VENTRICULAR DYSFUNCTION AND HEART FAILURE

Is neurohormonal activation a major determinant of the response to ACE inhibition in left ventricular dysfunction and heart failure?

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Chronic heart failure is characterised by varying degrees of symptoms and high mortality mainly from progressive myocardial failure and sudden death. Increased understanding of pathophysiological mechanisms has shown that heart failure is progressive and characterised by myocardial dysfunction and activation of complex adaptive and maladaptive processes. Moreover, a number of large clinical trials have shown that the progressive nature of and high mortality from the disorder may be affected by pharmacological interventions.

The initial event in the clinical pathophysiology of heart failure is myocardial damage, which may be caused by many different mechanisms such as toxins, infections, and prolonged volume or pressure overload. In Western societies the initial injury is most often an acute myocardial infarction, though the cause often remains unknown, as in idiopathic dilated cardiomyopathy. Clinical heart failure may develop immediately after the myocardial injury or after a period of asymptomatic left ventricular dysfunction. The pathophysiological events which follow an acute myocardial injury and ultimately lead to progressive heart failure are not exactly understood, although our knowledge of the complicated mechanisms involved in the development of left ventricular dilatation, hypotrophy, and dysfunction has recently increased. Activation of different neurohormonal systems as well as autocrine and paracrine mechanisms has an essential role in this process.

Pharmacological treatment of chronic heart failure has traditionally been aimed at the underlying cardiac disease and at reducing symptoms such as dyspnoea and fluid retention. More recently, treatment has been targeted increasingly at delaying the progression of the disorder and at reducing mortality. Treatment with angiotensin converting enzyme (ACE) inhibitors can positively influence prognosis. Moreover, β adrenergic blockers can reduce mortality in patients with heart failure after myocardial infarction, and they seem to delay the progression of the disorder among patients with idiopathic dilated cardiomyopathy. ACE inhibitors have multiple mechanisms of action, which involve both haemodynamic and neurohormonal factors as well as autocrine and paracrine mechanisms. In this article we will review the importance of neurohormonal mechanisms for the efficacy of ACE inhibitors in the treatment of asymptomatic left ventricular dysfunction and chronic heart failure. Although doctors focus on treatment of patients with systolic dysfunction of the left ventricle, it is important to remember that, in some cases of heart failure, alterations in myocardial relaxation (diastolic dysfunction) may predominate.

Although the initial event in the development of left ventricular dysfunction is structural damage to the myocardium, heart failure is not merely a disease of the heart. Patients with left ventricular dysfunction frequently have no symptoms of heart failure, probably because compensatory mechanisms enable maintenance of cardiac output and peripheral perfusion. These adaptive responses are the result of a complex interplay between myocardial, haemodynamic, and neurohormonal mechanisms which are activated almost immediately after the myocardial injury. Compensatory mechanisms may, however, become exhausted, and many patients ultimately develop symptoms of heart failure. At this stage, activation of the sympathetic nervous system and the renin-angiotensin system seems to be maladaptive and may cause further harm to the myocardium, leading to progression of the disorder. Furthermore, baroreflex responses are not able to limit the magnitude of activation of the vasoconstrictor hormones as baroreceptor function may be impaired. Thus, sustained neurohormonal activation is partly maintained by altered baroreceptor function, which may reduce inhibitory signals to the vasomotor centre and thereby diminish the inhibition of sympathetic outflow.

The time course of neurohormonal activation, from the onset of myocardial injury to the development of chronic heart failure, has never been studied in detail in the same population of patients. Several studies have, however, investigated neurohormonal activation in patients with acute myocardial infarction, asymptomatic left ventricular dysfunction, or chronic heart failure.

