Heart failure and neuroendocrine activation: diagnostic, prognostic and therapeutic perspectives

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Summary

The important neuroendocrine systems involved in heart failure are reviewed with special emphasis on their possible role in pathophysiology and their relation to prognostic and diagnostic information. Plasma levels of noradrenaline (NA), renin, vasopressin, endothelin-1, atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and tumour necrosis factor-α (TNF-α) are all elevated in heart failure. Activity of the sympathetic nervous system as reflected by NA is correlated to mortality and seems to possess independent prognostic information. Several studies have now documented the beneficial effect of β-blockade in chronic heart failure (CHF). Renin seems to be a poor prognostic marker in CHF possibly because of the interference with diuretic treatment, angiotensin converting enzyme (ACE)-inhibitors and angiotensin II antagonist, and probably also because of the significance of tissue renin-angiotensin system (RAS), poorly reflected by plasma renin. On the other hand, several large-scale trials with ACE-inhibitors and angiotensin II antagonists have demonstrated reduced mortality and morbidity in CHF. Plasma vasopressin does not seem to possess prognostic information but testing of non-peptide antagonists is ongoing. Endothelin-1 seems to have independent prognostic information and endothelin receptor antagonists may represent a therapeutic possibility.

The natriuretic peptides ANP and BNP are correlated to prognosis and possess independent information. Brain natriuretic peptide and N-terminal ANP seem to increase early, i.e. in asymptomatic heart failure. Plasma BNP being more stable than ANP is therefore a promising measure of left ventricular dysfunction. Increase in ANP and BNP, potentially beneficial, may be achieved by administration of neutral endopeptidase inhibitors, at present an unsettled therapeutic possibility. Several cytokines are increased in heart failure and especially TNF-α has drawn attention. Experimental studies suggest that TNF-α is important in the pathophysiology of heart failure and preliminary studies indicate that inhibition of TNF-α seems to be a possible therapeutic approach. Thus, neuroendocrine markers seem to (i) have a role in diagnosis and classification of heart failure, (ii) be useful in providing a ‘neuroendocrine profile’ which enlightens different aspects of heart failure, and therefore (iii) in the future probably will be valuable in the choice of medical treatment of the individual patient. In addition to β-blockers, ACE-inhibitors and angiotensin II antagonists several new drugs based on neuroendocrine modification are on their way and might become important in the future.

Keywords: aldosterone, atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), endothelin,
noradrenaline (NA), renin-angiotensin system, tumour necrosis factor-α (TNF-α), vasopressin.

Introduction

Development and progression of chronic heart failure (CHF) depends on the aetiology and severity of the underlying disease. Typically, an initial injury causes dysfunction of the left ventricle (LV) and leads to decrease in cardiac output and blood pressure. The haemodynamic balance is partially restored by activation of the neuroendocrine system through vasoconstriction and retention of salt and water. However, at the same time this also contributes to progression of CHF both by haemodynamic effects and by direct harmful hormonal effects on the cardiomyocytes. Thus, neuroendocrine activation has a key role in the development of CHF, and as treatment of myocyte dysfunction is rarely possible, pharmacological treatment of CHF is largely based on modification of neuroendocrine activation. The purpose of the present review is to describe the most important neuroendocrine systems and factors involved in CHF with respect to prognostic, diagnostic and therapeutic perspectives.

Conventional diagnosis of CHF

The history and clinical evaluation are crucial for diagnosis and classification of CHF. ECG is of limited value but may have importance for diagnosis of the underlying disease. Chest X-ray may demonstrate cardiomegaly, and demonstration of flow-shift in the lungs is of value in evaluating pulmonary stasis. Exercise capacity is not strongly correlated with mortality, clinical CHF or ejection fraction but gives important information about the physical capacity of the patient. More information is obtained by determination of relative, maximal oxygen uptake but being fairly laborious it is hardly used as a routine. Several methods may be used for estimation of the global and regional systolic function of the heart, commonly described by left ventricular ejection fraction (LVEF) and wall motion scores. Echocardiography is very popular because of its availability, price and the additional information about cardiac structure and thereby the underlying disease. The utility of echocardiography is therefore high in the evaluation of possible CHF and it should probably be used in all patients with suspicion of heart failure. It also allows for differentiation between systolic and diastolic dysfunction. Other methods include ECG-gated radionuclide ventriculography, ECG-gated myocardial perfusion scintigraphy, magnetic resonance imaging (MRI) as well as invasive methods.

