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# Myocardial function and haemodynamics in extensive burn trauma: evaluation by clinical signs, invasive monitoring, echocardiography and cytokine concentrations. A prospective clinical study

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**Background:** The objectives of this study were to (1) describe the haemodynamic profile of patients with extensive burns during the early fluid resuscitation phase, (2) evaluate myocardial performance by invasive monitoring and echocardiography and (3) analyze the relations between serum cytokine (IL-6, IL-8, TNF) and natriuretic peptide (ANP, BNP) concentrations and myocardial function in these patients.
**Methods:** Prospective, clinical study in a tertiary care burn centre. Invasive haemodynamic measurements including a pulmonary artery catheter, echocardiography, blood samples for cytokine and atriopeptide analyses. The follow-up time was up to 72 h postinjury.
**Results:** According to echocardiography, patients were hypovolaemic despite aggressive (median 7,9 ml $kg^{-1}$ $h^{-1}$, range 3.3–11.7) fluid resuscitation and adequate urine output (median 0.9 ml $kg^{-1}$ $h^{-1}$, range 0.46–1.35) during the first day postinjury. There were no consistent findings of hyperlactatemia, metabolic acidosis or low mixed venous oxygen saturations. Daily highest and lowest values of cardiac index and stroke volume index increased and the lowest and highest values of systemic vascular resistance decreased. Cardiac performance (stroke volume index) improved during the study period even though there were no initial signs of myocardial depression in echocardiography. Three patients received a dobutamine infusion based on clinical judgement. There was no consistent association between haemodynamic changes and plasma cytokine concentrations.
**Conclusion:** Persisting hypovolaemia is evident in the resuscitation phase of extensive burns despite aggressive fluid therapy and the lack of classic signs of hypoperfusion. Cardiac performance improves during the first days after extensive burn injury without association with plasma cytokine profile.

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**Key words:** Atriopeptide; burns; cytokine; echocardiography; haemodynamics; myocardial depression.



VASCULAR permeability is increased by several mediators released during the course of the inflammatory response in burn trauma. Loss of plasma into tissues causes hypovolaemia, decreases cardiac output and predisposes to tissue hypoperfusion. On the other hand, excessive infusion of fluids may lead to massive swellings, which further worsen tissue perfusion and wound healing, and may also cause pulmonary oedema.

Poor myocardial performance after severe burn trauma can also contribute to tissue hypoperfusion. Baxter et al. first suggested the existence of a myocardial depressant factor in burn shock (1). In dogs, burn trauma results in a sharp decrease in cardiac output (2), which remained low for 7 h. Burns decrease left ventricular contractility and preload during early postburn period in anaesthetized dogs (3). Tumour necrosis factor alfa (TNFα) and interleukin-1 beta (IL-1β) have been found to synergistically depress human myocardial function in freshly obtained human myocardial trabeculae (4). Besides cytokines, exogenous neopterin causes cardiac contractile dysfunction in isolated perfused rat hearts (5). Resuscitation with hypertonic dextran in sheep (6) and arginine in rats (7) has improved cardiac performance in burn injury. However, there are only a few clinical studies focusing on cardiac problems in patients with extensive burns (8–10). In addition, despite the often-cited clinical problem, there is no precise definition of myocardial depression in burn patients.

Routine fluid resuscitation in burn patients can be performed according to different formulae and it can be guided by either clinical monitoring of tissue perfusion or by means of invasive haemodynamic monitoring devices. Early, aggressive fluid resuscitation has been shown to reverse the abnormalities of contraction and relaxation in heart muscle after burn injury, emphasizing the importance of early interventions (11).

The hypothesis was that there is evidence of myocardial depression in transoesophageal echocardiography and that there is correlation between the haemodynamic profile of the patients and the cytokine profile.

The aims of this study were to (1) describe the haemodynamic profile of patients with extensive burns during the early fluid resuscitation phase, (2) evaluate the occurrence of myocardial depression by means of two independent methods (invasive monitoring and echocardiography) and (3) to analyze the relationship between serum cytokine concentrations and myocardial function.

## Methods

### *Patients*

With the approval of the local Ethics Committee a convenience sample of nine burn patients admitted to the Intensive Care Unit of Kuopio University Hospital within 48 h of extensive burn trauma were prospectively studied. Informed consent was obtained from each patient or from the family, when appropriate.

