Neuroendocrine excitation in heart failure

A J G Rieger

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.12

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.24 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.6,11 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 \( \leq 35\% \)) 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-

<table>
<thead>
<tr>
<th>Neuroendocrine mechanisms activated in heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vasoconstrictor mechanisms:</strong></td>
</tr>
<tr>
<td>Sympathetic nerve activity</td>
</tr>
<tr>
<td>Renin-angiotensin-aldosterone system</td>
</tr>
<tr>
<td>Arginine vasopressin</td>
</tr>
<tr>
<td>Endothelin</td>
</tr>
<tr>
<td><strong>Vasodilator mechanisms:</strong></td>
</tr>
<tr>
<td>Natriuretic peptides (ANP, BNP, CNP, urodiatin)</td>
</tr>
<tr>
<td>Prostaglandins (E(_2), I(_1))</td>
</tr>
<tr>
<td>Endothelium derived relaxing factor</td>
</tr>
<tr>
<td>Bradykinin</td>
</tr>
<tr>
<td>Dopamine</td>
</tr>
<tr>
<td>Endogenous digitalis-like factor</td>
</tr>
</tbody>
</table>
Neuroendocrine activation in heart failure

In the SOLVD treatment group in which patients with overt mild and moderate heart failure were included (ejection fraction ≤35%) a profound activation of neuroendocrine factors was shown. 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. 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) and found heterogeneous neurohumoral stimulation without close correlation with clinical variables.


Neuroendocrine excitation in heart failure

A J G Riegger

Br Heart J 1994 72: S28-S30
doi: 10.1136/hrt.72.2_Suppl.S28

Updated information and services can be found at:
http://heart.bmj.com/content/72/2_Suppl/S28.citation

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/