

Neurohormonal Hypothesis in Heart Failure

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According to the neurohormonal model, heart failure is a syndrome that develops because an initial heart injury activates endogenous neurohormonal systems that exert a deleterious effect to the myocardium and on the circulation. This new model regards heart failure primarily as a neurohormonal disorder with main pathophysiologic abnormality the activation of various neurohormonal systems^{1,2}.

Arterial underfilling whether from high or low output heart failure is the predominant determinant of the neurohormonal hypothesis since it leads to activation of various compensatory - competitive mechanisms in order to restore intrarterial volume and thus preserve blood flow to organs like brain and kidneys. In detail this arterial underfilling is sensed by certain mechanoreceptors on the high-pressure side of the circulation like the left ventricle, the carotid sinus, the aortic arch and the renal afferent arterioles. Arterial underfilling stimulates these mechanoreceptors and afferent and efferent signals leads to activation of several compensatory - competitive mechanisms which restore arterial circulatory integrity³ (Figure 1).

These compensatory - competitive mechanisms are^{6,7}:

1. Activation of the sympathetic adrenergic system.
2. Activation of the renin - angiotensin - aldosterone system (RAAS).
3. Non-osmotic vasopressin release.
4. Stimulation of thirst.
5. Release of biologically active molecules like natriuretic peptides, pro-

staglandins, endothelins, nitric oxide and cytokines.

The use of two contradictory terms to describe the above mechanisms, ie compensatory - competitive is due to that, these mechanisms when activated for a short term are truly compensatory since they appear able to sustain and modulate LV function in a setting of arterial underfilling⁸, whereas if activated for long term like in chronic heart failure, are competitive since they adversely affect the hemodynamic condition and exert deleterious effect on the heart and on the circulation^{1,11,12} (Figure 2).

Two are the main key points of the neurohormonal hypothesis:

a. These mechanisms exert their deleterious effects on the heart and the circulation independently of the hemodynamic status of the patient^{1,9,11}.

b. The long-term activation of these mechanisms leads to overexpression of biologically active molecules which in turn produce direct end-organ damage in the heart (LV remodeling) and the circulation (endothelium, kidneys) leading to progression of heart failure^{1,9,11}.

In other words, the activation of these compensatory - competitive mechanisms according to neurohormonal hypothesis is not simply the result of cardiac dysfunction but can also contribute to the development of cardiac dysfunction^{3,11}.

In terms of the neurohormonal hypothesis, the means by which the above compensatory - competitive mechanisms accomplish their short-term beneficial effects as well as their long-term adverse effects is the overexpression of portfolios