### *Haemodynamic monitoring and therapy*

All patients had invasive haemodynamic monitoring, including a pulmonary artery catheter. Systemic and central pressures were recorded with quartz pressure transducers and displayed on a multimodular monitor and recorder (AS3, Datex-Ohmeda, Helsinki, Finland). Continuous heart rate and haemodynamic data were collected automatically as 2-min intervals (Clinisoft, Datex-Ohmeda, Espoo, Finland). All pressure transducers were zeroed to the level of the heart. The pulmonary artery occlusion pressure and cardiac output were recorded with at least 60-min intervals. Cardiac output was measured with either cold water boluses or continuously.

The following data were recorded: total amount of fluid infused during the first 24 h postburn and urine output (UO) during the first 24 h in the ICU, the lowest (l) and highest (h) values of cardiac index (CI), and the respective values of haemoglobin (Hb), lactate, mixed venous oxygen saturation ($SvO_2$), blood gas analysis, heart rate (HR), pulmonary artery occlusion pressure (PAOP), central venous pressure (CVP) and mean systemic arterial pressure (SAPm). Stroke volume index (SVi) and systemic vascular resistance (SVR) were calculated. Haemodynamic parameters were recorded also at the times of the transoesophageal echocardiography. In addition, age, sex, total percentage of body surface area burned (TBSA), Baux index (age + TBSA), presence of inhalation injury assessed by bronchoscopy, time delay until arrival to burn unit and hospital mortality were recorded. The use of vasoactive drugs was noted. The follow-up time was up to 72 h postinjury.

Fluid resuscitation was started with Ringer's lactate according to Parkland formula ($4\,ml\,kg^{-1}$ %TBSA burned half of the amount given during the first 8 h postburn and half during 8–24 h postburn). Fluid replacement was considered adequate when SAPm was >60 mmHg, peripheral temperature 32°C, UO > 0.5–1 $ml\,kg^{-1}\,h^{-1}$, haematocrit <0.45, SvO2 > 65% and serum lactate concentration <2 $mmol\,l^{-1}$. If these criteria were not met, extra crystalloids were given. When fluid requirement was exceptionally high, a hypertonic infusion (1000 ml of Ringer's lactate + 160 mmol NaCl) was started. Colloids (hydroxyethyl starch) were started at 12–18 h postburn. At day 2, Ringer's lactate and colloids were given. Norepinephrine was started to correct hypotension (SAPm was <60 mmHg). If CI was considered inadequate clinically, a dobutamine infusion was started. The use of vasoactive drugs was based on clinical judgement by the individual physician only, and no detailed criteria were set for vasoactive treatment.

### *Transoesophageal echocardiography*

Transoesophageal echocardiography (TEE) was performed using Hewlett-Packard Sonos 5500 ultrasound system (Hewlett-Packard Co, Andover, MA) with a 2.5-MHz transoesophageal transducer. All patients were intubated prior to TEE. During the echocardiography the patients were sedated with intravenous thiopenthone or propofol. First, the echo probe was advanced to lower oesophagus or ventricular fundus to depict the left ventricle in a short axis view at the mid-papillary level. The thickness of the anterior and posterior walls during end-diastole, as well as the diameters and areas of left ventricle during end-diastole and end-systole, were measured. The fractional area shortening was defined as the end-diastolic area minus the end-systolic area divided by the end-diastolic area. Next, the echo probe was pulled back in

the oesophagus in order to record the left ventricular filling during diastole at the tip of the mitral valve leaflets with a 5-MHz pulsed Doppler probe. The sample volume of 5 mm was used. The peak velocity of the early (PEm) and atrial (PAm) filling phase as well as the peakA/peakE ratio (A/E ratio) were calculated. Finally, the probe was withdrawn further to visualize the left upper pulmonary vein. Pulmonary vein flow was measured *c.* 1 cm from the orifice of the vein with the sampling volume of 5 mm. The peak velocity of forward flow during ventricular systole (PSpv) and diastole (PDpv) and a peak velocity of reversal flow during atrial systole (PApv), as well as the peak S/peak D ratio (PS/PD ratio), were calculated. For all variables, a mean value of 3 consecutive cardiac beats was used. The first examination was performed as soon as possible after the patient's arrival at the burn unit and the second and third examinations at postburn days 2 and 3, respectively. The TEE analysis was performed blinded to other data.

