Systemic inflammation in patients with heart failure

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Aims We hypothesized that chronic heart failure as a model of systemic hypoxia may result in systemic inflammation. The signs of a systemic inflammatory response should disappear after successful mechanical circulatory support using biventricular assist device systems.

Methods and Results Plasma levels of cytokines (IL-6, IL-8, TNF-α) and soluble adhesion molecules (sVCAM, sE-, sL-, sP-Selectin) were determined in samples obtained from patients with chronic heart failure NYHA classes II–III, patients with overt cardiogenic shock before and after implantation of a mechanical assist-device system (‘Berlin Heart’) and in patients with coronary artery disease as a control. Elevated levels of cytokines and soluble adhesion molecules could be observed in patients with cardiogenic shock, although slightly decreased levels of soluble adhesion molecules were also detectable in patients with chronic heart failure NYHA classes II–III. The signs of systemic inflammation disappeared following successful mechanical circulatory support, but persisted in patients who developed infectious complications.

Conclusions Our data suggest that a systemic hypoxic and inflammatory syndrome is manifested during end-stage heart failure, such as in patients with sepsis or who have suffered non-infectious insults. During mechanical circulatory support, elevated levels of inflammatory mediators may be indicative of persistent peripheral hypoxia associated with a high risk for infection or sepsis. Therefore, the monitoring of inflammatory mediators should be evaluated as markers of the effectiveness of this therapy (Eur Heart J 1998; 19: 761–765)

Key Words: Chronic heart failure, cardiogenic shock, Biventricular assist device system, systemic inflammatory response syndrome, cytokines, adhesion molecules.

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Introduction

A systemic inflammatory response is characterized by activation of various cell types and a massive release of endogenous mediators of inflammation, which may produce clinical sequelae. Bacterial sepsis is one of several causes inducing systemic inflammation. In vitro studies have demonstrated the activating potential of hypoxia to leukocytes and endothelial cells[1,2]. In a mouse model, alterations of immunological functions were produced by haemorrhage/resuscitation or chemically induced hypotension[3,4].

We hypothesized that chronic heart failure, as a model of systemic ischaemia and hypoxia in man, would affect the immune system. Therefore we determined plasma levels of some pro-inflammatory cytokines (IL-6, IL-8 and TNF-α) and soluble adhesion molecules (sVCAM-1, sE-, sL- and sP-Selectin) as markers for activation of different cell types.

Biventricular assist device systems (BVAD) have been shown to be effective tools for bridging the time until heart transplantation in patients with irreversible cardiogenic shock. During mechanical assist device support, hormonal responses of heart failure returned to baseline levels[5]. Skin microcirculation in patients receiving biventricular assist device systems support is not statistically different from healthy volunteers[6]. We assumed that systemic inflammation due to peripheral hypoxia should disappear in patients who underwent successful mechanical circulatory support. Therefore plasma levels of inflammatory mediators were monitored during the course of mechanically assisted circulation.

Methods

The first patient group consisted of 10 patients suffering from chronic heart failure in the New York Heart Association (NYHA) classes II–III. Chronic heart...
failure was caused by coronary artery disease (n=5) or dilated cardiomyopathy (n=5). The patients' ages ranged from 31 to 64 years. Additionally, 14 patients suffering from overt cardiogenic shock with low cardiac output, low arterial blood pressure, high right and left ventricular filling pressures despite optimal inotropic and vasodilator support were included in this study. Blood was taken immediately before starting mechanical circulatory support as a bridge to transplantation. Heart failure was caused by dilated cardiomyopathy (n=13) or coronary artery disease (n=1). The patients' ages ranged from 13 to 54 years. Mechanical circulatory support was performed using the Berlin-Heart Biventricular Assist Device System (Berlin Heart Mediproduct GmbH, Berlin, Germany). The Berlin Heart consists of a sac-type blood pump with polyurethane housing and two mechanical valves (Serono®) which direct the inflow and outflow of the blood. The blood pumps were connected to the right and left atrium and to the aorta and pulmonary artery via transcutaneous silicone cannulas. Hydraulic energy was generated by a pneumatic system (Heimes HD 7 drive, Heimes GmbH, Aachen, Germany).

The duration of mechanical circulatory support ranged from 12 to 125 days (mean 53 days). One patient died from haemorrhage (day 62) and two patients died from septic multiple organ failure (day 37 and 125, respectively). A patient experienced an adult respiratory distress syndrome with fatal outcome on day 28. All other patients received heart transplants.

Patients with coronary artery disease without signs or symptoms of heart failure and with normal left ventricular wall motion and angiographic ejection fraction represented the control population. The patients' ages ranged from 52 to 69 years (mean 57). All patients have given written informed consent to the study.