Neurohormonal activation in acute myocardial infarction

Neurohormonal systems are activated in the early phase of acute myocardial infarction. High plasma concentrations of catecholamines, angiotensin II, and atrial natriuretic...
peptide occur during the first few hours after the onset of infarction.\(^6\)\(^7\) This activation subsides over the subsequent days, and at hospital discharge neurohumoral activation is present predominantly among patients with heart failure.\(^4\)\(^5\) In the SAVE trial neurohumoral activation was related to the degree of left ventricular dysfunction among asymptomatic patients with reduced left ventricular ejection fraction after a recent myocardial infarction.\(^8\) Sustained neurohumoral activation is also related to the extent of myocardial damage among patients with a first myocardial infarction and without signs of heart failure.\(^9\) Thus, prolonged neurohumoral activation after myocardial infarction is confined to patients with clinical signs of heart failure and to those with extensive myocardial damage. Activation of neurohumoral systems during the early phase after myocardial infarction is associated with early complications and subsequent mortality.\(^10\)\(^11\) Recently, plasma concentrations of atrial natriuretic peptide and noradrenaline and plasma renin activities on days 3 to 16 after the onset of infarction were found to be related to long term mortality.\(^12\) The consequences of prolonged neurohumoral activation after myocardial infarction have yet to be determined. In one small study patients with the highest plasma noradrenaline concentrations one week after myocardial infarction also had the greatest increase in left ventricular size during subsequent follow up for 4–6 months.\(^13\) This may indicate a relation between neurohumoral activation and left ventricular dilatation after myocardial infarction.

**Neurohumoral activation in asymptomatic left ventricular dysfunction**

In a substudy of the SOLVD trial plasma concentrations of noradrenaline, atrial natriuretic peptide, and arginine vasopressin and plasma renin activity were raised in patients with a left ventricular ejection fraction lower than 35% when compared with a group of healthy subjects.\(^14\) Patients with symptomatic heart failure had the highest hormone concentrations, but asymptomatic patients still had significantly higher concentrations than control subjects. In asymptomatic patients raised plasma renin activity was confined to patients who were taking diuretics for treatment of hypertension. These results show that neurohumoral systems are activated in patients with reduced ejection fractions but no symptoms of heart failure and that activation is more pronounced in patients with symptoms of heart failure who are taking diuretics than it is in those without symptoms.

**Neurohumoral activation in chronic heart failure**

Neurohumoral activation frequently occurs in chronic heart failure\(^25\)\(^26\) and is most pronounced among patients with severe symptoms, though the degree of activation varies widely.\(^31\)\(^32\) Factors other than the disease itself such as diuretic treatment may influence neurohumoral mechanisms.\(^33\)\(^34\) A strong connection has been found between mortality and plasma noradrenaline, atrial natriuretic peptide, and angiotensin II concentrations and renin activity in both moderate and severe chronic heart failure.\(^35\)\(^36\) Recently, by using a mathematical model which included left ventricular ejection fraction, peak oxygen consumption, and cardiothoracic ratio, plasma noradrenaline concentration was found to be a significant predictor of prognosis among patients with mild or moderate congestive heart failure.\(^38\)

**INFLUENCE OF ACE INHIBITORS ON NEUROHUMORAL ACTIVATION**

The actions of ACE inhibitors differ from those of other vasodilators mainly because of their effects on endogenous neurohumoral systems. Aside from the humoral effects, the regional conversion of angiotensin I to angiotensin II in many tissues is affected, including in the heart and kidneys.\(^39\)\(^40\)\(^41\) Plasma ACE activity is suppressed by ACE inhibitors in patients with acute myocardial infarction and chronic heart failure.\(^25\)\(^32\)\(^42\) In several studies ACE inhibitors have reduced circulating concentrations of angiotensin II in patients with heart failure.\(^43\)\(^46\) This may not be the case in all patients during long term treatment, possibly because angiotensin II may be generated by enzyme systems that are not dependent on ACE.\(^39\)\(^47\) An alternative pathway, via cardiac chymase, has been suggested for the formation of angiotensin II,\(^48\)\(^49\) with only 10% of the total angiotensin II formed by cardiac membranes being blocked by captopril. Human chymase converts angiotensin I to angiotensin II but is not affected by ACE inhibition.\(^39\)\(^49\) In most studies a reduction in aldosterone concentrations and a rise in plasma renin activity has been found during treatment with ACE inhibitors in patients with heart failure.\(^44\)\(^46\)\(^50\)\(^51\)