### *Laboratory measurements*

Blood samples were obtained at 6-h intervals up to 72 h from burn trauma to measure interleukin-6 (IL-6) (Quantikine Human IL-6-Elisa-kit cat D6050, R & D Systems, Minneapolis, MN), interleukin-8 (IL-8) (Quantikine Human IL-8-Elisa-kit cat D8050, R & D Systems), tumour necrosis factor alfa (TNF-α; TNF-alfa-Easia-kit KAC 1752, Fleurus, Belgium) and neopterin (Neopterin ELISA-kit RE 59321, IBL Immuno-Biological Laboratories, Hamburg, Germany) concentrations. Atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP) and N-terminal pro-atrial natriuretic peptide (NT-proANP) were extracted from plasma using SepPak C18 cartridges. Natriuretic peptide-proANP was assayed directly from unextracted plasma. The radioimmunoassay protocols have been described previously for ANP[12] and NT-proANP[13]. With these methods, the following plasma concentrations (mean ± SD) were detected in healthy adults aged 20–55 years: ANP, $10.9 \pm 4.0\,\text{pmol}\,l^{-1}$; BNP, $3.8 \pm 3.4\,\text{pmol}\,l^{-1}$; and NT-proANP, $227 \pm 84\,\text{pmol}\,l^{-1}$. The medians of all daily values were used for statistical analysis.

### *Statistical analysis*

Nonparametric Friedman test was used for statistical analysis. All analyses were performed using the SPSS for Windows (SPSS Inc, Chicago, IL) program. Data are expressed as medians and interquartile ranges unless otherwise indicated. *P*-value $<0.05$ was considered statistically significant.

## Results

Patient characteristics are presented in Table 1. The median delay from burn injury to the first haemodynamic measurement was 12 h (range 6–18 h).

Cardiovascular data are expressed as respective values corresponding to the daily highest and lowest CI values (Table 2). During the study period, the daily highest and lowest CIs and SV is increased, and the highest and lowest SVRs decreased. The PAOPs were low and remained unchanged. Median amount of fluids administered during the first 24 h postburn was $7.9\,\text{ml}\,\text{kg}^{-1}\,\text{h}^{-1}$ (range 3.3–11.7) and median urinary output during the first 24 h in the ICU was $0.9\,\text{ml}\,\text{kg}^{-1}\,\text{h}^{-1}$ (0.46–1.35). There were no changes in serum lactate concentrations (daily medians 1.8, 1.8 and $1.9\,\text{mmol}\,l^{-1}$) or mixed venous oxygen saturations (daily medians 74, 70 and 76%). Despite the overall haemodynamic profile, clinicians made a decision to infuse dobutamine to three patients from whom two patients needed dobutamine during the first 24 h postinjury only (for 12 and 22 h, respectively). Norepinephrine was used in six patients

*Table 1*

Description of the patients.

| Patient | Sex | Age (years) | TBSA (%) | Baux index | Etiology | Inhalation injury | ICU days | DMV | Death | Cause of death |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 52 | 22 | 74 | Hot air | No | 45 | 43 | No | |
| 2 | M | 44 | 21 | 65 | Flame | Yes | 21 | 9 | No | |
| 3 | F | 57 | 28 | 85 | Flame | No | 11 | 9 | No | |
| 4 | M | 52 | 53 | 105 | Flame | No | 3 | 3 | Day 3 | Multi-organ failure |
| 5 | M | 52 | 27 | 79 | Flame | Yes | 7 | 0 | No | |
| 6 | M | 50 | 27 | 77 | Flame | No | 23 | 9 | No | |
| 7 | M | 32 | 96 | 128 | Scald | No | 35 | 31 | Day 35 | Multi-organ failure |
| 8 | M | 71 | 13 | 84 | Flame | Yes | 1 | 1 | No | |
| 9 | M | 43 | 22 | 65 | Flame | No | 4 | 0 | No | |
| Median | | 52 | 27 | 79 | | | 11 | 9 | | |

TBSA = total body surface area burned; Baux index = age + TBSA burned; DMV = days of mechanical ventilation.

