Organ dysfunction among patients with major burns

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To all my supporters, friends and colleagues
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Abstract

The number of patients who are admitted for in-hospital care in Sweden because of burns is about 12/100,000, and only a small proportion of these have larger burns. Among them, and particularly among those who die in hospital, a condition referred to as “organ dysfunction” is common and an important factor in morbidity and mortality. The fact that the time of the initial event is known, and the magnitude of the insult is quantifiable, makes the burned patient ideal to be studied. In this doctoral thesis organ dysfunction and mortality were studied in a descriptive, prospective, exploratory study (no interventions or control groups) in patients admitted consecutively to a national burn centre in Sweden.

The respiratory dysfunction that is seen after burns was found to be equally often the result of acute respiratory distress syndrome and inhalation injury. We found little support for the idea that this early dysfunction is caused by pneumonia, ventilator-induced lung injury, or sepsis. Acute kidney injury (AKI) was also common, and mortality was associated with severity. Importantly, renal dysfunction recovered among the patients who survived. Pulmonary dysfunction and systemic inflammatory response syndrome developed before the onset of AKI. Sepsis was a possible aggravating factor for AKI in 48% of 31 patients; but we could find no support for the idea that late AKI was mainly associated with sepsis. We found that older age (over 60 years), greater TBSA%, and respiratory dysfunction were associated with increased mortality, but there was no association between the overall mortality and sex. We also found that early transient liver dysfunction was common, and recorded early hepatic “hyper”-function among many young adults. Persistent low values indicating severe liver dysfunction were found among patients who eventually died.

We conclude from this investigation that overall organ dysfunction is an early and common phenomenon among patients with severe burns. Our data suggest that the prognosis of organ dysfunction among these patients is good, and function recovers among most survivors. Multiple organ failure was, however, the main cause of death. The findings of the early onset in respiratory dysfunction and a delay in signs of sepsis are congruous with the gut-lymphatic hypothesis for the development of organ dysfunction, and the idea of the lung as an inflammatory engine for its progression. We think that the early onset favours a syndrome in which organ dysfunction is induced by an inflammatory process mediated by the effect of the burn rather than being secondary to sepsis.

Our data further suggest that clinical strategies to improve burn care further should be focused on early interventions, interesting examples of which include: selective decontamination of the gastrointestinal tract to prevent translocation of gut-derived toxic and inflammatory factors; optimisation of fluid replacement during the first 8 hours after injury by goal-directed resuscitation; and possible improvement in the fluid treatment given before admission.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AKI</td>
<td>Acute kidney injury</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>ARDS</td>
<td>Acute respiratory distress syndrome</td>
</tr>
<tr>
<td>BW</td>
<td>Body weight</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>EVLW</td>
<td>Extravascular lung water</td>
</tr>
<tr>
<td>FiO₂</td>
<td>Inspiratory fraction of oxygen</td>
</tr>
<tr>
<td>FTB</td>
<td>Full thickness burn</td>
</tr>
<tr>
<td>HSD</td>
<td>Honest Significant Difference test</td>
</tr>
<tr>
<td>ICG</td>
<td>Indocyanine green</td>
</tr>
<tr>
<td>IISS</td>
<td>Inhalation injury scoring scale</td>
</tr>
<tr>
<td>ITBV</td>
<td>Intrathoracic blood volume</td>
</tr>
<tr>
<td>ITBVI</td>
<td>Intrathoracic blood volume index</td>
</tr>
<tr>
<td>LIS</td>
<td>Lung injury score</td>
</tr>
<tr>
<td>PaO₂</td>
<td>Arterial partial pressure of oxygen</td>
</tr>
<tr>
<td>PDR&lt;sub&gt;ICG&lt;/sub&gt;</td>
<td>Plasma disappearance rate of indocyanine green</td>
</tr>
<tr>
<td>PEEP</td>
<td>Positive end expiratory pressure</td>
</tr>
<tr>
<td>RIFLE</td>
<td>Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease</td>
</tr>
<tr>
<td>SIRS</td>
<td>Systemic inflammatory response syndrome</td>
</tr>
<tr>
<td>SOFA</td>
<td>Sequential organ failure assessment score</td>
</tr>
<tr>
<td>SVRI</td>
<td>Systemic vascular resistance index</td>
</tr>
<tr>
<td>TBSA</td>
<td>Total body surface area</td>
</tr>
<tr>
<td>VAP</td>
<td>Ventilator-associated pneumonia</td>
</tr>
<tr>
<td>VILI</td>
<td>Ventilator-induced lung injury</td>
</tr>
<tr>
<td>WCC</td>
<td>White cell count</td>
</tr>
</tbody>
</table>
List of original papers

This thesis is based on the following papers, which will be referred to by their roman numerals.

I  Acute respiratory distress syndrome is as important as inhalation injury for the development of respiratory dysfunction in major burns.
Ingrid Steinvall, Zoltan Bak, and Folke Sjoberg. Burns 2008;34:441-451

II  Acute kidney injury is common, parallels organ dysfunction or failure and carries appreciable mortality in patients with major burns: a prospective, exploratory cohort study.
Ingrid Steinvall, Zoltan Bak, and Folke Sjoberg. Critical Care 2008;12:R124

III  Mortality after thermal injury: no sex-related difference
Ingrid Steinvall, Mats Fredrikson, Zoltan Bak, and Folke Sjoberg.
J Trauma 2010;70:959-964

IV  Incidence of early burn-induced effects on liver function as reflected by the plasma disappearance rate of indocyanine green: a prospective descriptive cohort study
Ingrid Steinvall, Mats Fredrikson, Zoltan Bak, and Folke Sjoberg.
Burns (in press)
Introduction

The number of patients who are admitted for in-hospital care in Sweden because of burns is about 1000/year (mean over 12 years), which corresponds to 12/100,000 residents. This number has been decreasing over the years, among both men and women (Figure 1), but the 2:1 ratio between the sexes has not changed (Figure 2). The total group of burned patients is relatively small, being barely 1% of all patients who are admitted for in-hospital care of injuries as classified by the International Statistical Classification of Diseases and Related Health Problems (ICD) 10: S00-T98. Most of the burned patients who are admitted for in-hospital care do not have severe or life threatening burns.

Figure 1. Number of patients treated for burns (ICD 10: T20-25; T27; and T29-31) admitted for inpatient care/100,000 residents in Sweden during the years 1998 to 2009. Men=solid squares, rho -0.97, p<0.001; women=open squares, rho -0.77, p=0.004; all (not shown in graph) rho -0.94, p<0.001 (Spearman correlation to year). Data are from the open access database of The National Board of Health and Welfare (www.socialstyrelsen.se).
Introduction

Figure 2. The number of patients treated for burns (ICD 10: T20-25; T27; and T29-31) admitted for inpatient care in Sweden has decreased from 1236 patients in 1998 to 962 patients in 2009, but the the distribution of men (67%) and women (33%) has not changed during these years. rho -0.17, p=0.61 (Spearman correlation to year). Data are from the open access database of The National Board of Health and Welfare (www.socialstyrelsen.se).