The effects of ACE inhibitors on the activity of the sympathetic nervous system are less clear. Experimentally, angiotensin II may facilitate the release of noradrenaline from sympathetic nerve endings.\(^52\)\(^53\) However, no change in plasma noradrenaline concentration or systemic venous spillover of noradrenaline was found in patients with heart failure who were treated with intravenous infusion of angiotensin II or enalaprilat.\(^54\) In some small studies in patients with heart failure plasma noradrenaline concentration was reduced by treatment with ACE inhibitors.\(^43\)\(^55\) In larger clinical studies a reduction in plasma noradrenaline concentration has mainly been found among patients with high plasma values at the start of treatment.\(^56\) ACE inhibitors lower arterial blood pressure and ventricular filling pressures without inducing reflex tachycardia. Baroreflex sensitivity may also be improved by treatment with these drugs.\(^57\) Plasma concentrations of atrial natriuretic peptide among patients with moderate or severe heart failure are also reduced by ACE
inhibitors, possibly reflecting haemodynamic changes, including a reduction in atrial wall stress. It has not been proved that the ACE inhibitors directly influence the secretion or clearance of atrial natriuretic peptide in humans, although angiotensin II may directly stimulate the secretion of atrial natriuretic peptide in isolated rabbit hearts.68 ACE inhibitors also increase the concentration of circulating bradykinins, as ACE and kininase II are one and the same. Bradykinin may in turn release vasodilating prostaglandins.59 This may be important therapeutically as the haemodynamic effects of ACE inhibition may be inhibited by a bradykinin antagonist as well as by inhibitors of prostaglandin synthesis.60 61 Furthermore, increased bradykinin in tissues may augment production of endothelium derived relaxing factor.62

NEUROHORMONAL ACTIVATION AND CLINICAL EFFICACY OF ACE INHIBITORS
Several clinical trials suggest that the beneficial effects of ACE inhibitors in patients with left ventricular dysfunction or heart failure relate mainly to their effects on neurohormonal mechanisms.

Trials with ACE inhibitors in survivors of acute myocardial infarction
The table shows an overview of trials investigating the effects on mortality of ACE inhibitors after myocardial infarction. In the CONSENSUS II trial 6090 patients with acute myocardial infarction were randomly allocated to treatment with enalapril or placebo at 103 Scandinavian centres.63 Treatment was initiated intravenously within 24 hours after the onset of infarction. The duration of treatment varied between 41 and 180 days because the study was stopped prematurely. Patients were eligible for inclusion if they presented within 24 hours after the onset of chest pain that was likely to be due to an acute myocardial infarction and showed either electrocardiographic changes or raised plasma concentrations of enzymes indicating myocardial damage. Mortality in the groups given enalapril and placebo was respectively 7.2% and 6.3% after the first month and 11.0% and 10.2% after six months. The differences between the groups were not significant. Heart failure was associated with the index infarction among 1109 patients (18%). There was no difference in survival between the two treatment groups in the subgroup of patients with heart failure.

In the SAVE trial 2231 patients with ejection fractions of 40% or less but without overt heart failure or symptoms of myocardial ischaemia were randomly assigned to treatment with captopril or placebo within 3 to 16 days after myocardial infarction.69 At the time of randomisation 35% of the patients were taking diuretics, but patients whose symptoms of heart failure were not readily controlled were excluded from the trial. Thus, the SAVE trial studied a mixed population of patients with mild symptomatic heart failure and asymptomatic left ventricular dysfunction. The patients were followed up for an average of 42 months. Mortality from all causes was 20% in the group given captopril and 25% in the group given placebo. This corresponds to a risk reduction of 19% (P = 0.019). The proportion of patients who needed to be admitted to hospital for congestive heart failure was higher in the placebo group (17%) than in the captopril group (14%) (risk reduction 22%; P = 0.019). Furthermore, the risk of developing a fatal or non-fatal myocardial infarction was reduced by 25% (P = 0.015) in the captopril group compared with the placebo group.