*Table 2*

Results of haemodynamic measurements (median, interquartile range and *P*-value). The values of days 1, 2 and 3 are presented as respective values of the daily lowest (low) and highest (high) values of cardiac index.

| Parameter/day | Day 1 median | iq-range | Day 2 median | iq-range | Day 3 median | iq-range | *P*-value |
|---|---|---|---|---|---|---|---|
| CI ($l\,min^{-1}\,m^{-2}$) | | | | | | | |
| low | 2.3 | 1.7–2.7 | 3.2 | 2.4–3.5 | 3.6 | 2.4–4.6 | 0.008 |
| high | 5.4 | 4.9–6.6 | 6.4 | 5.7–7.6 | 7.0 | 6.1–8.7 | 0.062 |
| SVi ($ml/m^2$) | | | | | | | |
| low | 22.4 | 12.3–25.3 | 25.3 | 22.5–34.8 | 31.2 | 29.9–40.10 | 0.003 |
| high | 55.1 | 48.4–64.5 | 60.8 | 46.7–68.5 | 74.5 | 54.4–79.6 | 0.032 |
| CVP (mmHg) | | | | | | | |
| low | 2.0 | 1.6–3.3 | 4.4 | 1.4–5.5 | 5.0 | 3.0–6.8 | 0.013 |
| high | 1.4 | 0.3–4.3 | 4.0 | 2.4–6.2 | 4.2 | 2.3–6.1 | NS |
| SVR ($dyne^*s\,cm^{-5}$) | | | | | | | |
| low | 2584 | 2237–3159 | 1434 | 1383–1632 | 1281 | 880–1774 | 0.001 |
| high | 872 | 769–1245 | 814 | 651–912 | 710 | 538–835 | 0.032 |
| PAOP (mmHg) | | | | | | | |
| low | 3.0 | 2.0–4.0 | 4.0 | 0.5–5.5 | 6.0 | 3.0–8.25 | NS |
| high | 3.0 | 2.0–5.5 | 5.0 | 3.5–5.5 | 5.5 | 3.5–8.9 | NS |

CI = cardiac index; SVi = stroke volume index; CVP = central venous pressure; SVR = systemic vascular resistance; PAOP = pulmonary artery occlusion pressure; iq = interquartile.

(duration 1, 2, 36, 45, 45 and 48 h, respectively) due to low systemic vascular resistance and hypotension.

Invasively measured CI, SVi, PAOP or SAPm did not change during different time-points (Table 3). There were no signs of compromised left ventricular systolic function in echocardiography during the study (left ventricular fractional area shortening <36%). However, there was a trend towards an increase in left ventricle diastolic area during the course of the study ($P = 0.066$). Considering cardiac diastolic function, the peak early velocity of the mitral flow (PEm)($54\,cm\,s^{-1}$) as well as the pulmonary vein peak velocity of reversal flow during atrial systole (PApv)($14.5\,cm\,s^{-1}$) were very low during day 1.

There were no changes in the serum concentrations of IL-6 and TNF-$\alpha$, although 80% of the values of TNF-$\alpha$ exceeded the normal upper limits. However, IL-8 and neopterin concentrations increased slightly during the study (Figs 1 and 2). Natriuretic peptide-proANP concentrations did not change but p-ANP

*Table 3*

Results of echocardiographic measurements and haemodynamic data at these same time points (median, interquartile range and *P*-value) at days 1, 2 and 3.

| Parameter/day | Day 1 median | iq-range | Day 2 median | iq-range | Day 3 median | iq-range | *P*-value |
|---|---|---|---|---|---|---|---|
| Echocardiography | | | | | | | |
| LVEDA ($cm^2$) | 12.5 | 9.6–17.6 | 12.6 | 9.2–16.3 | 15 | 11.7–17.6 | 0.066 |
| LVESA ($cm^2$) | 6.1 | 4.8–7.3 | 5.6 | 4.8–6.2 | 6.4 | 5.1–8.7 | NS |
| AFS (%) | 48.5 | 43–51.2 | 48.4 | 38.4–70 | 55.4 | 47.8–59.2 | NS |
| PEm ($cm\,s^{-1}$) | 54 | 37.8–57 | 59.8 | 48–68 | 60.4 | 50.2–69.5 | NS |
| PAm ($cm\,s^{-1}$) | 55 | 48–75.6 | 58.7 | 52.1–82.2 | 58.5 | 56–71.9 | NS |
| PEAm (ratio) | 1 | 0.7–1.3 | 1.1 | 0.6–1.2 | 0.9 | 0.9–1 | NS |
| PSpv ($cm\,s^{-1}$) | 43.9 | 34.6–50 | 55.1 | 38.9–72.3 | 45.8 | 38.8–51.2 | NS |
| PDpv ($cm\,s^{-1}$) | 26 | 25.1–62.1 | 52 | 33.1–59.4 | 43.7 | 33–56 | NS |
| PApv ($cm\,s^{-1}$) | 14.5 | 7.4–30 | 12.6 | 11.1–19.3 | 15.5 | 9.7–21.2 | NS |
| Haemodynamics | | | | | | | |
| CI ($l\,min^{-1}m^{-2}$) | 3.7 | 2.7–4.6 | 4.3 | 3.7–5.8 | 4.3 | 3.7–5.0 | NS |
| SVi ($ml\,m^{-2}$) | 35.4 | 26.8–41.6 | 40.4 | 32.8–55.3 | 40 | 36.6–47.8 | NS |
| HR ($b\,min^{-1}$) | 111 | 83–120 | 112 | 100–123 | 116 | 81–128 | NS |
| PAOP (mmHg) | 3.5 | 2.1–4.8 | 3.8 | 3.5–4.6 | 5 | 3.5–7.4 | NS |
| SAPm (mmHg) | 64 | 60–79 | 69 | 60–77 | 68 | 59–72 | NS |