Neuroendocrine activation

Several neurohormonal systems are activated in CHF. The most important systems will be described below with emphasis on prognostic, diagnostic and therapeutic aspects.

Catecholamines and the sympathetic nervous system

The catecholamine noradrenaline (NA) is synthesized by hydroxylation and decarboxylation of the amino acid tyrosine and stored in presynaptic vesicles of sympathetic nerves. Plasma NA (Thomas & Marks, 1978; Cohn et al., 1984; Viquerat et al., 1985; Francis et al., 1990, 1993; Swedberg et al., 1990) is increased in CHF and is generally correlated to the degree of haemodynamic abnormalities (Levine et al., 1982). It has been shown that plasma NA reflects sympathetic activity in CHF patients fairly well (Ferguson et al., 1990).

Initially, activation of the sympathetic nerve system leads to vasoconstriction and preservation of cardiac output via inotropic and chronotropic effects. However, chronic heart failure is accompanied by down-regulation of myocardial β1-receptors, but not β2- or α1-receptors (Bristow et al., 1986, 1988) reducing the contractile response to adrenergic stimulation (Bristow et al., 1982). This down-regulation is limited to the heart, as the response to a given adrenergic stimulus is normal in other tissues (Creager et al., 1991). Noradrenaline has also a direct effect on the myocardium leading to hypertrophy and cell death, probably mediated via α1- and β1-receptor (Mann, 1998; Packer, 1998). Finally, NA has a mainly β2-mediated pro-dysrhythmic effect (Billman et al., 1997).

The plasma level of NA correlates with mortality in CHF patients (Cohn et al., 1984; Swedberg et al., 1990; Francis et al., 1993; Benedict et al., 1996). By multivariate analysis NA has been found to contain independent prognostic information when heart rate (HR), renin, sodium and strokework index (Cohn...
et al., 1984), LVEF, maximal oxygen uptake, cardio-thoracic ratio and plasma-renin (Francis et al., 1993) or LVEF, New York Heart Association (NYHA) class, age, sex, cause of CHF and plasma ANP (Benedict et al., 1996) were also taken into consideration. It is therefore not surprising that adrenergic blockade has beneficial effects in the treatment of CHF with reduction in cardiac morbidity and mortality, as shown in several large interventional studies (Table 1).

The underlying mechanism of the β-blocker effect in CHF has been studied experimentally in a series of studies, where it has been shown that β1-blockade counteracts/weaks the down-regulation of β1-receptors and thereby tends to normalize the inotropic response. The α1-blockade could at least in theory inhibit the α1-mediated actions (hypertrophy and myocyte toxicity). Some of the effect may also be because of the antioxidative properties of the compounds.

The renin-angiotensin-aldosterone system
According to the classical concept of the renin-angiotensin system (RAS), renin is a proteolytic enzyme that is synthesized in the kidneys and released from the juxtaglomerular cells. It converts angiotensinogen, produced by the liver, to angiotensin I. Angiotensin converting enzyme (ACE) is the rate limiting enzyme for the generation of the biologically active component of the system, angiotensin II. Angiotensin II is among other things a potent vasoconstrictor and increases release of aldosterone. The effects of angiotensin II are exerted via at least two receptor subtypes AT1 and AT2.

