Tumour necrosis factor $\alpha$ in severe congestive cardiac failure

D P Dutka, J S Elborn, F Delamere, D J Shale, G K Morris

Abstract

Objective—To examine the concentration of circulating tumour necrosis factor $\alpha$ (TNF $\alpha$) in patients with severe congestive heart failure (New York Heart Association class IV) during one year and to correlate changes in this cytokine with changes in plasma noradrenaline, plasma renin activity, and weight.

Design—A prospective study of the role of TNF $\alpha$ in severe chronic heart failure. Blood samples were collected at intervals of three months.

Setting—Medical research centre of a teaching hospital.

Patients—16 patients with chronic stable severe heart failure.

Interventions—Vasodilator treatment with captopril or flosequinan.

Main outcome measures—Changes in TNF $\alpha$ and the correlation with changes in plasma noradrenaline, plasma renin activity, and weight during optimal medical treatment for one year.

Results—The mean concentration of TNF $\alpha$ was greater than the upper 95% confidence interval for healthy controls throughout the year of the study but there was considerable between and within patient variation. No correlation was seen between TNF $\alpha$ and plasma noradrenaline, plasma renin activity, or weight.

Conclusions—The stimulus resulting in enhanced plasma concentrations of TNF $\alpha$ in congestive heart failure remains unclear and concentrations at any particular time were not prognostic.

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Various explanations have been proposed for the weight loss that is often noted in patients with severe heart failure including reduced appetite and caloric intake,1,2 malabsorption,3 and impaired delivery of oxygen to peripheral tissues.4 Resting energy expenditure in chronic heart failure is noticeably increased with increased oxygen consumption, ventilation, and heart rate compared with controls.5 The increased concentrations of circulating catecholamines have been implicated in mediating the catabolism of severe heart failure and the hypothesis is proposed that the resultant accelerated breakdown of adipose tissue and muscle is a consequence of the increased metabolic demands of the heart and respira-

tory muscles.1,4,6 Weight loss may also result from the enhanced secretion of an endogenous hormone with antianabolic or catabolic properties that has not yet been identified.

Tumour necrosis factor $\alpha$ (TNF $\alpha$) is a cytokine secreted by macrophages and monocytes in response to a variety of stimuli and concentrations were found to be high in patients with heart failure, in association with noticeable activation of the renin angiotensin system.7 There was, however, a wide variation in TNF $\alpha$ between patients and in many it was not detected. The effects of TNF $\alpha$ in chronic diseases may relate more to the duration of exposure and therefore this study was undertaken to assess serial changes in TNF $\alpha$ during one year and the relations between the concentration of this cytokine and plasma noradrenaline, plasma renin activity, and weight in a group of patients with severe congestive heart failure who were receiving optimal medical treatment.

Patients and methods

Sixteen patients (mean aged 56 SEM 4.2 years) with severe heart failure (New York Heart Association class IV) entered the study. The mean cardiothoracic ratio was 59% (0.01%). The aetiology of the heart failure was coronary artery disease in nine patients and idiopathic dilated cardiomyopathy in seven. At the start of the study the diuretic dose was titrated to eliminate peripheral oedema before the patient received vasodilator treatment (captopril or flosequinan). The diuretic dose was adjusted as necessary during the study but the dose of vasodilator was kept constant if possible. None of the patients had any evidence of inflammatory or neoplastic disease.

After 20 minutes supine rest, venous blood was taken for measurement of packed cell volume, serum electrolytes, urea, and creatinine concentrations, plasma renin activity, and noradrenaline and TNF $\alpha$ concentrations. Blood for hormone analysis was placed on ice, separated immediately, and stored at $-70^\circ$C until assay in batches. Samples were taken before vasodilator treatment, and after three, six, nine, and 12 months of vasodilator treatment.

ASSAYS

Plasma renin activity was measured by radioimmunoassay and noradrenaline by high performance liquid chromatography. The TNF $\alpha$ was measured by enzyme linked
50 μl/well of rabbit anti-TNFα was allowed to act for two hours, the plates were washed, antirabbit IgG antibody was added. After a further hour, peroxidase substrate mixture (100 μl/well) was added and allowed to act for 30 minutes and the reaction was then stopped by the addition of 50 μl 3M sodium hydroxide into each well. Absorbance was read at 455-5 nm. Each plate consisted of eight wells without TNFα (buffer only) and a standard curve for TNFα of 62.5 to 2000 pg/ml in duplicate. The concentration of TNFα in each sample was calculated from a regression line derived from the standard curve. The sensitivity of the assay was 28.25 pg/ml. The upper limit for TNFα in healthy controls in our laboratory is 65 pg/ml (upper 95% confidence interval (95% CI)]. All results are expressed as mean (SEM).

**STATISTICAL METHODS**

The two tailed Wilcoxon paired rank sum test was used for all statistical analyses.