LVEDA = left ventricle end diastolic area; LVESA = left ventricle end systolic area; AFS = fractional area shortening; PEm = peak early velocity of the mitral flow; PAm = peak atrial velocity of the mitral flow; PEAm = PE/PA ratio; PSpv = peak velocity of forward flow in the pulmonary vein during systole; PDpv = peak velocity of forward flow in the pulmonary vein during diastole; PApv = peak atrial velocity of the pulmonary vein; CI = cardiac index; SVi = stroke volume index; HR = heart rate; PAOP = pulmonary artery occlusion pressure; SAPm = mean arterial pressure.

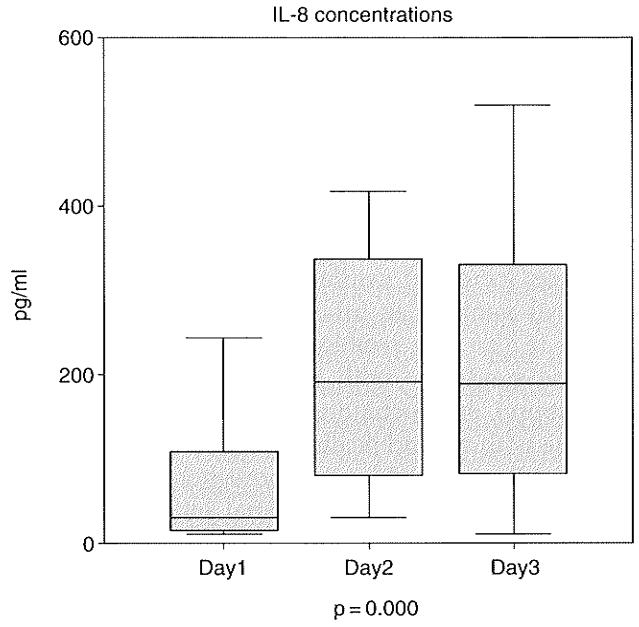


*Fig. 1. Daily plasma IL-8 concentrations presented as median, iq-range and outliers.*

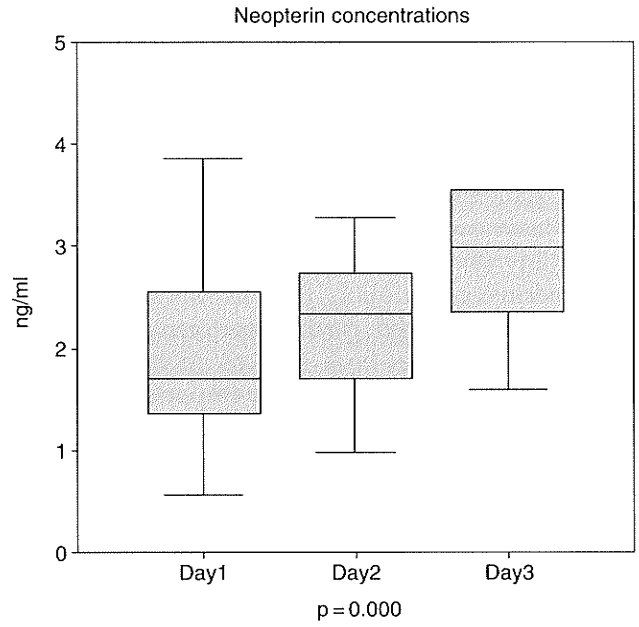


*Fig. 2. Daily plasma neopterin concentrations presented as median, iq-range and outliers.*