In animal experiments it has been shown that angiotensin II has a direct effect on the myocardium which eventually leads to hypertrophy, remodelling and fibrosis (Sadoshima & Izumo, 1993; Brilla et al., 1994; Crawford et al., 1994) and thereby to loss of function. Angiotensin II from tissue-RAS seems to be of importance for these effects. Where the AT1 receptor is believed to be responsible for the direct effects on the myocardium (Dostal & Baker, 1992; Kabour et al., 1994) the AT2 receptor seems also to be involved in apoptosis (Yamada et al., 1996). The latter is of potential importance in CHF as the AT1 receptors are selectively down-regulated in this disease, leading to an increased, relative importance of the AT2 receptors (Asano et al., 1997; Haywood et al., 1997). Aldosterone seems also to have direct effect on the myocytes leading to fibrosis (Brilla et al., 1993, 1994).

In addition to the circulating RAS a tissue-RAS exists, probably with all the components of the system in several organs including the heart and the arterial walls. Furthermore, in tissue-RAS other enzymatic pathways exist, including that of chymase. It should also be noted that ACE contributes to the degradation of the vasodilator bradykinin, which in several ways seems to be an angiotensin antagonist and is believed to possess cardioprotective effects.

Although plasma renin is increased in CHF (Levine et al., 1982; Francis et al., 1990, 1993) determination of plasma renin is of no diagnostic or prognostic value in CHF, primarily because of the influence of medical treatment: diuretics, ACE-inhibitors and angiotensin II blockers increase whereas β-blockers decrease the level of renin. The increased renin values found in

### Table 1

Larger interventional studies demonstrating beneficial effects of treatment with β-blockers in chronic heart failure (CHF) on morbidity and mortality.

<table>
<thead>
<tr>
<th>Study name</th>
<th>Drug</th>
<th>Blockade of</th>
<th>Mortality</th>
<th>Sudden death</th>
<th>Hospital admission</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>MERIT-HF</td>
<td>Metoprolol</td>
<td>β1</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>MERIT-HF Study Group (1999)</td>
</tr>
<tr>
<td>CIBIS II</td>
<td>Bisoprolol</td>
<td>β1</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>CIBIS-II Investigators and Committees (1999)</td>
</tr>
<tr>
<td>US Carvedilol HF study</td>
<td>Carvedilol</td>
<td>β1 + α1</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Packer et al. (1996)</td>
</tr>
<tr>
<td>Australia–New Zealand carvedilol HF Study</td>
<td>Carvedilol</td>
<td>β1 + α1</td>
<td>↓</td>
<td>NR</td>
<td>↓</td>
<td>Australia/New Zealand Heart Failure Research Collaborative Group (1997)</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>Carvedilol</td>
<td>β1 + α1</td>
<td>↓</td>
<td>NR</td>
<td>↓</td>
<td>Witte et al. (2000); Thackray et al. (2001)</td>
</tr>
</tbody>
</table>

↓, Decrease; NR, not reported.
some studies may have been the result of the diuretic treatment. Thus, it was found in the Studies of Left Ventricular Dysfunction (SOLVD) study that the renin levels were normal and not related to the degree of CHF in patients untreated with diuretics (Francis et al., 1990).

In the vasodilator-heart failure trials (V-HeFT) II study (The V-HeFT VA Cooperative Studies Group, 1993) a correlation between high levels of renin and increased mortality was found. However, this effect disappeared in the multivariate analysis where plasma renin had no independent prognostic value when other factors such as left ventricular end-diastolic diameter were taken into consideration (Francis et al., 1993). In the Cooperative North Scandinavian Enalapril Survival (CONSENSUS) study angiotensin II and aldosterone were related to mortality, but again in an univariate analysis (Swedberg et al., 1990). Finally, measurements of plasma renin do not reflect the activity in the tissue-RAS, which may be of pathophysiological importance. Whereas plasma renin may be increased in acute or in compensated heart failure, it may be within normal limits, in compensated CHF (Dzau et al., 1981), highly dependent on the drug treatment, as described above. In contrast to circulating-RAS, tissue-RAS seems also to be activated in chronic compensated failure (Dzau, 1993). The prognostic value of renin seems limited.