However, there is considerable morbidity and mortality among those patients who have severe burns. The reported incidence of multiple organ dysfunction among patients with burns of 20% total body surface area (TBSA) or more varies between 16% and 48%\(^1\)-\(^5\) (Table 1), and mortality between 6% and 38% as been reported.\(^1\)-\(^15\) The wide variation in reported mortality is mainly because different inclusion criteria have been used in terms of TBSA%. (Figure 3, Table 2).

Figure 3. Mortality (%) together with mean TBSA%, as reported in 14 papers over 20 years (mortality: blue; TBSA: magenta) (Table 2).
Table 1. Multiple organ failure among patients with major burns.

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Years of study; number of patients.</th>
<th>Multiple organ dysfunction</th>
<th>Mortality</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Majetschak</td>
<td>2008</td>
<td>(Before 2008); 55 patients, mean TBSA 39%.</td>
<td>46% (25)</td>
<td>24% (13)</td>
<td>MOF score</td>
</tr>
<tr>
<td>Fitzwater</td>
<td>2003</td>
<td>1998-2000; 175 patients, 32% TBSA.</td>
<td>27% (47)</td>
<td>22% (39)</td>
<td>MODS</td>
</tr>
<tr>
<td>Cumming</td>
<td>2001</td>
<td>1998-99; 85 patients, median 30% TBSA.</td>
<td>28% (24)</td>
<td>15% (13)</td>
<td>MODS</td>
</tr>
<tr>
<td>Sheridan</td>
<td>1998</td>
<td>1989-94; 71 patients who died.</td>
<td>67% (48)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Aikawa</td>
<td>1987</td>
<td>1979-85; (all) 158 patients, mean TBSA 22%, (subgroup) 54 patients, TBSA&gt;30%.</td>
<td>16% (26)</td>
<td>14% (22)</td>
<td>Study specific</td>
</tr>
<tr>
<td>Marshall</td>
<td>1983</td>
<td>1975-1979; 168 patients, mean TBSA 59%.</td>
<td>48% (81)</td>
<td>58% (97)</td>
<td>Study specific</td>
</tr>
</tbody>
</table>

Percentage of the total number of patients with major burns in each study, number of patients in brackets. TBSA=total body surface area. MODS=multiple organ dysfunction score (Marshall et al. 1995). MOF score=multiple organ failure score (Goris et al. 1985).

According to a report based on the National Burn Repository during the years 1995-2005 (data gathered by the American Burn Association) 27% of those who died did so from multiple organ dysfunction, and an additional 22% of the deaths were the result of pulmonary or cardiovascular failure.17 Organ dysfunction can be found among patients with less severe burns but the incidence has been explored less, as most of the studies have been done among patients with severe burns and patients who died.

The prognosis after multiple organ dysfunction has improved over the last decades among injured patients,18 and particularly in burn intensive care (Table 1), probably because the underlying cause (the burn) can be treated more successfully among these patients today.19,20 Burn injuries provide an interesting model for trauma studies because the time of injury is known as well the extent of injury, which is also highly correlated to outcome. The
TBSA% burned is associated with virtually all variables of physiological morbidity used in different studies.\textsuperscript{6,19,21-23}

Table 2. Mortality among patients with major burns

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Years of study</th>
<th>Patients (number)</th>
<th>Inclusion/ TBSA%</th>
<th>TBSA% (mean)</th>
<th>Mortality (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galeiras\textsuperscript{6}</td>
<td>2009</td>
<td>1992-2005</td>
<td>851</td>
<td>20 %</td>
<td>28%</td>
<td>18% (150)</td>
</tr>
<tr>
<td>McGwin\textsuperscript{7}</td>
<td>2008</td>
<td>Before 2008</td>
<td>68,661</td>
<td>14%</td>
<td>6%</td>
<td>3951 (3951)</td>
</tr>
<tr>
<td>Majetschak\textsuperscript{1}</td>
<td>2008</td>
<td>Before 2008</td>
<td>55</td>
<td>39%</td>
<td>24%</td>
<td>(13)</td>
</tr>
<tr>
<td>Mustonen\textsuperscript{8}</td>
<td>2008</td>
<td>1989-2001</td>
<td>238 Burn ICU</td>
<td>31%</td>
<td></td>
<td>21% (51)</td>
</tr>
<tr>
<td>Bloemsma\textsuperscript{9}</td>
<td>2008</td>
<td>1996-2006</td>
<td>1946</td>
<td>11%</td>
<td>7%</td>
<td>(135)</td>
</tr>
<tr>
<td>Akita\textsuperscript{10}</td>
<td>2006</td>
<td>1996-2004</td>
<td>20</td>
<td>20%</td>
<td>53%</td>
<td>35% (7)</td>
</tr>
<tr>
<td>Cancio\textsuperscript{11}</td>
<td>2006</td>
<td>1995-2002</td>
<td>162 HFPV</td>
<td>38%</td>
<td>34%</td>
<td>(55)</td>
</tr>
<tr>
<td>Holm\textsuperscript{12}</td>
<td>2006</td>
<td>1999-2002</td>
<td>50</td>
<td>25%</td>
<td>41%</td>
<td>36% (18)</td>
</tr>
<tr>
<td>Palmieri\textsuperscript{13}</td>
<td>2006</td>
<td>2002</td>
<td>666</td>
<td>20%</td>
<td></td>
<td>20% (136)</td>
</tr>
<tr>
<td>Holm\textsuperscript{14}</td>
<td>2004</td>
<td>1999-2002</td>
<td>50</td>
<td>20%</td>
<td>42%</td>
<td>36% (18)</td>
</tr>
<tr>
<td>Fitzwater\textsuperscript{2}</td>
<td>2003</td>
<td>1998-2000</td>
<td>175</td>
<td>32%</td>
<td>22%</td>
<td>(39)</td>
</tr>
<tr>
<td>Cumming\textsuperscript{3}</td>
<td>2001</td>
<td>1998-1999</td>
<td>85</td>
<td>30%*</td>
<td></td>
<td>15% (13)</td>
</tr>
<tr>
<td>Holm\textsuperscript{15}</td>
<td>2000</td>
<td>1998-1999</td>
<td>24</td>
<td>45%</td>
<td></td>
<td>38% (9)</td>
</tr>
<tr>
<td>Aikawa\textsuperscript{4}</td>
<td>1987</td>
<td>1979-1985, all:</td>
<td>158</td>
<td>22%</td>
<td></td>
<td>14% (22)</td>
</tr>
<tr>
<td>subgroup:</td>
<td></td>
<td></td>
<td>54</td>
<td>30%</td>
<td>45%**</td>
<td>41% (22)</td>
</tr>
<tr>
<td>Marshall\textsuperscript{5}</td>
<td>1983</td>
<td>1975-1979</td>
<td>168</td>
<td>40%</td>
<td>59%</td>
<td>58% (97)</td>
</tr>
</tbody>
</table>

Percentage of the total number of patients in each study, number of patients who died in brackets. HFPV= High-frequency percussive ventilator. TBSA=total body surface area. ICU=intensive care unit. *Median; **estimated.