In all patients, blood specimens were drawn from a peripheral vein. Plasma concentrations of IL-6, IL-8, TNF-α, sP-Selectin (source: activated endothelial cells [EC] and/or thrombocytes), sE-Selectin (EC), sVCAM-1 (EC and/or leukocytes) and sL-Selectin (leukocytes) were measured by commercially available ELISA assays (TNF-α — Medgenix, Ratingen, Germany; sL-Selectin — Serva, Heidelberg, Germany; all others — Biermann, Bad Nauheim, Germany). The lower limit of sensitivity was 0.35 pg.mL⁻¹ IL-6, 18 pg.mL⁻¹ IL-8 and 7.5 pg.mL⁻¹ TNF-α. During mechanical circulatory support blood was collected twice a week. Statistical analysis was performed using the Wilcoxon test for unpaired samples.

**Results**

High plasma levels of IL-6 and IL-8 were found in patients with cardiogenic shock, whereas cytokines could not be detected in plasma from controls and patients with chronic heart failure NYHA classes II–III. IL-8 ranged from 91 to 985 pg.mL⁻¹ (mean: 201 pg.mL⁻¹) in the plasma of 11 of our 14 patients; IL-6 was found in the plasma of every patient of this group in a range from 10 to 598 pg.mL⁻¹ (mean: 138 pg.mL⁻¹). In contrast, tumour necrosis factor-α was only detectable in the plasma of one patient who showed clinical signs of infection (leukocytosis, fever). Soluble adhesion molecules were also statistically significantly elevated in the plasma of patients suffering from cardiogenic shock, as demonstrated by sE-Selectin (Fig. 1). Additionally, patients with chronic heart failure NYHA classes II–III also had higher levels of sE-Selectin as compared to controls, but the difference was statistically not significant. However, in two of ten patients with chronic heart failure, NYHA classes II–III, strongly elevated sE-Selectin plasma concentrations could be detected.

Similar results were observed for all other soluble adhesion molecules, such as sL-Selectin, sVCAM-1 and sP-Selectin (Table 1). Patients with cardiogenic shock showed significantly elevated levels of these...
parameters. The same tendency was seen for patients with chronic heart failure NYHA classes II–III, although the differences in relation to controls were statistically not significant.

After initiation of the biventricular assist device system, a further increase in plasma levels of inflammatory mediators was recorded for up to 5 days in all patients. After the first week of mechanical circulatory support, plasma concentrations returned to lower levels in most patients. We have analysed the data from survivors, who were successfully maintained on biventricular assist device systems until heart transplantation, and non-survivors, who died during mechanical support before transplantation, separately. There was no difference between survivors and non-survivors regarding age, sex, causative disease, duration of mechanical support, pre-operative levels and post-operative levels until day 5. But while in the survivor group, sE-Selectin concentrations returned to nearly normal values after the first week, they remained elevated in non-survivors (Fig. 2). The difference between survivors and non-survivors was statistically significant after the first week of mechanical support (Fig. 3). Similar results were obtained for IL-8 and sL-Selectin (Table 2). There was a significant correlation between IL-8 and sE-Selectin ($r = 0.25; P < 0.05$), IL-8 and sL-Selectin ($r = 0.48, P < 0.01$) as well as sE-Selectin and sL-Selectin ($r = 0.50, P < 0.01$) after the first week of mechanical circulatory support.

### Discussion

In summary, in cardiogenic shock a significant increase in plasma concentrations of IL-6 and IL-8 as well as of soluble adhesion molecules could be observed, suggesting systemic inflammation similar to septic disease or polytrauma. These findings are evidence of activation of leukocytes (IL-8, IL-6, sVCAM, sL-Selectin), endothelial cells (IL-8, IL-6, sE-Selectin, sVCAM, sP-Selectin), and thrombocytes (sP-Selectin). Our data are in accordance with the results published by Wiedermann et al.\textsuperscript{[7]} who found signs of monocytic activation in chronic heart failure patients.

In contrast to other studies, we could not detect TNF-$\alpha$ in patients with chronic heart failure\textsuperscript{[8,9]}. This is consistent with results of Münger et al., who detected elevated levels of IL-6, but not of TNF-$\alpha$ in patients with moderate chronic heart failure\textsuperscript{[10]}. However,
non-detection of TNF-α does not exclude biologically active levels of this cytokine in vivo. TNF-α could have been present at levels under the detection limit of the assay we used. Furthermore, as in septic disease TNF-α may be secreted in a pulsatile manner. In addition, soluble TNF-receptors, which have been shown to be elevated in chronic heart failure, may inhibit detection in immunoassays. However, there was no interference between TNF-α levels and an added recombinant soluble TNF-receptor I/II in the ELISA we used (own observation, not published).