On the basis of the above mentioned it is not surprising that inhibition of the system by means of ACE-inhibitors has proven to be effective. In the SOLVD (enalapril) study (The SOLVD Investigators, 1991) and in the CONSENSUS (enalapril) study (The CONSENSUS Trial Study Group, 1987) as well as in several other studies it has been found that treatment with ACE-inhibitors increased survival in CHF patients. The reduction in mortality could especially be ascribed to a reduction in mortality because of progressive CHF, whereas no significant effect was seen on sudden cardiac death (The CONSENSUS Trial Study Group, 1987; The SOLVD Investigators, 1991).

Another interventional possibility is blockade of AT₁ receptors: in the Evaluation of Losartan in the Elderly (ELITE) study (Pitt et al., 1997) that was primarily designed to investigate the tolerability, treatment with a selective AT₁ receptor antagonist (losartan) was compared with ACE-inhibitor treatment (captopril). Apart from a lower rate of side-effects in the AT₁ receptor antagonist group, it was found that the mortality and morbidity was lower compared with the ACE-inhibitor group. Based on these results the ELITE-II study was then launched in order to investigate differences in mortality and morbidity. The study, which has recently been published, found no difference between the two treatments (Pitt et al., 2000).

During long-term ACE-inhibitor treatment the inhibition of aldosterone is limited which is termed ‘aldosterone escape’. In the Randomized Aldactone Evaluation Study (RALES) addition of an aldosterone antagonist (spironolactone) to ACE-inhibitor and loop diuretic treatment reduced both mortality and morbidity (Pitt et al., 1999), supporting the clinical significance of aldosterone escape.

An important theoretical difference between ACE-inhibition and AT₁ blockade is the different influences on bradykinin degradation. During ACE-inhibitor treatment but not during AT₁ antagonist treatment the concentration of bradykinin is increased and bradykinin is believed to possess cardioprotective effects. It has been shown that bradykinin acts as a vasodilator via nitric oxide (NO) and thereby improves endothelium-dependent vasodilatation. Furthermore, studies in knockout mice suggest an antihypertrophic effect on myocyte level (Emanueli et al., 1999). However, at present it is still uncertain whether the different effects on bradykinin is of clinical significance. Some of the unsettled questions related to the renin-angiotensin-aldosterone system (RAAS) are summarized in Table 2.

### Table 2

Unsettled questions with regard to the RAAS.

<table>
<thead>
<tr>
<th>Relative importance of circulating and tissue-RAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative importance of non ACE-pathways in tissue RAS</td>
</tr>
<tr>
<td>Differences in angiotensin II (AT₂) receptor blockade and ACE-inhibition</td>
</tr>
<tr>
<td>Importance of differential effects on bradykinin</td>
</tr>
<tr>
<td>Relative importance of AT₁ and AT₂ receptors</td>
</tr>
<tr>
<td>Importance of aldosterone escape</td>
</tr>
</tbody>
</table>

Vasopressin

The non-peptide vasopressin is synthesized as a larger prehormone in nerve cells located in the hypothalamus. From here the precursor is transported through the axons of the nerve cells to their end located in the
neurohypophysis. The physiological actions of vasopressin are vasoconstriction mediated via V$_1$-receptors and decrease in free-water clearance mediated via renal V$_2$-receptors. In CHF the vasopressinergic system is activated, contributing to vasoconstriction and water retention. The sensitivity of the vasopressin system for changes in osmolality and volume is decreased in CHF (Goldsmith et al., 1986; Goldsmith, 1992). In some studies it has been found that vasopressin is increased in CHF (Goldsmith et al., 1983; Francis et al., 1990) and that the increase could not be explained by changes in osmolality. Vasopressin is especially elevated in CHF with hyponatraemia. Vasopressin does not seem to contain any prognostic information (Richards et al., 1999).

From a theoretical point of view vasopressin antagonists could be useful drugs. In addition to animal experiments non-peptide antagonists have been used in healthy volunteers (Ohnishi et al., 1993; Shimizu, 1995) and in one patient with CHF (Miura et al., 1993). The development and use of oral non-peptide V$_1$- and V$_2$-antagonists in controlled clinical studies will probably reveal whether this is true.