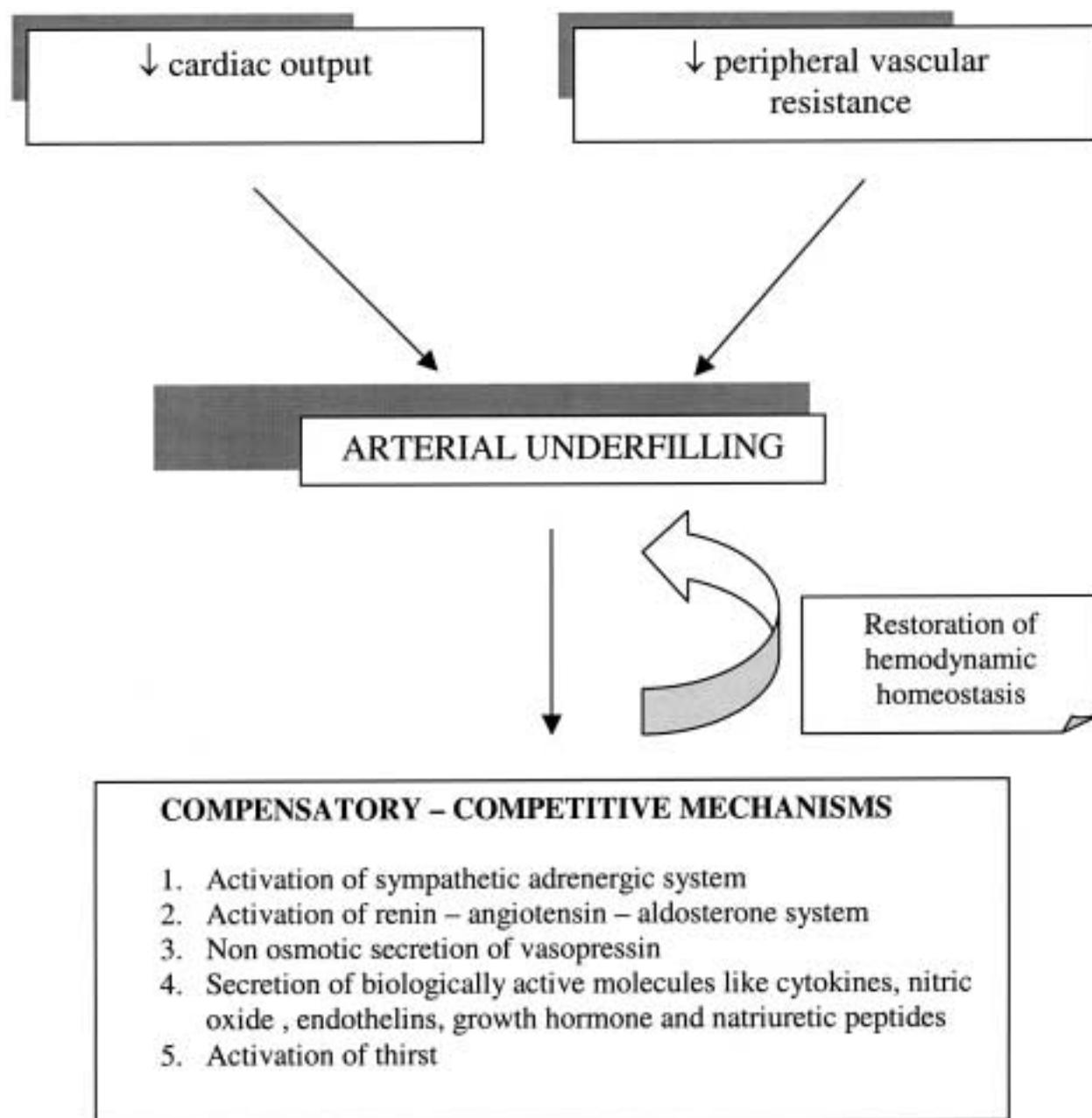


Figure 1. Causes, according to the neurohormonal model that lead to activation of compensatory - competitive mechanisms in order to restore hemodynamic homeostasis in heart failure.

of biologically active molecules. Table 1 summarizes the “neurohormones” that have been well studied in heart failure¹⁰.

Two sets of neurohormones with opposing effects appear to be activated in heart failure. The vasoconstrictor hormones are anti-natriuretic and anti-diuretic with growth-promoting properties. The vasodilator hormones on the other hand are natriuretic and diuretic with anti-mitogenic properties (Table 2).

We can speculate that during the course of heart failure there is a fragile balance between these two rather complex opposing systems. As the syndrome progresses, however natriuretic and vasodilator effects are clearly overwhelmed by influences that lead to vasoconstriction and salt water retention^{2,5,13}.

Beyond observations that many neurohormonal systems were activated in patients with heart failure and that many biologically active molecules were