**Multiple organ dysfunction or failure**

The syndrome of multiple organ dysfunction was recognised in the fifties and sixties among patients who developed acute renal failure after operation for ruptured abdominal aneurysm.\textsuperscript{24} Later papers referred to this as the study that first established the association between hypovolaemic shock and organ failure.\textsuperscript{25} However, at the time it was the observation that certain combinations of trauma and diseases that were individually treatable seemed together to induce a lethal cycle of progressive, sequential, organ failure. Postoperative acute renal failure
was therefore reported as a disease related to the operation, not as an organ failure in itself. Mechanical and metabolic consequences of the operation, including shock and resuscitation, were outlined as the injurious mechanisms after the trauma. Sepsis was at this time not regarded as an initiating event. The course of the failing organs among the 18 patients who were studied started with: (renal failure), the lungs and pancreas (on postoperative day 2), followed by the liver (day 4), the central nervous system (day 5), lower intestinal tract (day 7), heart (day 9), and upper gastrointestinal tract (day 11).24

The syndrome of acute respiratory distress was recognised during the sixties. The idea of a common mechanism of injury was suggested, because various stimuli seemed to cause similar responses in the lung.26 A few years later came a report of an association of sepsis with pulmonary failure, jaundice, and stress-mucosal haemorrhage.27

The concept of a physiological insult (blood loss, shock, or trauma) that resulted in damage to distant organs was formalised as “multiple, progressive, or sequential system failure” in the early seventies.24,28 The terms “multiple organ failure” and “multiple system organ failure” came a few years later. At that time the initiating event of multiple organ failure after trauma or operation was thought to be uncontrolled or occult infection,25,29,30 and it was reported that refractory organ failure could be treated by evacuating postoperative abscesses.29 This was one of the first times when it was reported that the syndrome was treatable. Other clinical factors were identified among trauma patients, such as haemorrhagic shock, massive fluid or blood transfusion, and chest injury, but these clinical factors were not associated with multiple organ failure in the absence of sepsis. The reported temporal sequence of organ failure was: (sepsis on day 2) the lung (day 2), liver (day 6), gastric mucosa (day 10), and kidney (day 11).25

The relation between invasive infection and organ failure was modified in the eighties when a study showed that two-thirds of the patients who had developed organ failure in more than one organ did not have an invasive infection; the hypothesis of a generalised inflammatory reaction as the underlying mechanism was suggested.31 The concept was further revised as clinical observations gave rise to new hypotheses of the multiple organ failure syndrome, such as the macrophage, the microcirculatory, and the gut hypotheses. In the nineties it was described by Deitch as an uncontrolled or persistent immune-inflammatory response to a combined tissue hypoxia.32 Endotoxaemia as a result of infection, an inflammatory response to injured or necrotic tissue, and hypoxia (shock), were all considered as possible initiating events. Cytokines and other metabolic products produced and released by activated macrophages and neutrophils would cause a cascade effect that involved other effector systems. The
effects on multiple homeostatic systems would be aggravated by subsequent interactions between the systems, modulating or amplifying each other. The syndrome was described as sequential organ failure with a predictable course beginning with the lungs, followed by hepatic, intestinal, and renal failure; myocardial and haematological failure were considered to be later manifestations.32

Studies in burns from the eighties that assessed multiple organ failure found that almost half the patients with severe burns developed multiple organ failure (Table 2). There was a strong relation between the number of organs failing and mortality (failure of more than 2 organ systems at this time was fatal), as well as between the development of organ failure and the extension of injury, shock, inhalation injury, and sepsis.4,5

In the nineties the sequential order of organ failure was described in a study of 71 patients who died after severe burns. Sixty-seven percent of the patients had developed two or more failed organs before death, and the sequence of failing organs started with: the lung and the gut (on day 3 after injury), followed by the central venous and the vasomotor systems (days 5 and 7), the cardiac, haematological, and hepatic (day 9), and ending with renal failure (day 11), which occurred about three days before death. Another finding was that the patients were clinically uninfected at the time of death.16 The idea of non-septic multiple organ failure among burns was a novelty at this time. The idea that organ dysfunction develops late after injury, and is mainly caused by sepsis, has been questioned in the light of the results of more recent studies.33

The gut is susceptible to the initial ischaemia and reperfusion injury that follows the early vasoconstriction and resuscitation after trauma, including thermal injury.34,35 Ischaemic gut and intestinal mucosal injury can lead to loss of barrier function with translocation of bacteria and endotoxins, and these may trigger the gut to produce proinflammatory injurious factors. The host response to the translocation and the release of gut-derived factors may contribute to the development of sepsis and organ failure in burned patients. According to the gut-lymphatic hypothesis (which is a modification of the gut origin hypothesis of the multiple organ dysfunction syndrome), gut-derived toxic and inflammatory factors, including bacteria, leave the intestine through the intestinal lymphatics rather than the portal blood flow. A consequence of this would be that the lung rather than the liver would be the first major vascular bed to be exposed to gut-derived toxic and inflammatory factors.36

In the "two hit" hypothetical model for multiple organ dysfunction, an initial insult primes the host in such a way that the reactivation by subsequent insults causes a greatly amplified host response.32 According to this model the burn would be the priming event that re-
sulted in an initial inflammatory response, and the release of toxic products and bacteria from the ischaemic gut would be an example of the second event.

Another perspective is the imbalance between the proinflammatory and anti-inflammatory responses, as an exaggerated or poorly-timed inflammatory response can lead to organ dysfunction and an increased susceptibility to infections. A severe burn initiates a pronounced systemic inflammatory response syndrome (SIRS), which can be thought of as a pro-inflammatory response to eliminate dead tissue and pathogens. The compensatory anti-inflammatory response syndrome (CARS) can be thought of as an anti-inflammatory response to counterbalance the proinflammatory response.\(^37\)

**Assessing physiological changes after major burns**

Burn injury elicits a comprehensive and characteristic physiological response, including a profound hypermetabolic response, activation of the cascade system, and massive production of acute phase proteins, to mention some important examples.\(^38\) Thermal injury produces a cascade of local and circulating mediators, including histamine and bradykinin (increasing vascular permeability), thromboxane (acting as a vasoconstrictor), cytokines (proinflammatory and anti-inflammatory), and stress hormones (mediating hypermetabolism).\(^39\) Neutrophils are activated and migrate from the intravascular space to organs where they can cause tissue injury by releasing proteases and oxygen intermediaries.\(^40,41\)

One immediate consequence of thermal injury is an acute fluid shift from the intravascular space to the interstitium and simultaneous vasoconstriction. The initial fluid shift is mainly the result of the development of a strong negative interstitial pressure (imbibition pressure) within minutes of the burn.\(^42,43\) The main mechanism has been suggested to be degradation of the collagen matrix in the interstitium.\(^44\) The burn oedema is formed within hours of the burn, and is likely to have been caused by a combination of the release of osmotically active particles, changes in interstitial compliance, and increased capillary permeability.\(^45\) The initial consequences of the acute fluid shift and vasoconstriction are hypoperfusion of vital organs, which leads to general hypoxia and acidosis, followed by the formation of oxygen radicals during resuscitation.\(^32,46\)