**Endothelin-1**

Endothelin-1 is synthesized from a larger pre-propeptide which after enzymatic cleavage becomes the propeptide ‘big endothelin-1’. By endothelin converting enzyme the active peptide endothelin-1 is formed from ‘big endothelin-1’.

Endothelin-1 levels are increased in CHF patients (Cody et al., 1992; Lerman et al., 1992; McMurray et al., 1992; Rodeheffer et al., 1992; Stewart et al., 1992) and correlate strongly with the pulmonary pressure (Cody et al., 1992; Cacoub et al., 1993). Endothelin-1 acting via selective receptors (ET$_A$ og ET$_B$) has strong vasoconstrictor effects and possibly also a trophic effect on cardiac myocytes, found in *in vitro* studies (Ito et al., 1991).

Endothelin-1 was found to contain prognostic information, in a multivariate analysis including other hormones [atrial natriuretic peptide (ANP) and NA] and haemodynamic measures (Pouset et al., 1997). ‘Big endothelin-1’ is also increased in CHF, correlates with pulmonary pressure and has prognostic value (Pacher et al., 1993).

Administration of a combined ET$_A$ and ET$_B$ receptor antagonist (bosentan) has in acute studies been shown to improve the haemodynamic parameters in CHF patients (Kiowski et al., 1995; Sutsch et al., 1998). In experimental chronic heart failure a selective ET$_A$ as well as a combined ET$_A$/ET$_B$ antagonist increased survival (Sakai et al., 1996; Mulder et al., 1997). A possible clinical value of ET antagonists in the treatment of chronic human heart failure remains to be demonstrated.

**Natriuretic peptides**

**ANP.** Atrial natriuretic peptide is primarily produced in the atria and released by atrial distention. ANP dilates arterioles and increases sodium excretion from the kidneys and is an antagonist to both the sympathetic and the renin system. Three known natriuretic receptors exist, A, B and C. ANP has highest affinity for the A receptor. The C receptor is believed to be a clearance receptor. In addition, the natriuretic peptides are broken down by a neutral endopeptidase, which also breaks down other peptides, e.g. angiotensin II, bradykinin and endothelin.

The plasma concentration of ANP is elevated in CHF and in general correlates with the degree of CHF (Nakaoka et al., 1985; Tikkanen et al., 1985; Francis et al., 1990; Swedberg et al., 1990; Richards et al., 1999).

In CHF the activation of ANP initially counteracts the effect of the vasoconstrictor systems, but the effect is not lasting. Accordingly, it has been shown that the natriuretic response to ANP is blunted in chronic failure (Cody et al., 1986). In addition to the haemodynamic effects, ANP also seems to have an antihypertrophic effect on the myocytes (Horio et al., 2000). In CHF the ventricular expression and release of ANP to the circulation become significant (Saito et al., 1989).

ANP has been found to be of prognostic value in dilated cardiomyopathy and CHF (Gottlieb et al., 1989; Keogh et al., 1990; Swedberg et al., 1990). Multivariate analysis revealed that ANP seems to have independent prognostic value in one study (Keogh et al., 1990), whereas this was not the case in another study where BNP was also included in the analysis (Tsutamoto et al., 1997). As the plasma half-life of ANP is relatively short (3 min) and ANP is secreted in...
a pulsatile manner, N-terminal pro-ANP (NT-ANP) may be preferred. NT-ANP is the remaining part of the prohormone when ANP has been cleaved off and has a somewhat longer half-life. NT-ANP therefore gives a better indication of the average ANP level over time. NT-ANP is increased in CHF and has independent prognostic value (Hall et al., 1994).

Increase in circulating ANP has been demonstrated to be beneficial for CHF by intravenous administration of ANP. Of greater clinical relevance is the effect of oral neutral endopeptidase inhibitors, which in a couple of small studies have demonstrated to be beneficial with respect to neurohormonal and hemodynamic parameters (Elsner et al., 1992; Northridge et al., 1999). As neutral endopeptidase inhibitors also inhibit the breakdown of angiotensin II concomitant ACE-inhibitor treatment seems to be relevant. Omapatrilat, is both a neutral endopeptidase and ACE inhibitor, which was tested against lisinopril in the Inhibition of Metaloprotease by Omapatrilat in a Randomized Exercise and Symptoms Study of Heart Failure (IMPRESS) trial (Rouleau et al., 2000). The study, which had exercise tolerance as a primary endpoint, found a trend in favour of omapatrilat regarding the secondary composite endpoint of death or worsening of heart failure. However, whether endopeptidase inhibitor treatment has any practical use in CHF is at present unsettled but the large-scale Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) will probably give an answer.