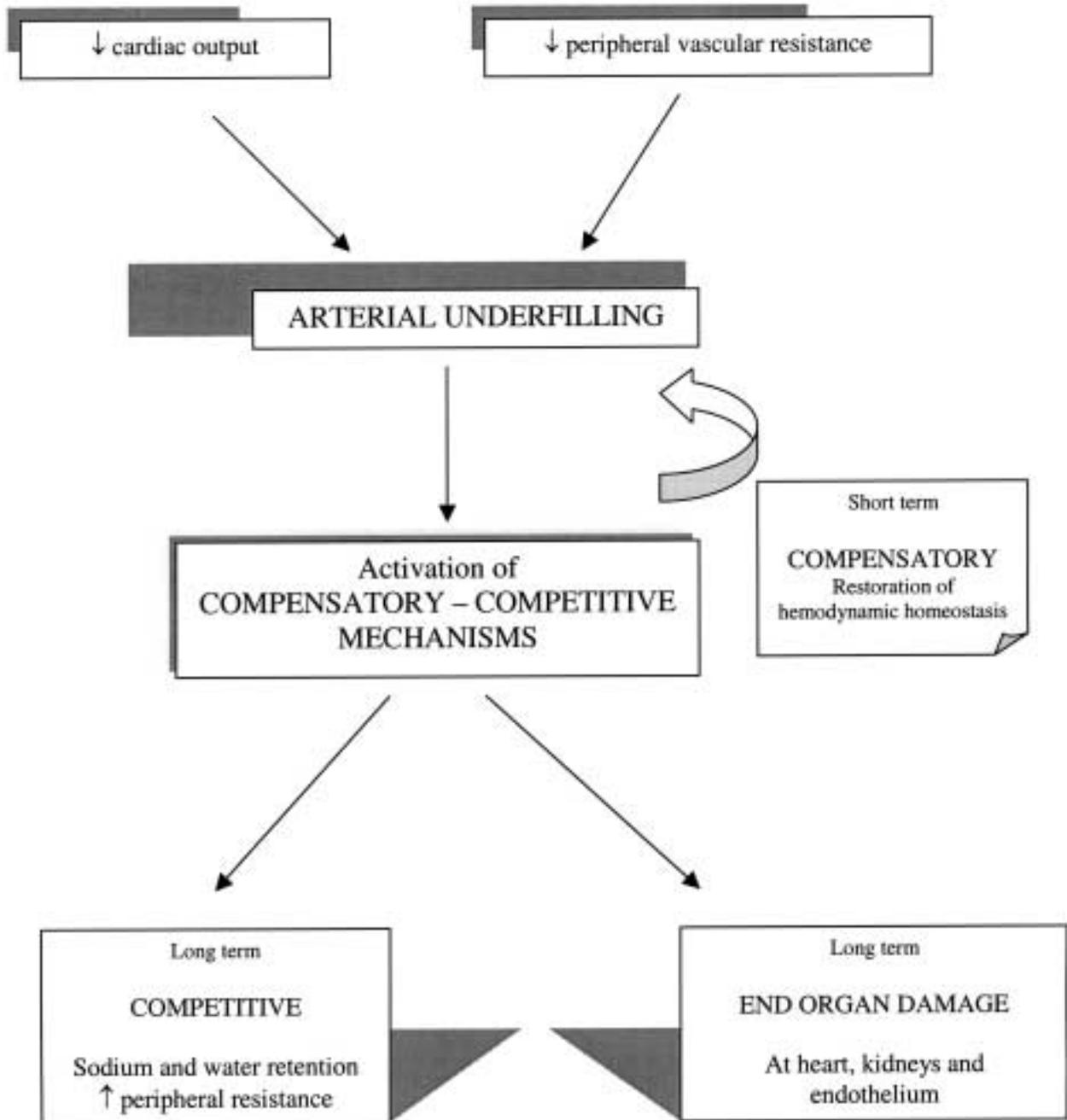


Figure 2. Hemodynamic disarrangement in heart failure activate several compensatory - competitive mechanisms. These mechanisms in the short term are beneficial since they try to compensate the arterial underfilling. On the contrary and in the long term they are competitive since from one hand they exert adverse hemodynamic effects, while on the other they exert deleterious effects on the heart and the circulation.

overexpressed in the same heart failure patients^{4,14}, the evidence to support the neurohormonal hypothesis is derived from two lines of investigation. First, many experimental animal models have shown that pathophysiologically relevant concen-

trations of neurohormones are sufficient to mimic some aspects of heart failure^{15,16}. Second, clinical studies have shown that antagonizing neurohormones lead to clinical improvement of patients with heart failure^{17,20}.

Table 1. “Neurohormones” that have been well studied in heart failure.

Norepinephrine
Epinephrine
Renin
Angiotensin
Aldosterone
Prostaglandins
Vasopressin
Neuropeptide Y
Vasoactive intestinal peptides
Natriuretic peptides
Endothelins
Endorphins
Calcitonin gene-related peptide
Growth hormone
Cortisol
Cytokines
Neurokinin A
Substance P
Nitric oxide
Kallikrein – kinin system

Analysis of neurohormonal systems that are activated in heart failure

1. Sympathetic adrenergic system

It has been known since the mid-sixties that activity of the sympathetic nervous system is increased in patients with heart failure^{21,22}. Since this pioneering observations, with the help of sophisticated new technology, high levels of norepinephrine were observed in the plasma of patients with heart failure. Moreover it was observed that norepinephrine levels are higher in patients with symptomatic heart failure and increase in proportion to the severity of the disease²³. The heart and the kidney contribute approximately 60% of the total plasma level of norepinephrine, an indirect indication of adrenergic activation^{2,13}. Levels of other catecholamines like epinephrine are not usually elevated in heart failure^{2,13}. Augmented sympathetic activity in chronic heart failure is initially beneficial. It increases inotropic cardiac contraction and heart rate and thus cardiac output, and causes vasoconstriction that redistributes blood flow from the splanchnic area to the heart and skeletal muscles. While renal vasoconstriction leads to salt and water retention which may help to increase the intravascular volume^{2,13,24}. However sustained sympathetic stimulation as seen in chronic heart failure, activates the renin angiotensin aldosterone system and increases the absorptive properties of the

Table 2. Vasoconstrictor and vasodilator hormones that are activated in heart failure.

