	24 *vs.* 23
Results	Decrease of ANP & BNP and increase of echocardiographic left ventricular function	40 % had an increased NT-proBNP, that was reduced with canacliflozin /placebo	At 24 wks, iSGLT2 group showed lower HbA1c, ANP and weight *vs.* iDPP4 group. The iSGLT2 group showed higher blood sodium /placebo & DPP4i. ANP & BNP not correlated with HbA1c & blood glucose	Two wks after discontinuation, body weight , plasma volume, and BNP were significantly increased and correlated. Plasma volume and BNP were significantly higher than baseline levels.	Decrease of ATII, blood pressure & ANP No change of RAAS & BNP