Fluid resuscitation is a life-saving treatment after severe burns, and it is important to start soon after injury. Delayed resuscitation has been found to be associated with increased incidences of organ dysfunction, infections, and mortality\(^47\) suggesting that hypoperfusion during the acute phase is also a trigger for later organ dysfunction.
Introduction

There are formulas for calculating volumes of fluid for resuscitation based on TBSA% and body weight, giving an approximate estimation of the volumes needed as a starting point. The clinical response has to be monitored to find out the actual volumes required to maintain sufficient organ perfusion for each patient. There are, however, no universal reference limits or endpoints that ensure sufficient organ perfusion in each case. Hourly urine output has been the traditional marker for the resuscitation effect in the care of burns, together with mean arterial pressure and central venous pressure. The increasing use of invasive haemodynamic monitoring in burn care has noticeably increased the amounts of fluids given for resuscitation, and resuscitation volumes well in excess of those predicted by traditional formulas have been described as over-resuscitation because they can be associated with oedema-related complications.

However, the accuracy of the traditional formulas has also been questioned. There seems to be a fluid deficit (as assessed by central circulatory variables) soon after injury if patients are resuscitated with traditional formulas and using traditional endpoints. It is possible that this transient hypovolaemia can explain the early increases in lactate concentration and base deficit that have been reported among patients with severe burns (mean TBSA 42%), and this early increase was found to be associated with mortality after adjustments for age and TBSA%. Goal-directed resuscitation with invasive markers may enable more accurate fluid replacement during the first 8 hours after injury, and this strategy may have beneficial effects on the oxidative stress and the inflammatory response after burns. Another recent study used intrathoracic blood volume index (ITBVI) (transpulmonary thermodilution) as a goal-directed endpoint for fluid resuscitation, and also suggested that more resuscitation fluids given soon after injury are beneficial, as this strategy seems to reduce the injurious effects of hypoperfusion and resuscitation on organ systems.

The extent of the burn (TBSA%) governs the magnitude of the physiological response. Another important factor for the physiological response and for outcome after a burn is age. Female sex should be expected to be an advantage after burn because of the protective effects of female sex hormones. If there was a difference in the physiological response between men and women it would increase our understanding about the underlying mechanisms of organ dysfunction after burns. There are, for example, studies of burns in animals that have shown that female sex hormones (oestrogen) can have beneficial effects on myocardial function and the myocardial inflammatory responses to injury. Results from studies based on large data-sets that have found a difference in mortality between the sexes have, however, found a male
survival advantage after burns, while other studies have found that sex is not an important predictor of outcome.

The markers used to assess organ dysfunction have varied over the years. The overall trend was that the early studies recorded refractory postoperative or post-traumatic complications that could be fatal. In more recent studies it has been more common to use assessment scales that grade the degree of organ dysfunction (rather than defining organ failure as present or absent). Graded assessment scales have made it possible to identify patients with modest degrees of organ dysfunction, patients with organ dysfunction before organ failure, and to record the course of deterioration and recovery. The concept "organ dysfunction" has been chosen for this thesis to capture a broader perspective than that of organ failure alone.

However, there are a number of unsolved questions about how to achieve a valid assessment of organ dysfunction after burns. One is whether the markers reflect a tissue injury or just the physiological consequence of the injury and its treatment. Definitions that are not clear are a challenge, and there are several questions that complicate the choice of markers and reference ranges, as well as the technique used to analyse the data. In short, at what point does a physiological response become a pathophysiological one? Are modest physiological responses signs of organ dysfunction, or are the physiological responses and the pathophysiological responses two parallel phenomena? These questions make the definitions of concepts such as the host response, dysfunction, and failure, imprecise and unclear. I have chosen also in this thesis to report the typical responses after burns, because it is important to acknowledge the physiological response to be able to study and discuss the pathophysiological responses.

The concept of transient organ stress during resuscitation has led to a recommendation (by the American Burn Association Consensus Conference) that there should be a withdrawal time of three days before the assessment of organ dysfunction is begun. According to this concept the typical changes soon after burn injury are variations in a normal response, and recordings of resuscitation-related reversible degrees of organ dysfunction should be avoided, because, according to this concept, they are not signs of organ dysfunction.

There are a number of studies that support the idea that the responses that occur soon after injury will affect the long-term outcome of severely burned patients, which would classify such early responses as pathophysiological responses, and it also suggests that it is important to assess organ dysfunction during this early period after injury.
Clinical perspective

Our knowledge of multiple organ dysfunction in general, and of the physiological response and organ dysfunction after burns in particular, has expanded considerably during the past 30 years. However, there are still clinical observations that do not fit the models, or findings, or both, of experimental studies. The fact that the time of the initial event is known and the magnitude of the insult is quantifiable makes the burned patient ideal for studying relations to the time of onset of organ dysfunction.

The overall aim of this thesis is to map the interplay between organ dysfunctions out of a clinical perspective to try to gain a better understanding of the mechanisms of organ dysfunction among patients with major burns. Some of the issues we wish to investigate are based on the effect and consequences that are encountered clinically in this group of patients. There are a number of common questions asked in the clinical care of burns and some of the more popular ones are: Is organ dysfunction after burns a predictable complication? To what extent and time? Is it mainly related to the burn, rather than the result of clearly infective complications? Is there a sequential order of organ dysfunction during the time in intensive care, or are there early signs of dysfunction in all organs? Is renal dysfunction a late event preceding death? What is the role of liver dysfunction - is it an early dysfunction with possible consequences for other organ systems? What is the main cause of pulmonary dysfunction after severe burns? Is there a sex-related difference in mortality after thermal burns when adjusted for % TBSA and age?

From questions like this the aims of the present thesis may be summarised as given below.
Aims

The following aims were addressed in the four studies:

Study I
To classify and examine the reasons for respiratory dysfunction after major burns.

Study II
To find out the incidence, time course, and outcome of acute kidney injury after major burns, and to evaluate the impact of possible predisposing factors (age, sex, and depth and extent of injury) and the relation to dysfunction of other organs and sepsis.

Study III
To find out if there is a sex-related difference in mortality after thermal injury, particularly in the age group 16-49 years when hormonal differences would be most influential.

Study IV
To assess the early burn-induced effects on liver function (plasma disappearance rate of indocyanine green) and relate these values to burn indexes, standard liver function tests (static), and the function of other organs.
Methods

Organ dysfunction and mortality were studied in consecutive patients admitted to a national burn centre in Sweden in a descriptive exploratory study (no interventions or control groups). A cohort model was used to select patients: the inclusion criteria in studies I, II, and IV were selected so that the cohort would comprise patients with severe burn injuries who had a high probability of developing organ dysfunction and failure. Details of selection of patients, years of study, and inclusion criteria, are listed in Table 3. There was an overlap of patients between the studies, and the extent of overlap is shown in Table 4.

Burn-related data were recorded in the prospectively maintained local burn registry. In studies I and IV clinical assessments were made prospectively; in study II clinical and laboratory data were collected according to a preset protocol and recorded during the study period; study III analysed the data retrospectively.