Vasoconstrictor hormones	Vasodilator hormones
Norepinephrine	Natriuretic peptides
Epinephrine	Prostaglandins
Renin-angiotensin-aldosterone	Kallikrein-kinin system
Vasopressin	Calcitonin gene-related peptide

proximal convoluted tubule. This activation leads to progressive salt and water retention, vasoconstriction and increase in pre-load and after-load. These developments in turn will increase ventricular wall stress and myocardial oxygen demand leading to a decrease in contractility and myocardial hypertrophy^{2,3,13,24}. Excessive sympathetic activity may also predispose to ventricular arrhythmias and increase the possibility of arrhythmogenic death. Finally this continuous activation of the sympathetic adrenergic system has many direct effects on the cardiac myocytes including expression of fetal genes, down regulation of calcium –regulating genes, hypertrophy, apoptosis and necrosis^{25,26} (Table 3).

These deleterious effects of norepinephrine in myocytes leads to a decrease on the intrinsic myocardial contractility as well as a decreased responsiveness to inotropic drugs^{2,3,27}. Paradoxically in the failing myocardium the density of the beta-adrenergic receptors may be reduced, especially beta 1 receptors. Furthermore the failing myocardium is characterized by alterations in beta adrenergic signal transduction like uncoupling of beta 1 and beta 2 adrenergic receptors, alterations in G proteins, alterations in adenylate cyclase and alterations in beta adrenergic receptor kinase. All the above make the failing myocardium less responsive to adrenergic stimuli either from endogenous or exogenous adrenergic agonists^{2,3,13,27}.

Until today, it is not known if the above alterations in beta adrenergic receptors are an adaptive mechanism of the human body in order to protect the myocardium from the adrenergic activation or if it is the deleterious results of the direct effect of norepinephrine on myocytes which in turn leads to the progression of the heart failure syndrome^{3,27}.

2. Renin - angiotensin - aldosterone system (RAAS)

The importance of the RAAS in the pathophysiology of heart failure has been known from 1960. In heart

Table 3. Activation of the adrenergic system in patients with heart failure.

COMPENSATORY – COMPETITIVE MECHANISMS	END-ORGAN MYOCARDIAL DAMAGE
<ol style="list-style-type: none"> 1. ↑ Heart rate - contractility <ul style="list-style-type: none"> ➢ increase in cardiac output ➢ ↑ possibility of arrhythmogenic death ➢ ↑ oxygen demand ➢ ↑ wall stress 2. ↑ Renal vasoconstriction <ul style="list-style-type: none"> ➢ retention Na and H₂O 3. ↑ Peripheral vasoconstriction <ul style="list-style-type: none"> ➢ increase preload ➢ increase afterload 4. RAAS activation <ul style="list-style-type: none"> ➢ retention Na and H₂O ➢ vasoconstriction 	<ol style="list-style-type: none"> 1. Fetal gene expression 2. Myocyte hypertrophy 3. Decreased expression of Ca metabolism related genes 4. Apoptosis 5. Myocyte necrosis <ul style="list-style-type: none"> ➢ myocardial hypertrophy ➢ left ventricular remodeling ➢ decrease of endogenous inotropic capacity ➢ reduced adrenergic response to endogenous and exogenous catecholamines

failure activation of tissue RAAS is very important²⁸.

Activation of RAAS varies considerably in heart failure. In asymptomatic left ventricular dysfunction²³ or untreated moderate heart failure²⁹ RAAS is not activated. However RAAS is activated in patients with severe heart failure³⁰. In contrast SOLVD investigators observed that plasma renin activity was increased in asymptomatic patients with heart failure and in addition was more increased in symptomatic patients under treatment²³.

The elegant studies reported by Watkins et al, in dogs³¹ help to explain the variability and lack of consistency in activity of the RAAS in patients with heart failure. According to that model, RAAS activation depends on the phase of fluid retention of each individual patient until a new steady state (hemodynamic homeostasis) is reached³².