**BNP.** The name of brain natriuretic peptide originates from it being first isolated from pig brain. BNP is especially located in the ventricles of the heart and is released primarily from the left ventricle in response to increased filling pressure (Mukoyama et al., 1991). The half-life of BNP is somewhat longer (20–25 min) than that of ANP. The physiological action of BNP is identical to that of ANP, i.e. vasodilatation and natriuresis.

As for ANP, BNP is elevated in CHF and the degree of activation is related to degree of CHF (Mukoyama et al., 1990, 1991; Yoshimura et al., 1993; Yasue et al., 1994). BNP has independent prognostic value (Tsutamoto et al., 1997) and has in some studies been found to be a stronger prognostic predictor than ANP (Tsutamoto et al., 1997; Richards et al., 1999). Both BNP and NT-ANP seem to be activated in an early phase of the course of CHF and were found to be elevated in asymptomatic CHF (McDonagh et al., 1998). Measurements of BNP have therefore been suggested as a screening method for left ventricular systolic dysfunction in groups at risk (McDonagh et al., 1998) and is for the time being the most promising biochemical marker for diagnosing CHF.

Also for BNP the N-terminal part of pro-BNP (NT-BNP) may be measured. NT-BNP is also increased in CHF and correlates with the severity of the disease (Hunt et al., 1997). The prognostic value of NT-BNP is still unsettled, but in a post-infarction study it was found that NT-BNP was a strong predictor of death (Richards et al., 1998). The information contained in BNP and NT-BNP is strongly overlapping and the relative use of the two measurements unsettled.

**Nitric oxide**
NO, formerly called endothelial derived relaxing factor (EDRF), is formed in the endothelial cells from l-arginine by the enzyme nitric oxide synthetase (NOS). NOS exist in a constitutive (cNOS) and an inducible (iNOS) form. From endothelial cells NO is spread locally to smooth muscle cells in the vascular wall leading to relaxation and thereby vasodilatation. The activity of endogenous NO is often measured as endothelial-dependent vasodilatation, e.g. with acetylcholine. NO may be increased exogenously, e.g. by nitroglycerine.

Experimentally it has been shown in animals as well as in humans that the endothelium dependent vasodilatation is decreased in CHF (Kubo et al., 1991). The decreased response seems to be reversible, as the response in extracardial vasculature is improved after heart transplantation (Kubo et al., 1996). Furthermore, it has been shown that NO inhibits the positive inotropic response to β-adrenergic stimulation (Hare et al., 1995), as also mentioned below.

**Cytokines**
Several cytokines appear to be involved in CHF. Of the cytokines especially tumour necrosis factor-α (TNF-α) has drawn attention. It has been shown in animals that TNF-α causes dilatation and remodelling of the left ventricle (Bozkurt et al., 1998), and transgenic TNF-α over-expressing mice develop left
**Table 3** Neuroendocrine factors involved in CHF.