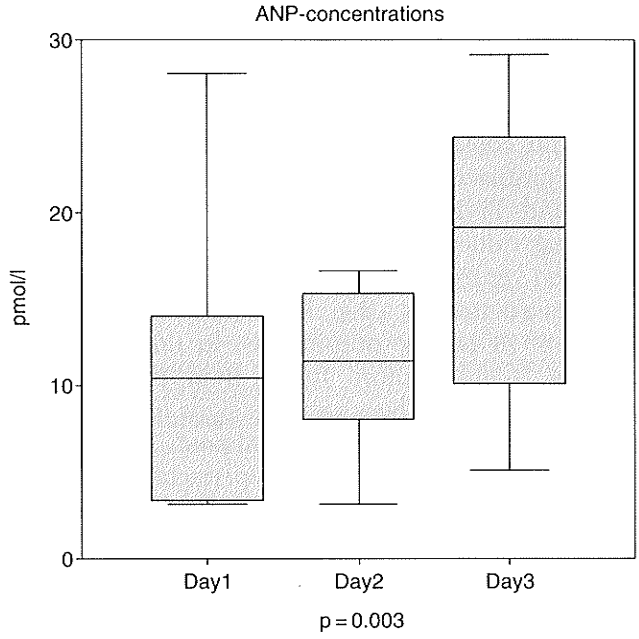


*Fig. 3. Daily plasma atrial natriuretic peptide (ANP) concentrations presented as median, iq-range and outliers.*

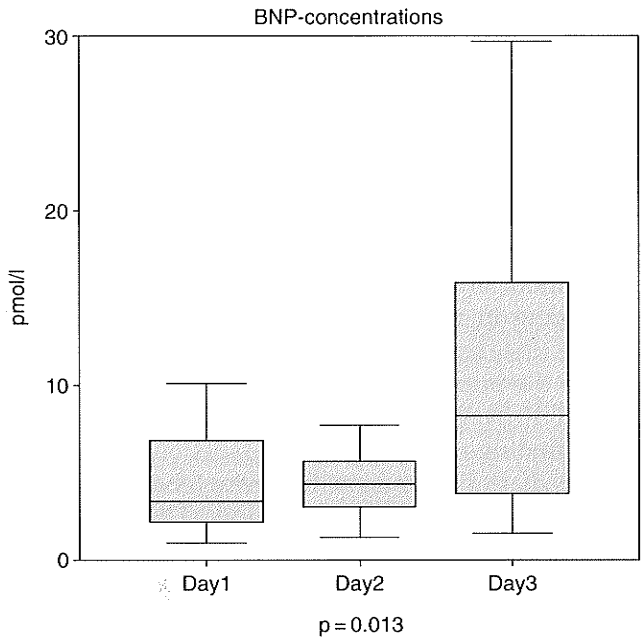


*Fig. 4. Daily plasma B-type natriuretic peptide (BNP) concentrations presented as median, iq-range and outliers.*

and p-BNP concentrations increased during the study period (Figs 3 and 4).

## Discussion

The haemodynamic profile in these burn patients was evaluated by means of clinical signs, haemodynamic parameters and echocardiography. The main finding of the study was that there were signs of hypovolaemia despite aggressive fluid resuscitation and lack of clinical signs of hypoperfusion, e.g. decreased urinary output, lactataemia, metabolic acidosis and low $SvO_2$. Furthermore, our study demonstrated that cardiac function improves during the first 3 days after burn

injury. According to our results, hypovolaemia associated with persisting capillary leakage, rather than myocardial depression, affects myocardial performance during the early postburn period. Finally, we found no consistent association between haemodynamic profile and cytokine concentrations. Plasma ANP and BNP concentrations increased, reaching their peak values on the third postburn day, suggesting atrial and ventricular response to volume expansion.

Hypovolaemia is the key component in the reduction in cardiac output (14). In this study, the patients received more fluids than the Parkland formula suggests. There were no signs of hypoperfusion: mean urine output of almost $1\,ml\,kg^{-1}\,h^{-1}$ together with the absence of hyperlactatemia, metabolic acidosis and low $SvO_2$ speak for sufficient fluid therapy. However, filling pressures (CVP and PAOP) and the findings in the TEE indicate hypovolaemia. Our results are in accordance with the study of Reynolds et al. who suggested that the use of a PA catheter could provide valuable additional information also in the treatment of burn patients (9). Accordingly, the Parkland formula seems to underestimate the need of fluid resuscitation in major burns.