The activation and deactivation of the RAAS goes on like an on/off switch depending upon fluid retention and hemodynamic homeostasis until a critical point. Beyond that, there is a continuous activation of RAAS. Another possible explanation for the variability in the activation of RAAS in patients with heart failure is that tissue renin may be involved, since tissue RAAS is activated throughout all stages of heart failure²⁸.

Angiotensin II

The result of the RAAS activation is the production of angiotensin II. Angiotensin II is a potent vasocon-

strictor which increases pre-load and after-load. In addition, it augments the presynaptic release of norepinephrine and stimulates the release of aldosterone, which promotes salt and water retention by the kidney. Angiotensin II has also direct effects on the kidney. It constricts the efferent arterioles and helps maintain the glomerular filtration rate. It also causes sodium re-absorption by direct action on the proximal renal tubules. Angiotensin II enhances water retention indirectly through stimulation of thirst and vasopressin release^{2,3,13}.

The initial short term effects of RAAS activation are beneficial for the failing heart since they preserve glomerular filtration rate, blood pressure and perfusion of vital organs, but may become deleterious if excessive and prolonged, since they worsen the loading conditions of the heart (increased pre-load and after-load) and abolish hemodynamic homeostasis. In addition prolonged RAAS activation instead of preserving glomerular filtration rate reduces it by causing vasoconstriction in the afferent as well as the efferent arterioles^{2,3,13}.

Finally, prolonged activation of RAAS beyond the above adverse hemodynamic consequences through angiotensin II, influences the behavior of myocytes and fibroblasts. In detail, angiotensin II effects on heart cells leads to myocyte hypertrophy, necrosis, apoptosis and disarrangement of the extracellular matrix. Furthermore angiotensin II, promotes expression of fetal genes as well as genes that promote cardiac hypertrophy. Collectively the effects of an-

Table 4. Activation of the renin – angiotensin – aldosterone system in patients with heart failure.

COMPENSATORY – COMPETITIVE MECHANISMS	END-ORGAN DAMAGE
<ol style="list-style-type: none"> 1. Peripheral vasoconstriction <ul style="list-style-type: none"> ➤ ↑ preload ➤ ↑ afterload 2. Norepinephrine release 3. Aldosterone <ul style="list-style-type: none"> ➤ Retention Naα and H$_2$O 4. Vasoconstriction of the efferent arteriole <ul style="list-style-type: none"> ➤ ↑ GFR 5. Vasoconstriction of the afferent arteriole <ul style="list-style-type: none"> ➤ ↓ GFR 6. Retention Naα and H$_2$O at the proximal convoluted tubule 7. Vasopressin release <ul style="list-style-type: none"> ➤ retention Naα and H$_2$O 8. Activation of thirst 	<ol style="list-style-type: none"> 1. Myocyte hypertrophy 2. Myocyte necrosis 3. Apoptosis 4. Disorganization of the extracellular matrix 5. Fetal genes expression <ul style="list-style-type: none"> ➤ myocardial hypertrophy ➤ left ventricular remodeling

giotensin II on myocytes leads to myocardial hypertrophy and progressive ventricular remodeling^{2,3,13} (Table 4).

Angiotensin receptors

It is worth mentioning at this point, that all the effects of angiotensin II are mediated through angiotensin receptors (AR). There are two species of AT receptors, the AT1 and the AT2 receptors. In the vasculature there are AT1 receptors while in the myocardium there are AT2 receptors. The functional differences between the two species of AT receptors are summarized in Table 5³³.

Aldosterone

Another product of the RAAS activation is the synthesis of aldosterone. Aldosterone acts directly on distal convoluted tubules and collecting ducts inducing water and sodium re-absorption. Not only the activity of RAAS is increased in heart failure, but also the action of aldosterone is more persistent than in normal subjects. This is due to the fact that the escape mechanism of mineralocorticoid sodium retention does not occur in heart failure patients. In normal subjects mineralocorticoids initially increase renal sodium retention so that about two liters of water are absorbed. However renal sodium retention then ceases due to a mechanism dependent upon an increase in delivery of sodium to the site of action of

Table 5. Effects of angiotensin II through AT1 and AT2 receptors.