In the AIRE study 2006 patients with clinical evidence of heart failure at any time after the index infarction were randomly allocated to treatment with ramipril or placebo on the third to tenth day after the onset of infarction.68 Clinical evidence of heart failure was defined as at least one of the following: signs of left ventricular failure in a chest radiograph, bilateral auscultatory crackles extending at least one third of the way up the lung fields in the absence of chronic pulmonary disease, or auscultatory evidence of a third heart sound with persistent tachycardia. The average time of follow up was 15 months with a minimum of six months. Mortality from all causes at the end of the study was 17% in the ramipril group and 23% in the placebo group (risk reduction 27%; P = 0.002).

In the large ISIS-4 study 58 000 patients were randomly assigned treatment with captopril or placebo within 24 hours after the onset of a suspected or definite acute myocardial infarction. Mortality after five weeks was compared between the treatment groups. When data from 54 824 patients had been analysed, mortality was 7.33% in the placebo group and 6.87% in the captopril group (relative risk reduction 6%). Although the absolute risk reduction was small (<0.5%), it was significant (P = 0.04). Fourteen per cent of the patients had heart failure at the time of inclusion.69

In the GISSI-3 study 18 895 patients were randomly allocated to treatment with lisinopril or open controls within 24 hours of the onset of symptoms.
of acute myocardial infarction. After six weeks of treatment, mortality was 7.1% among controls and 6.3% among patients receiving lisinopril, a relative risk reduction of 11%, which was significant (P = 0.03).47

There are some major differences between these five large clinical trials: different patient populations were selected, the duration of treatment and follow-up was different, the time at which treatment was started varied, and different ACE inhibitors were used. These differences must be considered when the results of these trials are compared. Given that only patients with sustained neurohormonal activation will benefit from treatment with ACE inhibitors after myocardial infarction, however, some of the results may be explained. As previously mentioned, patients with sustained neurohormonal activation are those with clinical symptoms of heart failure and those with reduced ejection fractions at time of admission. This may explain some of the differences seen in these trials. In the AIRE and SAVE trials, only a fraction of the patients included in the CONSENSUS II trial, however, can be presumed to have had prolonged neurohormonal activation, and the study would not have had statistical power to detect possible differences in survival, even if such differences existed in this subgroup. In the ISIS-4 and GISSI-3 studies a small difference in mortality was observed. This effect may have been confined to patients with clinical characteristics similar to those of patients in the AIRE trial. Although this may be an attractive hypothesis, it is not supported by recent data from the SAVE trial showing that the clinical benefits produced by captopril were not limited to the group with neurohormonal activation at inclusion in the study.22 Thus, the importance of neurohormonal activation for the effects of ACE inhibition after acute myocardial infarction is still uncertain.

Trials with ACE inhibitors in patients with chronic heart failure

The CONSENSUS trial showed convincingly that survival may be improved by treatment with an ACE inhibitor in patients with severe heart failure.1 Blood samples for hormone analyses were drawn at baseline from 239 patients who were randomly allocated to treatment with enalapril or placebo in this trial.32 A significant reduction in mortality in the group of patients treated with enalapril, compared with patients receiving placebo, was consistently found among patients with plasma concentrations of noradrenaline, adrenaline, angiotensin II, aldosterone, or atrial natriuretic peptide above the median. No significant differences in survival between the treatment groups were found among patients with hormone concentrations below the median. However, the few patients studied demanded caution in interpretation.

In the V-HeFT II trial 804 men receiving digoxin and diuretics for heart failure were randomly allocated to treatment with enalapril or a combination of hydralazine and isosorbide dinitrate.4 Mortality after two years was significantly lower in the enalapril arm than in the hydralazine-isosorbide dinitrate arm. Plasma noradrenaline concentration and renin activity at baseline were analysed in 743 and 737 patients respectively.39 The survival benefit of enalapril compared with hydralazine-isosorbide dinitrate was most evident in patients with a plasma noradrenaline value higher than 900 pg/ml and among patients with a plasma renin activity higher than 4.4 ng/l/s.