**Results**

Plasma TNFα was increased in the group of patients with severe heart failure at entry to the study (173.5 (63.5) (mean SEM)) pg/ml, range 0–855 pg/ml, n = 16) and after one year (142.2 (58.75) pg/ml, range 0–405 pg/ml, n = 10; p = 0.844). There was considerable variation in individual patients during the year of the study, and in all of the 16 patients TNFα was not detected on at least one occasion (fig 1). In two of the six patients who died during the study circulating TNFα was never detected.

There was no suggestion of a direct relation between plasma TNFα and either plasma noradrenaline (fig 2) or plasma activity (fig 3). No correlation was found between TNFα and noradrenaline either at entry into the study (r² = 0.03, p = 0.52, n = 16) or in the survivors at one year (r² = 0.37, p = 0.06, n = 10). The same was found between TNFα and plasma noradrenaline at entry (r² = 0.17, p = 0.11, n = 16) and at one year (r² = 0.15, p = 0.27, n = 10). The mean (SEM) plasma noradrenaline of the group did not change significantly during the study after the introduction of vasodilator treatment (751.6 (111.6) pg/ml at entry, 793.9 (108) pg/ml at one year). The mean plasma renin activity, however, did increase from 10.4 (3.4) ng/ml/h at entry to 27.4 (7.4) ng/ml/h at one year (p = 0.046).

No significant changes were seen in mean sodium, potassium, urea, and creatinine in serum although there was a trend for creatinine to rise during the study (table). There was a significant fall in packed volume but the decrease in haemoglobin concentration was not significant. The dose of frusemide required by these patients with severe heart failure increased significantly during the course of the study (table).

Little change occurred in the mean weight of the group. The mean (SEM) weight change from entry to the last recorded weight

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**Biochemical, diuretic, and weight characteristics (mean (SEM)) of patients with severe heart failure**

<table>
<thead>
<tr>
<th></th>
<th>As entry (n = 16)</th>
<th>One year later (n = 10)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum sodium (mmol/l)</td>
<td>138.75 (1.17)</td>
<td>137.60 (0.64)</td>
<td>0.11</td>
</tr>
<tr>
<td>Serum potassium (mmol/l)</td>
<td>4.34 (0.09)</td>
<td>4.26 (0.11)</td>
<td>0.81</td>
</tr>
<tr>
<td>Urea (mmol/l)</td>
<td>9.04 (1.14)</td>
<td>9.01 (1.21)</td>
<td>0.42</td>
</tr>
<tr>
<td>Creatinine (μmol/l)</td>
<td>129.0 (6.41)</td>
<td>142.18 (11.42)</td>
<td>0.64</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>15.37 (0.48)</td>
<td>14.69 (0.24)</td>
<td>0.22</td>
</tr>
<tr>
<td>Packed cell volume (%)</td>
<td>48.25 (1.39)</td>
<td>48.81 (0.48)</td>
<td>0.012</td>
</tr>
<tr>
<td>Frusemide dose (mg/day)</td>
<td>90.0 (4.47)</td>
<td>130.6 (11.66)</td>
<td>0.009</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.55 (4.01)</td>
<td>80.24 (4.11)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

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Figure 1: Plasma tumour necrosis factor α (TNFα) in 16 patients with severe heart failure studied prospectively for one year. Median values are represented by horizontal lines. D indicates patients who died during the study.

Figure 2: Plasma noradrenaline and tumour necrosis factor α (TNFα) during one year in 16 patients with severe heart failure (r² = 0.26).

Figure 3: Plasma renin activity (PRA) and tumour necrosis factor α (TNFα) during one year in 16 patients with severe heart failure (r² = 0.23).
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was −1.82 (0-9) kg, with a maximum fall of 5-35% of the initial weight (table 1).

Discussion

In our study of patients with severe heart failure the mean concentration of plasma immunoreactive TNF α was increased during the year of the study. There was, however, considerable between and within patient variation and no correlation was found between the concentration of circulating TNF α and mortality (one year mortality was 40%). All patients were treated with vasodilators throughout the study and the dose of diuretic adjusted to eliminate oedema if necessary. The dose of diuretic required increased significantly during the study and may account for some of the increase in plasma renin activity. Body mass indices were not measured but the mean weight of the group did not change. There was no significant relation between TNF α and noradrenaline or renin plasma levels. We have shown a good relation between the ELISA toxic cytotoxicity bioassay and its effects of concentrations of corticosterone in severe heart failure. Some of these cross sectional studies should be interpreted with caution. In the study by McMurray et al, TNF α was not detected in 90% of their non-cachetic patients with severe heart failure or in 44% of patients with cachexia. Levine et al found increased concentrations of TNF α in their group of patients with high renin concentrations. Again there was a wide variation and in many of these patients circulating TNF α was not detected. The wide variation in the concentration of circulating TNF α in these studies and in our prospective study warrants further investigation before the suggestion that the therapeutic manipulation of TNF α in severe heart failure might be beneficial. The role of this cytokine in the natural history of chronic heart failure remains unknown.

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