Variables

The main variables that were studied and assessments that were done in the different studies were:

Study I: The incidence of acute respiratory distress syndrome (ARDS), inhalation injury, ventilator-associated pneumonia (VAP), ventilator-induced lung injury (VILI), and sepsis were assessed prospectively, together with respiratory viscoelastic properties including extravascular lung water (EVLW), to elucidate the time course, characteristics, and underlying reasons for respiratory dysfunction.

Study II: The incidence, time course, and outcome of acute kidney injury (AKI) were assessed, together with age, sex, and depth and extent of injury, to evaluate the impact of possible predisposing factors. Sepsis and dysfunction in organs other than the kidney were also assessed to evaluate the relation to acute kidney injury after major burns.

Study III: The impact of sex, age, TBSA%, type of burn, and mechanical ventilation on mortality after thermal injury was analysed using a regression model.

Study IV: The incidence of early hepatic dysfunction after severe burns was assessed prospectively. The impact of specific aspects of a burn injury, physiological status after injury, organ dysfunction, and general health on liver function as reflected by the plasma disappearance rate of indocyanine green (PDR$_{ICG}$) were analysed using a regression model.
Table 5 gives an overview of the above.

**Clinical assessments made using well-known techniques**

Viscoelastic properties of the lung (pulmonary airway static compliance and the dynamic characteristic assessment) were assessed by measurements made through the ventilator (Study I, Siemens 300 A, Solna, Sweden), together with recordings of respiratory airway pressures and expiratory volumes.

Transpulmonary thermodilution (PiCCO, Pulsion Medical Systems, Munich, Germany) can provide a number of assessments, such as extra vascular lung water, intrathoracic blood volume, cardiac output, and other variants of the variables. The actual measurements of thermodilution (thermal difference, mean transit time, and down slope time) provide a measure of cardiac output and two thermal volumes, from which other variables can be calculated using the relation between the thermal sub-volumes, the measurements of cardiac output and blood pressures, and the weight and height of the patient for indexed variables. We have used the combination of extra vascular lung water and intrathoracic blood volume in particular, as it gives an assessment of pulmonary vascular permeability controlled for the degree of intravascular filling. We have also used the cardiac index as a marker of circulation and perfusion, and intrathoracic blood volume index as a marker of fluid resuscitation.

The plasma disappearance rate of indocyanine green (PDR\textsubscript{ICG}) is one of the assessments that can be obtained by the liver function monitoring system used (LiMON, Pulsion Medical Systems, Munich, Germany). The others are variants of variables that are also calculated on the down slope measurement of the ICG curve, such as the retention of ICG 15 minutes after injection (R15) (which in a log form correlates (negatively) with the PDR\textsubscript{ICG}), blood volume, and blood clearance. For calculation of the last two variables the system also needs manual entry of cardiac output.

The assessment scales used are listed in Table 6. Standard laboratory tests were analysed by routine methods at the University Hospital laboratory.
Table 3. Patient selection

<table>
<thead>
<tr>
<th>Study</th>
<th>Admissions total</th>
<th>Patients studied</th>
<th>Inclusion</th>
<th>TBSA%</th>
<th>Age</th>
<th>Exclusion</th>
<th>Study duration</th>
<th>Data collection years</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>174</td>
<td>16</td>
<td>Mech. ventilation</td>
<td>≥20%</td>
<td>Adult</td>
<td>Early death</td>
<td>21 days</td>
<td>2002-2005</td>
</tr>
<tr>
<td>II</td>
<td>611</td>
<td>127</td>
<td></td>
<td>≥20%</td>
<td>All</td>
<td>Early death Superficial burn</td>
<td>LOS</td>
<td>1997-2005</td>
</tr>
<tr>
<td>III</td>
<td>1119</td>
<td>1119</td>
<td>Thermal injury</td>
<td>All</td>
<td>All</td>
<td>LOS</td>
<td>1993-2008</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>233</td>
<td>17</td>
<td>Thermal injury</td>
<td>≥20%</td>
<td>Adult</td>
<td>Early death ICG contraindication&lt;br&gt;Superficial burns</td>
<td>14 days</td>
<td>2006-2009</td>
</tr>
</tbody>
</table>
Table 4. Overlap, number of patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>127</td>
<td>117</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>119</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The table is structured as a correlation table: the total number of patients included in each study are shown in the matrix position of one study; the overlap number of patients are shown in the matrix position of two studies.
Table 5. Overview of the main variables and the assessments done in studies I-IV.

<table>
<thead>
<tr>
<th>Study</th>
<th>Organ</th>
<th>Outcome</th>
<th>Assessment</th>
<th>General</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Lung</td>
<td>Oxygenation</td>
<td>ARDS; inhalation injury; sepsis; VAP; VILI; SOFA and inflammation</td>
<td>Age; TBSA%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Viscoelastic properties of the lung</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulmonary vascular permeability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Kidney</td>
<td>Acute kidney injury (RIFLE)</td>
<td>Sepsis; SIRS; SOFA</td>
<td>Age; TBSA%; sex</td>
</tr>
<tr>
<td>III</td>
<td>Sex</td>
<td>Mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Liver</td>
<td>Dynamic liver function (PDR\text{ICG})</td>
<td>ARDS; inhalation injury; septic liver dysfunction (plasma tests)</td>
<td>Age; TBSA%; comorbidity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stat-ARDS; sepsis;SOFA; enteral dysfunction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ARDS: acute respiratory distress syndrome; VAP: ventilator-associated pneumonia; VILI: ventilator-induced lung injury; RIFLE: Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; SIRS: systemic inflammatory response syndrome; SOFA: sequential organ failure assessment score; TBSA%: total body surface area burned.
Table 6. Assessment scales used

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>I, IV</th>
<th>I</th>
<th>I, II, IV</th>
<th>I</th>
<th>I, II, IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIS</td>
<td>the Lung Injury Score (ARDS)\textsuperscript{55}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IISS</td>
<td>the Inhalation Injury Scoring Scale\textsuperscript{56}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>the international sepsis conferences (I-II\textsuperscript{57} IV\textsuperscript{58})</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPIS</td>
<td>the Clinical Pulmonary Infection Score (VAP)\textsuperscript{59}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOFA</td>
<td>the Sequential Organ Failure Assessment score\textsuperscript{60}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RIFLE</td>
<td>Risk, Injury, Failure, Loss, and End-stage kidney disease\textsuperscript{61}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Statistics

Different statistical tests have been used for different parts of the data, as appropriate. Details of all the study specific tests are listed in Table 7.

