Br Heart J 1994;72 **(Supplement)**:S 28–30

Neuroendocrine excitation in heart failure

A J G Riegger

Chronic congestive heart failure (CHF) is a syndrome in which cardiac dysfunction is associated with high morbidity and mortality. Severe symptomatic heart failure is the end point of a lengthy sequence of events, in which the functional state of the left ventricle is an important determinant of the prognosis. As well as the severity of the symptoms of heart failure and the depression of left ventricular ejection fraction, which are independent predictors of survival in heart failure, the neuroendocrine activation found in these patients is directly related to the outcome. It has been shown in controlled trials that one of the most important therapeutic aims to improve survival in patients with chronic CHF must be the inhibition of vasoconstrictor and sodium and water retaining neurohumoral factors.[1 2]

The table summarises neuroendocrine mechanisms that may be activated in heart failure.

Stimulation of the renin angiotensin-aldosterone system in patients with severe CHF was first described in the 1940s.[3 4] There is convincing experimental and clinical evidence that neuroendocrine systems are already activated in the very early stages of heart failure and that they interact in different ways in different phases of the disease.[5 6] Even when plasma renin activity is within the normal range in early heart failure, there is experimental evidence for at least transient local activation of a renin-angiotensin system within the myocardium—namely, increased messenger RNA for angiotensinogen and angiotensin converting enzyme (ACE).[7 8]

Neuroendocrine factors in symptomless left ventricular dysfunction

During the first 72 hours after infarction nearly all neurohumoral factors are increased, but the extent and pattern varies widely.[9–11] Seven to 10 days later, circulating neurohumoral concentrations have returned to normal in most patients. Nevertheless, in a group of patients with left ventricular dysfunction but no overt heart failure, neurohumoral activation persists. Immediately after infarction sympathetic nervous activity is increased in relation to infarct size and the amount of left ventricular dysfunction. Patients with the highest circulating catecholamines have been found to have the poorest prognosis.[12 13] For 10 days after myocardial infarction the activity of the sympathetic nervous system gradually subsides, even in patients with significant left ventricular dysfunction.

The renin-angiotensin system is activated in nearly all patients early after infarction and rises progressively over the first three days not only in patients with overt heart failure but also in patients with no clinical complications. Increased concentrations of catecholamines, renin, and angiotensin II up to 10 days after admission to hospital were associated with extensive myocardial infarction, low left ventricular ejection fraction, heart failure, ventricular tachycardia, and death. In uncomplicated cases, when diuretics are not used, plasma renin activity gradually returns to normal, so that patients with asymptomatic left ventricular dysfunction have normal plasma renin concentrations at discharge from hospital.[9 14]

In the survival and ventricular enlargement trial (SAVE) more than 500 patients had plasma neurohumoral concentrations measured at a mean of 12 days after infarction.[11 15] All patients had left ventricular dysfunction (ejection fraction <40%) without overt heart failure. In these patients, all neurohumoral concentrations (plasma renin activity, noradrenaline (norepinephrine), arginine vasopressin, atrial natriuretic peptide) were increased compared with age matched controls. These data show that in a subgroup of patients with significantly reduced left ventricular function at the time of discharge from hospital after an infarction, a persistent neurohumoral activation can be found.

The data contrast with results of the studies of left ventricular dysfunction (SOLVD) prevention group where asymptomatic patients with left ventricular dysfunction (ejection fraction $\leqslant 35\%$) were studied.[16] Eighty per cent of the patients had had a myocardial infarction >30 days previously (mean 3·5 years). In this trial patients had similar plasma noradrenaline concentrations as in the SAVE trial, but had lower plasma renin activity and plasma concentrations of arginine vaso-

Neuroendocrine mechanisms activated in heart failure

Vasoconstrictor mechanisms:
Sympathetic nerve activity
Renin-angiotensin-aldosterone system
Arginine vasopressin
Endothelin
Vasodilator mechanisms:
Natriuretic peptides (ANP, BNP, CNP, urodilatin)
Prostaglandins (E_2, I_2)
Endothelium derived relaxing factor
Bradykinin
Dopamine
Endogenous digitalis-like factor

Klinik und Poliklinik für Innere Medizin II, Universität Regensburg, Regensburg, Germany
A J G Riegger

Correspondence to:
Professor Dr A J G Riegger, Klinik und Poliklinik für Innere Medizine II, Universität Regensburg, Franz-Josef-Strausse-Allee 11, 93053 Regensburg, Germany.

pressin.[17] These data, and those found in experimental heart failure[6], show that one of the first neurohumoral factors to be augmented after an injury to the myocardium is atrial natriuretic peptide (ANP), which is predominantly synthesised and secreted from the atria and correlates closely with cardiac dysfunction.[18] Also, brain natriuretic peptide (BNP), which is highly similar in structure and cardiovascular and renal actions to ANP, was found to be significantly raised in patients after an infarction to a proportionally greater degree than was ANP.[19] Unlike ANP, BNP is primarily synthesised and secreted from the cardiac ventricles rather than the atria,[20 21] and after an infarction may be a more sensitive and specific indicator of alterations to ventricular function than ANP.

Preliminary data suggest that measurements of circulating BNP may be able to discriminate patients with important left ventricular dysfunction after an acute myocardial infarction,[19] who should be treated with ACE inhibitors, as it was shown that plasma BNP concentrations were higher in patients with ejection fractions <40%.

Recently circulating N-terminal ANP has been proposed as a sensitive marker for symptomless left ventricular dysfunction. The ANP is stored as a 126 amino acid prohormone within atrial granules.[21 22] In response to atrial stretch, the prohormone is cleaved by a membrane protease and released into the circulation as a 28 amino acid C-terminal peptide (C-ANP) and a 98 amino acid N-terminal peptide (N-ANP).[23 24] As N-ANP has a reduced clearance compared with C-ANP, much higher concentrations of N-ANP can be measured in the circulation.

In a recent study it has been shown that patients with symptomless left ventricular dysfunction can be detected with a much higher sensitivity and specificity by measurement of plasma concentrations of N-ANP than by the determination of C-ANP.[25] This could have very important implications in the identification of patients with symptomless left ventricular dysfunction in order to start early treatment with ACE inhibitors. This may have an important impact on prognosis.

Neuroendocrine activation in overt heart failure

In the SOLVD treatment group in which patients with overt mild and moderate heart failure were included (ejection fraction $\leqslant$35%) a profound activation of neuroendocrine factors was shown.[17 26] In contrast with symptomless patients, patients with symptoms have considerably increased plasma renin activity and a further increase in plasma noradrenaline, ANP, and arginine vasopressin.

In patients with severe heart failure (New York Heart Association (NYHA) functional class IV), as was found in the cooperative north Scandinavian enalapril survival study (CONSENSUS), neuroendocrine mechanisms can be excessively active, showing a close association with survival.[2 27] Cohn and co-workers investigated the neurohumoral state in more than 600 patients with mild and moderate heart failure (NYHA, functional classes II and III) who participated in the second Veterans Administration cooperative vasodilator-heart failure trial (V-HeFT II)[28] and found heterogeneous neurohumoral stimulation without close correlation with clinical variables.[29]

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