<table>
<thead>
<tr>
<th>Biochemical properties</th>
<th>Most common technique for measurement</th>
<th>Postsynaptic receptors</th>
<th>Effects on heart</th>
<th>Other effects with relevance to CHF</th>
<th>Effect on preload</th>
<th>Effect on afterload</th>
<th>Pharmacological intervention</th>
<th>Effect of pharmacological intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathetic nervous system</td>
<td>Noradrenaline: catecholeamine (MW 169)</td>
<td>HPLC or Radioenzymatic</td>
<td>$\alpha_n$, $\beta_1$, $\beta_2$</td>
<td>Inotropism, chronotropism ($\beta_1$), myocyte hypertrophy and cell death ($\alpha_n$, $\beta_1$)</td>
<td>$\uparrow$</td>
<td>$\uparrow$</td>
<td>$\beta$-blockers</td>
<td>Mortality ↓, sudden death ↓, morbidity ↓</td>
</tr>
<tr>
<td>Renin-angiotensin-aldosterone system</td>
<td>Renin: proteolytic enzyme (41 kDa)</td>
<td>RIA</td>
<td>$\text{AT}_1$, $\text{AT}_2$</td>
<td>Inotropism ($\text{AT}_1$), myocardial hypertrophy, fibrosis ($\text{AT}_1$), apoptosis ($\text{AT}_2$?)</td>
<td>$\uparrow$</td>
<td>$\uparrow$</td>
<td>ACE-inhibitors; Ang. II antagonists</td>
<td>Mortality ↓<em>; morbidity ↓</em></td>
</tr>
<tr>
<td></td>
<td>Angiotensin II: peptide (8 AA)</td>
<td>RIA</td>
<td>$\text{AT}_1$, $\text{AT}_2$</td>
<td>Vasoconstriction ($\text{AT}_1$), sodium retention ($\text{AT}_1$), aldosterone stimulation</td>
<td>$\uparrow$</td>
<td>$\uparrow$</td>
<td>ACE-inhibitors; Ang. II antagonists</td>
<td>Mortality ↓<em>; morbidity ↓</em></td>
</tr>
<tr>
<td></td>
<td>Aldosterone: steroid (MW: 360)</td>
<td>RIA</td>
<td>Aldosterone receptor</td>
<td>Myocardial fibrosis</td>
<td>$\uparrow$</td>
<td>$\uparrow$</td>
<td>Aldosterone antagonists</td>
<td>Mortality ↓, sudden death ↓, morbidity ↓</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>Peptide (9 AA)</td>
<td>RIA</td>
<td>$V_1$, $V_2$</td>
<td>Vasoconstriction ($V_1$), water retention ($V_2$)</td>
<td>$\uparrow$</td>
<td>$\uparrow$</td>
<td>Non-peptide antagonists ($V_1$, $V_2$)</td>
<td>Unsettled</td>
</tr>
<tr>
<td>Endothelin-1</td>
<td>Peptide (21 AA)</td>
<td>RIA, ELISA</td>
<td>ET$\alpha$, ET$\beta$</td>
<td>Myocyte hypertrophy (ET$\alpha$)</td>
<td>$\uparrow$</td>
<td>$\uparrow$</td>
<td>Antagonists (ET$\alpha$ or ET$\alpha$/ET$\beta$)</td>
<td>Unsettled</td>
</tr>
<tr>
<td>ANP</td>
<td>Peptide (28 AA)</td>
<td>RIA</td>
<td>A, B, C</td>
<td>Natriuresis, vasodilation</td>
<td>$\downarrow$</td>
<td>$\downarrow$</td>
<td>Neutral endopeptidase inhibitors</td>
<td>Unsettled</td>
</tr>
<tr>
<td>BNP</td>
<td>Peptide (32 AA)</td>
<td>RIA</td>
<td>A, B, C</td>
<td>Natriuresis, vasodilation</td>
<td>$\downarrow$</td>
<td>$\downarrow$</td>
<td>Neutral endopeptidase inhibitors</td>
<td>Unsettled</td>
</tr>
<tr>
<td>TNF-$\alpha$</td>
<td>Polypeptide (17 kDa)</td>
<td>ELISA, RIA</td>
<td>TNF receptor family</td>
<td>Negative inotropism Left ventricle dilatation and dysfunction</td>
<td>$\downarrow$</td>
<td>$\downarrow$</td>
<td>Lowering synthesis through changes in intracellular cAMP</td>
<td>Unsettled</td>
</tr>
</tbody>
</table>