Effects	AT1 receptors	AT2 receptors
Myocyte hypertrophy	Yes	No
Apoptosis	Yes	Yes
Aldosterone synthesis	Yes	Unknown
Norepinephrine release	Yes	Unknown
Fibrosis	Yes	No
Vasoconstriction	Yes (through increase of intracellular Ca)	No
Toxicity	Yes	Unknown
Vasodilation	No	Yes (through bradykinin and NO)
Water retention	Yes (through aldosterone and vasopressin)	No

aldosterone in the collecting ducts. This escape from mineralocorticoid - mediated sodium retention explains why edema is not a characteristic feature of primary hyperaldosteronism³⁴. Escape from the sodium retaining action of aldosterone does not occur in patients with heart failure since adrenergic stimulation and angiotensin II increase sodium re-absorption in the proximal tubule and so there is decreased sodium delivery to the collecting duct. Therefore in patients with heart failure the escape phenomenon does not occur and these patients continue to retain sodium in response to aldosterone³.

Table 6. Activation of natriuretic peptides in patients with heart failure.

Natriuretic peptides (ANP and BNP)	
<p style="text-align: center;">COMPENSATORY MECHANISMS</p> <ol style="list-style-type: none"> 1. Diuretic and natriuretic action <ul style="list-style-type: none"> ➤ ↑ GFR ➤ ↓ retention of Na and H₂O at the proximal convoluted tubule and collecting ducts ➤ inhibition of renin secretion ➤ inhibition of aldosterone secretion and action 2. Vasodilation <ul style="list-style-type: none"> ➤ decrease in preload ➤ decrease in afterload 3. Inhibition of norepinephrine secretion 4. Shift of fluid from intravascular to the interstitium <ul style="list-style-type: none"> ➤ decrease in preload 	<p style="text-align: center;">END-ORGAN DAMAGE</p> <ol style="list-style-type: none"> 1. Antimitogenic action on myocytes 2. Reduction in the number of fibroblasts <ul style="list-style-type: none"> ➤ inhibition of left ventricular remodeling ➤ inhibition of myocardial fibrosis ➤ inhibition of myocardial hypertrophy

3. Natriuretic peptides

Since 1980, de Bold had observed that atria of the heart are capable of secreting a substance with natriuretic and diuretic properties³⁵.

There is the atrial natriuretic peptide (ANP) which is produced mainly in the cardiac atria in response to atrial stretching, the brain natriuretic peptide (BNP) which is produced mainly in the ventricles in response to changes in ventricular filling pressures and finally there is the C-type natriuretic peptide (CNP) which production and actions are limited primarily in the vasculature and the central nervous system^{3,24,36}.

ANP and BNP have mainly natriuretic and diuretic actions which are achieved by several mechanisms:

a. Increase of glomerular filtration rate by efferent renal arteriolar constriction and afferent arteriolar dilation.

b. Decrease of sodium reabsorption in the proximal convoluted tubules and collecting ducts, thereby increasing directly diuresis.

c. Inhibition of the secretion of rennin.

d. Inhibition of aldosterone secretion and action in the collecting tubules increasing thereby indirectly diuresis^{2,3,36}.

Beyond the above diuretic actions, natriuretic peptides have vasodilating properties, they inhibit norepinephrine release from nerve terminals and they contract intravascular volume by inducing a fluid shift from the capillary bed to the interstitium resulting in a pre-load decrease^{2,36}.

All these mechanisms act together to lower systemic vascular resistance, reduce pre-load and increase cardiac output. In addition to their effects on the hemodynamic homeostasis, natriuretic peptides have direct actions on myocardium. In detail they counteract myocyte hypertrophy (antimitogenic properties) and they are capable of reducing the number of fibroblasts in the myocardium inhibiting thereby its fibrosis^{37,38} (Table 6). These direct effects of natriuretic peptides inhibit left ventricle remodeling, thus exerting an anti-remodeling action.

4. Arginine - Vasopressin (antidiuretic hormone)

Arginine – vasopressin is a vasoconstrictor hormone with water retaining properties and mitogenic effects, that accordingly to the neurohormonal model may be potentially harmful in chronic heart failure^{2,3,13}. Antidiuretic hormone is increased in some but not all patients with heart failure^{23,30,39}. Under normal conditions antidiuretic hormone production from the posterior pituitary depends on osmoreceptors activation via hyper-osmolality. In patients with heart failure resulting hypo-osmolality due to water retention and hyponatremia, would suppress antidiuretic hormone secretion. In chronic heart failure however, non-osmotic control of arginine vasopressin secretion becomes more important. These non-osmotic stimuli emanate from mechanoreceptors (arterial underfilling), angiotensin II, prostoglandins,

ANP (atrial stretching), sympathetic activation and central dopaminergic activation^{2,3,13}.