Statistical software

Study I and II: Data were analysed with STATISTICA 7 (StatSoft. inc., Tulsa, OK, USA)
Study III and IV: Multiple regression was done with the help of STATA (STATA v10.1, Stata Corp. LP, TX, USA) while the remaining analyses were done with STATISTICA. Probabilities of less than 0.05 were accepted as significant.
Table 7. Study-specific statistical tests

<table>
<thead>
<tr>
<th>Method</th>
<th>Data</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Study I</td>
</tr>
<tr>
<td>Student’s t-test, independent samples</td>
<td>Continuous, two groups</td>
<td>Characteristics (demographic)</td>
</tr>
<tr>
<td>One way ANOVA</td>
<td>Continuous, more than two groups</td>
<td>Characteristics and outcome</td>
</tr>
<tr>
<td>Mann-Whitney U, independent samples</td>
<td>Ordinal or skewed, two groups</td>
<td>Data from day 1; maximum SOFA</td>
</tr>
<tr>
<td>Contingency tables: Pearson’s chi-square/ Fischer exact test</td>
<td>Categorical, two groups or more</td>
<td>Characteristics and outcome</td>
</tr>
<tr>
<td>Student’s t-test, dependent samples</td>
<td>Continuous, two variables</td>
<td>Progress time</td>
</tr>
<tr>
<td>Wilcoxon matched pairs test</td>
<td>Ordinal or skewed, two variables</td>
<td></td>
</tr>
<tr>
<td>Analysis of covariance: Tukey Unequal N HSD post-hoc test</td>
<td>Continuous, two groups or more, multiple variables</td>
<td>Differences between groups, data over the study period</td>
</tr>
<tr>
<td>Main effects ANOVA: Tukey Unequal N HSD post-hoc test</td>
<td>Continuous, multiple categorical predictors</td>
<td></td>
</tr>
</tbody>
</table>
### Cont. Table 7. Study-specific statistical tests

<table>
<thead>
<tr>
<th>Method</th>
<th>Data</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spearman rank correlation</td>
<td>Ordinal or skewed, two variables</td>
<td>Permeability, two methods</td>
</tr>
<tr>
<td>Multiple regression, best subset</td>
<td>Continuous outcome, multiple variables</td>
<td>WCC and development of ARDS over the study period</td>
</tr>
<tr>
<td>Multiple regression: Poisson log model</td>
<td>Dichotomous outcome, rare in large sample</td>
<td>Sex survival advantage, adjusted.</td>
</tr>
<tr>
<td>Multiple regression for longitudinal data</td>
<td>Continuous outcome, individuals, over time</td>
<td>Model: exploring burn induced effects on dynamic liver function</td>
</tr>
</tbody>
</table>
Results

Respiratory dysfunction (paper I)

The total group (n = 16) was assessed for five diagnoses: ARDS, inhalation injury, ventilator-associated pneumonia, sepsis, and ventilator-induced lung injury. Table 8 shows how many patients were classified as having each diagnosis, and the overlap of diagnoses among the patients.

Table 8. Delineation of the overlap of diagnoses, each row representing one patient.

<table>
<thead>
<tr>
<th>ARDS</th>
<th>INHAL</th>
<th>VAP</th>
<th>Sepsis</th>
<th>VILI</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=9)</td>
<td>(n=7)</td>
<td>(n=1)</td>
<td>(n=11)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

The patients who developed burn-induced ARDS had lower oxygenation, lower pulmonary compliance, increased pulmonary capillary permeability, worse renal function, and were older than the remaining patients. White blood cell counts were increased on admission, but decreased considerably during the following days, and lower values tended to be associated with the development of ARDS during the study period.

The patients who were classified as having inhalation injury had lower oxygenation than the remaining patients (no inhalation injury), but the remaining group had lower pulmonary compliance, and more increased pulmonary capillary permeability than the group with inhalation injury.

Sepsis was common, but we found no obvious association between sepsis and ARDS. The tendency was that burn-induced ARDS (ARDS but no inhalation injury, in combination with VAP or sepsis) seemed to be associated with the worst result. The second worst was the
Results

combination of ARDS and inhalation injury plus sepsis, followed by inhalation injury plus sepsis. The remaining group (sepsis but no ARDS or inhalation injury) did better in the variables assessed, except for in increased pulmonary capillary permeability. The time course (onset) of ARDS and sepsis did not suggest any causal relation between the two (Table 9).

Table 9. Onset of ARDS and sepsis. Data are number of patients.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARDS Before sepsis</td>
<td>3</td>
</tr>
<tr>
<td>ARDS After sepsis</td>
<td>3</td>
</tr>
<tr>
<td>ARDS Without sepsis</td>
<td>3</td>
</tr>
<tr>
<td>Sepsis Without ARDS</td>
<td>5</td>
</tr>
<tr>
<td>No sepsis or ARDS</td>
<td>2</td>
</tr>
</tbody>
</table>

Acute kidney injury (paper II)

One quarter of 127 patients with severe burns developed (AKI) (Figure 4). The incidence was 0.11 per 100,000 people per year during the study period. Mortality increased with increasing RIFLE class (Figure 4). Age, TBSA%, and the extent of full thickness burns (FTB) was higher among the patients who developed AKI.

The renal dysfunction occurred within 7 days in half the patients who developed AKI and it recovered among all survivors. Pulmonary dysfunction and SIRS developed before the onset of AKI was recorded. Sepsis was a possible aggravating factor in AKI in 48% (15 of 31). We could not find support for the idea that AKI of late onset would be associated mainly with sepsis.

We found that the patients with the most severe burns (FTB ≥ 25%, TBSA ≥ 50%) were at greater risk of developing AKI within the first week after injury. However, early AKI was not associated with a higher risk of death. The indication of a possible association between early AKI and the need for renal replacement treatment (see Table 5 in paper II) could not be fully tested because so few patients required dialysis. When we built a binomial multiple regression model for the analysis of risk factors (see Table 5 in paper II for risk factors) for the development of early AKI, none of the variables remained significant in the analysis (data not shown).
Results

AKI, % of total n

No AKI; 76%
Risk; 12%
Injury; 8%
Failure; 5%

Mortality, % of each AKI class

No AKI; 7%
Risk; 13%
Injury; 13%
Failure; 83%

Figure 4. The left handed figure shows the distribution of AKI over the three RIFLE categories (total n=127) and the right handed shows the percentage of patients who died in each RIFLE category (No AKI n=96, Risk n=15, Injury n=10, Failure n=6).

Sex-related difference in mortality (paper III)

Crude mortality was higher among women, but after analysing mortality in a model adjusted for age, TBSA%, mechanical ventilation, year, and type of burn we found no association between mortality and sex.

The factors that we found to be associated with mortality were older age (60 years and older), TBSA%, and respiratory dysfunction (that required mechanical ventilation). When we analysed subgroups we found that TBSA > 60% was the only factor significantly associated with mortality among younger adults (16-49 years old), while the risk of mortality was associated with all categories for TBSA% and age among older adults, and the risk of mortality was increased with increasing TBSA% and age.

Flame burns (including flames as the result of an accident with an explosion or involving contact with electricity) were the most common type of burn, and were more common among men than women (risk ratio 1.34, 95% CI 1.18 to 1.51). Figures 5 and 6 show the distribution of type of burn among men and women, and among adults (>15 years old) and children.
Results

Figure 5. The distribution (%) of type of burn among all patients with thermal injury, and the distribution among women and men separately (Chi square p<0.001). The flame burn category (yellow) includes flames that resulted from an accident with an explosion or involving contact with electricity; black=contact with a hot object; and blue=scalding.