MW, molecular weight; AA, amino acids; HPLC, high-pressure liquid chromatography; RIA, radioimmunoassay; ELISA, enzyme-linked immunosorbent assay; $\uparrow$, Increased; $\downarrow$, Decreased. *ACE-inhibitors.
ventricular dilatation and dysfunction (Kubota et al., 1997a; Bryant et al., 1998). It is believed that an initial myocardial injury causing left ventricular dysfunction, in contrast to what happens in normal subjects, leads to excessive myocardial TNF-α release that in turn via its toxic effects leads to progression of the disease. One of the effects of TNF-α is probably an induction of NOS and thereby NO, which has a negative inotropic effect. TNF-α is increased in CHF and seems to reflect the severity of the disease (Levine et al., 1990; Testa et al., 1996; Torre et al., 1996). It has been shown that TNF-α is of prognostic value as there is a relation between the level of TNF-α and mortality (Torre et al., 1996; Rauchhaus et al., 2000). It has furthermore been shown that TNF-α is increased especially in cachectic CHF patients (Parissis et al., 1999).

The first completed placebo-controlled study demonstrated a beneficial effect in CHF patients by inhibition of TNF-α with pentoxifyllin, a compound that increases complementary Adenosine Monophosphate (cAMP) (Sliwa et al., 1998). However, it is too early to speculate about the therapeutic perspectives.

For an overview of neuroendocrine factors involved in CHF, please see tables 3 and 4.

### Concluding remarks

The traditional concept of congestive heart failure has changed over the years from a clinical syndrome to imaging of a poorly contracting heart, maybe the time has come for thinking of it also as a ‘neuroendocrine’ disorder, both in relation to diagnosis and prognosis. There seems to be a series of promising uses for neurohormone measurements and therapeutic perspectives. However, at present none of the hormones alone are sufficient for the diagnosis of CHF. On the other hand a combination of, e.g. a geometric method like echocardiography and one hormone measurement, e.g. BNP, would give a more firm diagnosis than echocardiography alone.

Neuroendocrine parameters may be used for individualizing the treatment. Accordingly, it has been shown that increased ANP prior to treatment with a combined β/α₁-blocker (carvedilol) was predictive for reduction in mortality and that ANP and BNP were predictive for reduction in hospitalizations (Richards et al., 1999). Likewise, it has been shown that especially elevated NA, renin and ANP levels prior to ACE-inhibitor treatment were related to reduction in mortality (Swedberg et al., 1990; Francis et al., 1993). Finally, it has recently been shown that BNP may be used as an indicator for titration of ACE-inhibitor treatment (Murdoch et al., 1999) and that the use of NT-BNP as a treatment guide instead of treatment guided by clinical evaluation caused a reduction in cardiovascular events (Troughton et al., 2000).

### Table 4 Diagnostic and prognostic significance of neuroendocrine factors in chronic heart failure.

<table>
<thead>
<tr>
<th>Plasma levels</th>
<th>Independent prognostic value</th>
<th>Especially related to</th>
<th>‘Noise’ in plasma levels from medical treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noradrenaline</td>
<td>↑</td>
<td>+</td>
<td>Haemodynamic insufficiency</td>
</tr>
<tr>
<td>Renin</td>
<td>↑→</td>
<td>–</td>
<td>Incompensation, diuretic treatment</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>↑→</td>
<td>–</td>
<td>Hyponatraemia</td>
</tr>
<tr>
<td>Endothelin-1, big endothelin-1</td>
<td>↑</td>
<td>+</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>ANP, N-terminal ANP</td>
<td>↑</td>
<td>+/-a</td>
<td>Atrial distension</td>
</tr>
<tr>
<td>BNP</td>
<td>↑</td>
<td>+</td>
<td>Left ventricular filling pressure</td>
</tr>
<tr>
<td>TNF-α</td>
<td>↑</td>
<td>?</td>
<td>Cachexia</td>
</tr>
</tbody>
</table>

↑, Increased; ↓, decreased; ↑→, conflicting data/both possibilities. *Dependent on whether BNP is included in analysis.
Furthermore, when new agonists, antagonists and other modifiers become available in the near future, measurements of other of the neuroendocrine factors may become important for individualization of therapy.

References