Together the results of these studies indicate that neurohormonal activation is a major determinant of the clinical efficacy of treatment with ACE inhibitors in chronic heart failure. Furthermore, the importance of neurohormonal activation in the progression of this disorder and its high mortality is underscored.

Neurohormonal activation: therapeutic target in patients with left ventricular dysfunction or chronic heart failure

In patients with left ventricular dysfunction but no overt heart failure the actions of the vasoconstrictor system seem to be adequately counterbalanced by endogenous vasodilator factors. Increased secretion of atrial and brain natriuretic peptides from the atria and ventricles may antagonise many of the effects of the vasoconstrictor systems.68 69 Although these patients are asymptomatic and haemodynamically stable, some neurohormonal mechanisms may have already become maladaptive. High circulating concentrations of noradrenaline and angiotensin II may cause necrosis of myocardial cells, and angiotensin II may induce hypertrophy in cardiac myocytes.70 72 In symptomatic heart failure the activation of counter-regulatory vasodilator systems seems to be overwhelmed by activation of vasoconstrictor mechanisms such as the renin-angiotensin system and the sympathetic nervous system. Release of endothelin derived relaxing factor may be attenuated in patients with heart failure.73 In addition, the haemodynamic and hormonal response to atrial natriuretic peptide may become blunted.74 76 The haemodynamic consequences of this shift of balance is increased peripheral resistance and sodium retention, which will add further to the haemodynamic burden of the heart.

Optimally, treatment with an ACE inhibitor after an acute myocardial infarction should begin before neurohormonal activation becomes maladaptive. The time for maladaptation to develop cannot be defined accurately, however, because the interactions between myocardial, haemodynamic, and neurohormonal mechanisms are too complex. The positive effects of ACE inhibitors in patients with myocardial infarction are probably confined to certain subgroups, and therefore, despite the results from the ISIS-4 and GISSI-3 trials, treatment of all patients with an acute myo-
cardiac infarction cannot be generally recommended. An interesting question is whether biochemical markers, such as plasma neurohormone concentrations, may be used to select patients for ACE inhibition after myocardial infarction. Measurements of catecholamines and plasma components of the renin-angiotensin system may have limited value for individual patients, as there are large individual variations in the results. Measurements of plasma atrial natriuretic peptide or brain natriuretic peptide may be more helpful.7 8

Plasma noradrenaline concentration increases over time in patients with chronic heart failure.9 Although it was lower among patients treated with enalapril compared with those treated with isosorbide dinitrate-hydrallazine in the V-HeFT II trial, noradrenaline concentrations still increased over time among patients taking enalapril.10 These findings are important because, although survival is improved by ACE inhibitors in heart failure, mortality among patients treated with diuretics and ACE inhibitors remains high.10 Moreover, many patients with left ventricular dysfunction will develop progressive heart failure despite treatment with an ACE inhibitor. An important question is whether the progressive nature of heart failure may be affected and mortality reduced by further modulation of neurohormonal mechanisms by agents other than ACE inhibitors. Of special interest in this respect is treatment with β adrenergic blockers with or without α blocking activity, angiotensin II receptor antagonists, renal endopeptidase inhibitors, and dopamine receptor agonists. We hope that the clinical efficacy of these drugs will be determined in future clinical trials.

Conclusions

Neurohormonal activation in chronic heart failure is associated with the clinical progression of the disorder. Patients with pronounced activation of neurohormonal systems have the highest mortality, independent of other clinical variables such as symptoms and left ventricular ejection fraction. The beneficial effects of ACE inhibition on survival in heart failure are determined by the extent of neurohormonal activation. Prolonged neurohormonal activation after acute myocardial infarction is confined to patients with clinical signs of heart failure or patients with extensive myocardial damage. The same groups of patients benefit from treatment with ACE inhibitors. Thus, neurohormonal activation is a major determinant of the response to ACE inhibition after myocardial infarction, although this is less certain than its part in chronic heart failure.

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