Figure 6. The distribution (%) of type of burn among all children and all adults on the left, and the distribution among girls and boys (Chi square p=0.005), and women and men (Chi square p=0.005) separately on the two right-hand diagrams. The flame burn category (yellow) includes flames that resulted from an accident with an explosion or involving contact with electricity; black=contact with a hot object; and blue=scalding.
Liver function (paper IV)

Early transient liver dysfunction was common (Table 10), but the results from dynamic and different static liver dysfunction tests were not mutually exclusive. The regression model (Table 11) showed that changes in liver function, measured as PDR\textsubscript{ICG}, after major burns are associated with age, TBSA\%, plasma bilirubin concentration, plasma C-reactive protein (CRP), and cardiac index (Figure 7).

PDR\textsubscript{ICG} values above the reference interval were measured often. Forty-two (38%) of the total 111 PDR\textsubscript{ICG} measurements were high (>25.0 %/minute). Twenty-three of these high PDR\textsubscript{ICG} values were measured when the patients’ cardiac index was in the normal and subnormal range of (1.5-5.0 L/minute/m\textsuperscript{2}). Plasma C-reactive protein concentrations were increased during the study period (Figure 8).

The patients who developed liver dysfunction (as assessed by PDR\textsubscript{ICG}) were older than those who did not, otherwise there were no significant differences between the groups in basic characteristics, static liver function tests, resuscitation variables, and central circulatory variables on day one.

Persistent and advanced liver dysfunction was associated with mortality. Three of the patients showed low and decreasing PDR\textsubscript{ICG} values during the study-period, ending with death from multiple organ failure in two. The third patient, who survived, showed signs of partial recovery on day 28 (after the study period). All the patients had dysfunction of more than two organs, and 12 of the 17 patients developed multiple organ failure during the first week (Table 12). The SOFA score was increased from day one after injury (Figure 9). The different organs showed different patterns of severity of dysfunction and time course during the study period.

There were no significant correlations between resuscitation indicators on day one and the lowest PDR\textsubscript{ICG} measurement during the study period (data not shown). Significant correlations between indicators of resuscitation on day one, worst static liver function results, and SOFA organ dimension scores during day 5-18 are shown in Table 13.

Sepsis was common (Table 12), but its onset was not reflected in variations in liver function in all patients. We found both decreasing (n=5) and increasing (n=5) PDR\textsubscript{ICG} values after the onset of sepsis. All six patients who had plasma alanine aminotransferase activity increased above the reference range had sepsis before or on the same day, but another eight
patients also had sepsis, without increases in plasma alanine aminotransferase activity above the reference range.

Table 10. Occurrence of liver dysfunction measured with dynamic and static tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference limit</th>
<th>Patients</th>
<th>Onset day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma disappearance rate of indocyanine green</td>
<td>≤18 %/minute</td>
<td>7 (41)</td>
<td>1.0 (1.0-3.8)</td>
</tr>
<tr>
<td>Plasma bilirubin concentration</td>
<td>≥20 µmol/L</td>
<td>8 (47)</td>
<td>1.0 (1.0-3.4)</td>
</tr>
<tr>
<td>Plasma prothrombin complex</td>
<td>&gt;1.2 INR</td>
<td>17 (100)</td>
<td>2.0 (1.0-2.0)</td>
</tr>
<tr>
<td>Plasma alanine aminotransferase</td>
<td>≥1.20 µkat/L</td>
<td>6 (35)</td>
<td>6.0 (3.5-8.0)</td>
</tr>
<tr>
<td>Plasma alkaline phosphatase</td>
<td>&gt;1.80 µkat/L</td>
<td>11 (65)</td>
<td>7.0 (5.0-14.0)</td>
</tr>
</tbody>
</table>

Data are presented as number (%) of n=17, and median (10-90 centiles), INR= the international normalized ratio.
Table 11. Multiple regression model for longitudinal data

<table>
<thead>
<tr>
<th>Model</th>
<th>Variables before analysis</th>
<th>Variables significant after analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dependent variable</td>
<td>$\text{PDR}_{\text{ICG}}$</td>
<td></td>
</tr>
<tr>
<td>Panel (group) variable</td>
<td>Patient identity</td>
<td></td>
</tr>
<tr>
<td>Time variable</td>
<td>Day after injury</td>
<td></td>
</tr>
<tr>
<td>General health</td>
<td>Age</td>
<td>Age</td>
</tr>
<tr>
<td></td>
<td>Pre-existing medical condition</td>
<td></td>
</tr>
<tr>
<td>Burn injury</td>
<td>$\text{TBSA}%$</td>
<td>$\text{TBSA}%$</td>
</tr>
<tr>
<td></td>
<td>Inhalation injury</td>
<td></td>
</tr>
<tr>
<td>Static liver function tests</td>
<td>Plasma bilirubin concentration</td>
<td>Plasma bilirubin concentration</td>
</tr>
<tr>
<td></td>
<td>Plasma prothrombin complex</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plasma alanine aminotransferase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plasma alkaline phosphatase</td>
<td></td>
</tr>
<tr>
<td>Physiological status</td>
<td>Cardiac index</td>
<td>Cardiac index</td>
</tr>
<tr>
<td></td>
<td>Plasma C-reactive protein</td>
<td>Plasma C-reactive protein</td>
</tr>
<tr>
<td></td>
<td>Arterial blood partial pressure of oxygen</td>
<td></td>
</tr>
<tr>
<td>Organ dysfunction</td>
<td>SOFA respiratory</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SOFA cardiovascular</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SOFA coagulation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SOFA renal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SOFA hepatic</td>
<td></td>
</tr>
</tbody>
</table>
Table 12. Occurrence of organ dysfunction and sepsis

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Onset day</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOFA respiratory</td>
<td>17 (100)</td>
<td>1.0 (1.0-2.0)</td>
</tr>
<tr>
<td>SOFA cardiovascular</td>
<td>17 (100)</td>
<td>1.0 (1.0-2.4)</td>
</tr>
<tr>
<td>SOFA coagulation</td>
<td>17 (100)</td>
<td>2.0 (1.6-3.0)</td>
</tr>
<tr>
<td>SOFA renal</td>
<td>13 (76)</td>
<td>3.0 (1.0-7.0)</td>
</tr>
<tr>
<td>SOFA hepatic</td>
<td>8 (47)</td>
<td>1.0 (1.0-3.4)</td>
</tr>
<tr>
<td>SOFA MOF</td>
<td>12 (71)</td>
<td>2.0 (1.5-2.5)</td>
</tr>
<tr>
<td>ARDS</td>
<td>13 (76)</td>
<td>3.0 (1.2-7.6)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>15 (88)</td>
<td>4.0 (3.4-8.6)</td>
</tr>
<tr>
<td>Enteral dysfunction</td>
<td>5 (29)</td>
<td>10 (8.4-11.6)</td>
</tr>
</tbody>
</table>

Data are presented as number (%) of n=17, and median (10-90 centiles)

Table 13. Associations between resuscitation and liver- and other organ dysfunction