Arginine - vasopressin causes vasoconstriction via V1 receptors activation on vascular smooth muscle cells, while causes re-absorption of water via V2 receptors activation on distal convoluted tubules and collecting ducts^{2,3,13}.

5. Endothelins

Endothelins are a family of potent vasoconstrictor and mitogenic molecules (endothelin-1,-2,-3) that are produced in the endothelium of renal and systemic vasculature. Plasma endothelin concentrations are increased in patients with heart failure⁴⁰ and this increase is proportional to the symptomatic and hemodynamic severity of heart failure²⁴. Substances like angiotensin II, norepinephrine, arginine-vasopressin and cytokines promote endothelins production⁸ which in turn promote peripheral vasoconstriction leading to pre-load and after-load increase. In addition by local autocrine or paracrine actions, endothelins contribute to renal vasoconstriction promoting thereby, sodium and water retention. In patients with heart failure the main source of circulating endothelins are the pulmonary vascular bed and this suggests that endothelins play a key role to pulmonary vascular resistance⁴⁷. Besides the adverse effects of endothelins on hemodynamic status which contributes to the progression of heart failure, endothelins have toxic direct effects on the myocardium since they promote myocyte hypertrophy, apoptosis, disarrangement of extracellular matrix and myocardial fibrosis^{2,3}. These direct toxic effects of endothelins on myocytes through alterations in nuclear transcriptional events lead to left ventricular remodeling and progression of heart failure².

6. Prostaglandins

The renal arterioles (mainly the afferent), glomeruli and some parts of the renal tubules (mainly the collecting ducts) synthesize the vasodilator prostaglandins PGI₂, PGE₂ and PGF_{2a}. At the same sites and through the same metabolic pathways thromboxane A₂ is also synthesized which causes vasoconstriction¹³. Angiotensin II, norepinephrine, RAAS activation and sympathetic adrenergic activation increase the synthesis of the prostaglandins^{41,42}. They are primarily autocrine or paracrine hormones since they cause vasodilation predominantly in the affer-

ent arterioles and direct inhibition of sodium transport in the distal tubules, promoting thereby sodium excretion^{3,13}. The prominent effect of prostaglandins is to protect glomerular function during states of excess renal vasoconstriction as observed in heart failure¹³.

7. Nitric oxide

Nitric oxide (NO) was discovered in 1987 and since then it is known to have important regulatory functions in the cardiovascular system. It is established that nitric oxide causes peripheral vasodilation. Endothelial cells contain a constitutive nitric oxide synthase, the activity of which may be blunted in heart failure⁴³. Thus the constrictor action of vasoconstrictor substances whose concentrations are elevated in heart failure may be increased by decreased nitric oxide synthesis in endothelial cells⁴⁴. It has been observed that in patients with heart failure there is a lower production of nitric oxide in the endothelium of pulmonary vasculature during exercise compared to healthy individuals. This reduced production of nitric oxide may be responsible for increased pulmonary vascular resistance as well as for the experience of dyspnea during exercise in patients with heart failure⁴⁵. Furthermore increased expression of nitric oxide synthase and thus nitric oxide production in the skeletal muscle of patients with heart failure leads to impaired energy production and transport in mitochondria and thereby limited exercise capacity⁴⁶. Nitric oxide apart from having adverse effect on hemodynamic status exert deleterious effects directly on the myocardium. At low concentrations, nitric oxide may protect myocytes from toxic stimuli such as mechanical stress and norepinephrine⁴⁴. However at higher concentrations nitric oxide has deleterious effects such as loss of myocytes, apoptosis and reduced inotropic myocardial response to adrenergic stimulation^{3,44}. Expression of nitric oxide synthase, which is responsible for the synthesis of nitric oxide from L-arginine, is increased in the myocardium of patients with heart failure⁴⁴.