The increases of CI and SV during our study period suggest enhanced cardiac performance. Even though myocardial depression has been found in the acute resuscitation phase in burn patients, there are only a few studies focusing on cardiac problems in burn patients in actual clinical settings (2, 8, 9, 14). Monitoring of cardiac function in patients with burns is likely uncommon, since only 8% of burn units use invasive monitoring in more than half of their patients (15). Despite the term 'myocardial depression' is often used in the burn literature, but it has not been clearly defined. Kuwagata et al. (8) reported an echocardiography finding of a profound depression of left ventricular diastolic function following thermal injury. This was not seen in our study. This might be explained by the fact that in our study, TEE was carried out at 24-h intervals and not due to a specific clinical problem. Reynolds et al. (9) found in 28 paediatric patients with >60% TBSA burns that each patient had depressed left ventricular function persisting throughout the acute resuscitation period, but it could be improved by modifications of fluid resuscitation and initiation of vasopressors. Comparing these two study groups is difficult. Firstly because the study by Reynolds et al. is on paediatric patients, and secondly the patients in their study had more extensive burn injuries. In our study of adults with less extensive burns, no signs of depression of myocardial function were found in echocardiography. Hence, the improvement in cardiac performance might reflect either a subclinical myocardial depression not seen in echocardiography or the fact that the patients were actually hypovolaemic. The role of hypovolaemia is supported by increased filling pressures as well as increased ANP and BNP concentrations.

Burn trauma is comparable to septic shock with hypovolaemia, leakage of plasma into the extravascular space, increased cardiac output, tachycardia and abnormal ventricular function (16). Extensive burn trauma is also comparable to systemic inflammatory response syndrome with a burst of different mediators found in circulating blood. Cytokines may correlate with wound healing, infection, protein metabolism, cell-mediated immunity response and cardiovascular events following thermal injury (17–28). In our study, the concentrations of IL-6 exceeded the normal values in each patient although there were no significant changes during the study period. Increased IL-8 concentrations have been reported in patients with TBSA burns >40% (23). In the present study, all patients had detectable levels of IL-8 and the concentrations increased during the follow-up period. We had no changes in serum TNF-α-concentrations during the study period, although 80% of the values exceeded the normal upper limits. Neopterin is an inflammatory marker of cell-mediated immune response (18) and a potential indicator of infection in burned patients (17). Experimental studies suggest that at least exogenous neopterin may compromise contractility (4). In our study, there was an increase in neopterin concentrations but this was actually associated with enhanced cardiac performance. Hence, neopterin seemed to be a sign of an inflammatory reaction rather than a biologically important mediator of depressed cardiac function.

Atrial natriuretic peptide concentrations were higher in the burn patients (TBSA >20%) compared with the non-burned controls at admission and at 24 h postadmission (29). In the present study, ANP concentrations were normal during the first 2 days and increased on the third day. The increase in both the ANP and BNP concentrations suggest subsiding capillary leakage and increasing filling pressures leading to atrial and ventricular dilatation during the study period. These speak for an improved response to fluid therapy. Plasma concentrations of BNP and NT-proANP are sensitive indicators of left ventricle dysfunction (30). This was not seen in our study since BNP concentrations increased together with enhancing cardiac performance.

There are some limitations in this study. The small number of patients limits the interpretation of the results. The patients were not examined at exactly

the same time-points postinjury due to practical reasons or due to delays in transferring the patients to our unit. In addition, based on clinical judgement, three patients received inotropes, and therefore possible myocardial depression cannot be excluded in these patients. Unfortunately, no documentation of cardiac function by TEE was performed before and after initiation of the vasoactive treatment.

In conclusion, persisting hypovolaemia is evident in the resuscitation phase in patients with extensive burns despite aggressive fluid therapy and the lack of classic signs of hypoperfusion. Clinical indicators of perfusion do not always reveal relative hypovolaemia in major burns. Despite the lack of evidence of actual myocardial depression, cardiac performance enhances during the first days after extensive burn injury. More clinical studies are needed to characterize myocardial depression in critically ill burn patients.

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