Systemic inflammation in patients with cardiogenic shock may be caused by infections. However, this presumption is restricted by the fact that only one of these patients showed clinical and microbiological signs of infection at the time of blood sampling. Furthermore, patients with chronic heart failure NYHA classes II–III also showed signs of systemic inflammation although less dramatically.

Torre-Amine et al. have not found any correlation between cytokine and neurohormonal levels in chronic heart failure. This is in agreement with the finding that catecholamines usually act in an anti-inflammatory manner via cAMP-elevation (own observation, data not shown). As a result of these studies, which do not explain systemic inflammation in heart failure, the focus should be set on peripheral tissues.

Since both infectious (sepsis) and non-infectious (haemorrhage, pancreatitis, trauma etc.) insults can elicit similar systemic host responses, Benjamin et al.[13] defined a novel useful term encompassing these common conditions (cellular hypoxia, adaptative changes, inflammatory reaction, multiple organ dysfunction). They proposed the neologism systemic hypoxic and inflammatory syndrome to designate this set of symptoms.

In mouse models, it was demonstrated that hypoxia following haemorrhage or exposure to a hypoxic gas mixture can induce an inflammatory response by macrophages[14]. Hypoxia as well as endotoxin translocation are discussed as causes of inflammation in this setting. It is not clear whether whole body inflammation is involved in the pathogenesis of circulatory failure or represents an epiphenomenon. However, systemic inflammation should not be without influence on the course of cardiogenic shock. In vitro studies have demonstrated a negative inotropic effect of IL-6 and TNF-α[15,16]. Therefore, it should be worthwhile evaluating anti-inflammatory strategies as a novel therapeutic approach in chronic heart failure.

A further temporary increase in inflammatory mediators was seen after implantation of the assist device system in patients with cardiogenic shock. This may reflect surgical trauma, reperfusion and contact with the artificial surface. After the first week, serum

**Figure 3** Plasma concentrations of sE-Selectin in patients with good (□) or fatal (■) prognosis before implantation of the assist device, in the first week (days 1–5) and after the first week (after day 5) of mechanical support.

**Table 2** Plasma concentrations of IL-8 and sL-Selectin in patients with good (survivors) or fatal (non-survivors) prognosis in the first week (days 1–5) and after the first week (after day 5) of mechanical support. The differences between survivors and non-survivors were statistically significant after the first week for IL-8 (P < 0.05) and sL-Selectin (P < 0.01).

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<th>Days 1–5</th>
<th>After day 5</th>
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<td></td>
<td>Survivors</td>
<td>Non-survivors</td>
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<tr>
<td>IL-8 (pg. ml⁻¹)</td>
<td>216 ± 197</td>
<td>311 ± 334</td>
</tr>
<tr>
<td>sL-Selectin (ng. ml⁻¹)</td>
<td>1115 ± 344</td>
<td>1558 ± 432</td>
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Mean ± SEM. Differences were evaluated by Student’s t-test. Day 0 (before) compared with days 1–5 and after day 5.
Concentrations of inflammatory mediators dropped to lower levels in most of our patients. The disappearance of signs of systemic inflammation in patients who underwent successful mechanical circulatory assist supports the hypothesis that systemic inflammation in patients with cardiogenic shock reflects peripheral hypoxia. Remarkably, inflammatory signs persisted in patients who died despite mechanical support. A though these patients died from infection and septic multiple organ failure we found elevated levels of inflammatory mediators days to weeks before infections became clinically apparent. This may be indicative of persistent peripheral hypoxia in these patients as the cause of whole body inflammation rather than infection. In fact, a further increase of inflammatory mediators, including TNF-α, was detected when infections with clinical and microbiological signs occurred. This is an observation which might relate to the fact that systemic inflammation is followed by immunosuppression (especially of the cellular immune system) with increased susceptibility to infection[17].

We hypothesize that in some patients mechanical circulatory support is not effective in removing peripheral hypoxia which may be a result of dysregulated tissue perfusion (vasoconstriction, redistribution of peripheral blood flow). The induced chronic inflammatory response may increase susceptibility to infection by downregulation of the cellular immune system and activation of anti-inflammatory pathways. As a result, the patient is prone to septic disease.

The oxygenation of peripheral blood is commonly monitored in patients receiving biventricular assist device systems support. In nearly all of our patients, arterial pH and lactate levels are within normal limits. However, hypoxic conditions restricted to peripheral tissues are hardly detectable. Therefore, the monitoring of inflammatory mediators should be evaluated as markers of persistent hypoxia and of the effectiveness of therapeutic intervention, including mechanical circulatory support.

References