8. Cytokines

Cytokines are peptides of low molecular weight, which are secreted from a great variety of cells during immunologic and inflammatory responses. The main cytokines which have been implicated as playing a role in the pathophysiology of chronic heart

failure are tumor necrosis factor alpha (TNF- α) and interleukins 1 β and 6 (IL-1 β , IL-6)⁴⁴. Elevated TNF- α levels have been demonstrated in patients with heart failure, particularly associated with an increased severity of heart failure^{48,49,61}. The same observations have been demonstrated also for IL-1 β and IL-6^{50,51}. Cytokines are capable of exerting deleterious effects directly on myocytes by inducing hypertrophy, apoptosis, disarrangement of the extracellular matrix and expression of fetal genes, thereby depressing myocyte inotropic function⁵⁵. Cytokines are able also of exerting deleterious effects on myocardium as a whole since they promote left ventricular remodeling, fibrosis^{53,56} and attenuation of adrenergic myocardial response probably through abnormalities on G proteins of adrenergic receptors, abnormalities on calcium homeostasis and activation of nitric oxide synthase within the myocardium^{3,52,53}. TNF- α is capable of inducing apoptosis on skeletal muscles in patients with heart failure, which is associated with impairment of exercise capacity and cachexia⁵⁴. In the chronic phase of heart failure there are some patients that reach a "stable state" during which compensatory mechanisms adapt the failing myocardium to hemodynamic overloading. We may postulate that elevated cytokines levels are responsible for the decompensation of the "stable phase" and lead to clinical and hemodynamic progression of heart failure^{53,57}. The main theories for the production of cytokines during heart failure are the following:

1. Immunologic theory.
2. Myocardial production theory.
3. Theory of peripheral production.
4. Theory of toxinemia.

9. Bradykinin - kallikrein system

Kallikrein is a protease, which acts to kininogen producing bradykinin and kallidin. These two peptides are degraded by the enzyme kininase II which is the same as angiotensin converting enzyme. The distal tubules of kidney, myocardium and vascular endothelium synthesize kallikrein. Both bradykinin and kallikrein produce vasodilation through nitric oxide and vasodilating prostaglandins.

Furthermore they produce natriuresis and diuresis via increasing renal blood flow. Moreover bradykinin and kallidin seem to have cardioprotective effects mainly during myocardial ischemia and

increased ventricular wall stress since they preserve energy reserves in myocytes. In addition they have antimitogenic properties, inhibiting myocyte hypertrophy and thereby preserving their contractile function⁵⁸. However there are some studies showing that these peptides do not reduce myocyte hypertrophy⁶⁰.

In contrast the kinins appear to reduce interstitial fibrosis, myocardial hypertrophy and left ventricular remodeling⁵⁸. There is evidence that some of the beneficial effects of angiotensin converting enzyme inhibitors may be derived from an increase in bradykinin and kallidin.

10. Various biologically active molecules

Growth hormone

Growth hormone is secreted by the anterior pituitary and mediates its effects via insulin growth factor -1 (IGF-1). Levels of growth hormone are elevated in patients with heart failure as well as in patients with cardiac cachexia^{30,59}. Studies in laboratory animals have shown that growth hormone and IGF-1 may have beneficial effects on systemic vascular resistance and on left ventricular function (by increasing cardiac output and contractility) as well as having anti-mitogenic and anti-apoptotic properties thereby exerting a cardioprotective role. Treating heart failure with human growth hormone has been shown to be beneficial in some but not all, studies^{62,64}. In particular a recent study showed that treating heart failure patients with growth hormone may result in normalization of the abnormal immunological responses and in suppression of the excessive activation of biochemical apoptotic pathways in human cardiovascular system⁶⁵.

Cortisol

Cortisol is another anterior pituitary hormone that is also elevated in patients with chronic heart failure. Possibly the high levels of cortisol is a part of a general stress response to the adverse hemodynamic conditions observed in heart failure^{13,30}.

Calcitonin gene related peptide, a potent vasodilator is co-localized with substance P, vasoactive intestinal peptide (VIP) and neuropeptide A in parasympathetic nerve endings in the heart. Many of the above substances are released during heart failure and seem to have vasodilating properties^{13,63}.

Conclusions

The neurohormonal model explains satisfactory why heart failure syndrome progresses independently of the patient's hemodynamic status. According to neurohormonal hypothesis in heart failure, arterial underfilling leads to activation of several endocrine systems in order to restore hemodynamic homeostasis. In the long-term, this hormonal activation on one hand produce further adverse hemodynamic adverse effects which in turn preserve neuroendocrine activation, while on the other hand leads to direct end-organ damage of the myocardium, the kidneys and the endothelium (vasculature)³.

The neurohormonal model finally may explain why heart failure patients appears remarkably consistent as far as clinical presentation, hemodynamic adaptations and disease progression despite different etiologies and different pathophysiology (high and low cardiac output)¹².

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