<table>
<thead>
<tr>
<th>Highest value day 5-18</th>
<th>ITBVI</th>
<th>IV</th>
<th>Urine</th>
<th>pH</th>
<th>BD</th>
<th>Age</th>
<th>TBSA%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Day 1</td>
<td>Day 1</td>
<td>Day 1</td>
<td>Day 1</td>
<td>Day 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma alanine aminotransferase</td>
<td>-0.58</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.50</td>
</tr>
<tr>
<td>SOFA cardiovascular</td>
<td>0.51</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOFA respiratory</td>
<td>-0.52</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOFA renal</td>
<td>-0.61</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOFA hepatic</td>
<td>0.63</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.64</td>
<td>0.54</td>
<td></td>
<td>-0.61</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBSA%</td>
<td>-0.50</td>
<td>-0.76</td>
<td></td>
<td>-0.61</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Resuscitation variable day 1: ITBVI, intrathoracic blood volume index; IV, total intravenous fluids given; urine, output ml/kg/hour; pH, arterial blood pH; BD, arterial base deficit. Spearman rho., correlations significant at p <0.05 are shown.
Results

Figure 7. Associations between $\text{PDR}_{\text{ICG}}$ (%/minute) measurements 1-14 days after injury and physiological markers. Multiple regression model for longitudinal data. Variables that contributed significantly to the final result were retained in the model. Model-overall $R^2$ 0.54; between subjects $R^2$ 0.77; within subjects $R^2$ 0.19. Probabilities are from the regression model for longitudinal data. *The relative percentage of the contribution from the included variables to a hypothetical $R^2$ 1.00 was calculated ($(1$-overall $R^2) + \text{overall } R^2$) using the standardised coefficients (beta) from linear regression. TBSA, total body surface area; CRP, plasma C-reactive protein.
Results

Figure 8. Plasma C-reactive protein day 1-14 after injury (n=17). Reference value <10mg/L. Squares indicate the median, boxes extend from 25th to 75th percentile, error bars show the 10th and 90th percentiles.

Figure 9. Sequential organ failure assessment score (SOFA) day 1-14 after injury (n=17). Squares indicate the median, boxes extend from 25th to 75th percentile, error bars show the 10th and 90th percentiles.
Discussion

Respiratory dysfunction (paper I)

The respiratory dysfunction that is seen after burns appears early, and the two main causes are ARDS and inhalation injury. We found little support for the idea that this early dysfunction is caused by VAP, VILI, or sepsis, but the conclusions of this study should be adopted with caution as the study group was small and the diagnoses overlapped.

The results indicated that ARDS seems to affect the lung more than inhalation injury, as the decrease in oxygenation (PaO₂/FiO₂), the increase in pulmonary capillary permeability (EVLW/ITBV), and the effects on pulmonary compliance, tended to be more obvious among the patients in the ARDS group. It is possible that we could have found more pronounced changes in respiratory function among the patients who were classified as having inhalation injury if the smoke inhalation had been more severe. However, the inhalation injury scores were between 2.2 and 2.75 among this group of patients, indicating bronchoscopic findings of mucosal injury.

Animal studies have shown that the pathophysiological changes after inhalation of smoke (such as severe tracheobronchial injuries, pulmonary oedema, decreased oxygenation and pulmonary compliance, increased lung lymphatic flow, and infiltration by neutrophils) are comprehensive and lethal. It has also been suggested that the changes in pulmonary compliance after inhalation may be the result of depletion of functional surfactant; animal studies have shown that it leads to impairment of the viscoelastic properties of the lung and that the smoke-induced alveolar instability is dependent on the duration of exposure. The type of smoke can also be important as wood smoke, but not cotton smoke, inhibits surfactant function in vitro.

The clinical signs of inhalation among patients with thermal injury are not always as severe as among animals in experimental settings in which a large number of breaths are taken to create a substantial injury with effects that can be studied. Results from a recent study, which was based on a large dataset, showed that early mechanical ventilation, and not inhalation injury, was associated with mortality.

One explanation of why there may be a difference in the severity of respiratory dysfunction is that the pattern of cytokine response in the lung seems to differ after inhalation of smoke, compared with thermal injury without inhalation. Another explanation is that the site
and progress of the infiltrates in the lung seem to be different. When inhalation injury was assessed using computed tomography it was reported that pulmonary infiltrates developed adjacent to the larger airways soon after injury, and that extensive atelectasis was treatable with alveolar recruitment manoeuvres and PEEP titration soon after injury. The pulmonary changes of ARDS are more homogeneously distributed over the whole parenchyma, which can explain why pulmonary compliance is more decreased in ARDS.

We have found that the development of ARDS is associated with changes in the white cell count (WCC), which suggests that the white cells are involved in the pathophysiological process of ARDS in burns. Animal studies have shown that the migration of neutrophils into tissue, including the lung, is increased after burns. The capillary bed of the lung is the first to receive blood from burned tissue and from post-ischaemic tissue in other organs. Increased pulmonary vascular permeability and neutrophil tissue sequestration in the lung happens early after the burn (within the 4 first hours). Pulmonary dysfunction after trauma has been suggested to promote pathogenic inflammation and the development of multiple organ failure.

The lung injury score (LIS) was used in Study I for the classification of ARDS. About half the burned patients (45% of 126) who require mechanical ventilation have been found to develop ARDS as classified using the LIS. Age but not TBSA% has been reported to be higher among the group of patients who develop ARDS during mechanical ventilation after burns, compared to those who not develop ARDS, which is in line with our findings.

The LIS was originally designed to capture three functional features of this acute diffuse parenchymal lung injury (hypoxaemia, diffuse pulmonary infiltrations, and decreased pulmonary compliance). The graded scale makes it possible to identify patients with mild to moderate degrees of acute lung injury, and to monitor the course of deterioration and recovery. It has been questioned for its complexity and for its inability to predict mortality. A shortcoming of the score is that radiographs are not available every day, and that there are variations in their interpretation.

It is difficult to diagnose inhalation injury objectively, and bronchoscopy is commonly used. There are, however, studies that have suggested that histological are more reliable than the opinion of the bronchoscopist, particularly when the bronchoscopic signs are discrete. We used a classification score (by which the bronchoscopic findings give considerably more points than the clinical signs) to diagnose inhalation injury, and we cannot rule out the possibility that patients who were classified as not having an inhalation injury had some degree of smoke inhalation and that it was symptoms of a moderate inhalation injury that were appearing as ARDS.
Exposure to smoke is common and inhalation injury is usually seen among patients with indoor flame burns and extensive TBSA%. Its reported incidence is between 22% and 47%, but the incidence can be as high as 90% among patients with 80% TBSA or more. This inevitable relation makes it difficult to know to what degree the clinical signs of respiratory dysfunction are caused by the burned skin, or by the inhalation of smoke among patients with severe burns. An alternative definition would be to call it "burn-induced respiratory dysfunction" regardless of suspicions of injury caused by smoke inhalation injury, and to record different aspects of respiratory function that are important for treatment and outcome, such as viscoelastic properties of the lung (ventilatory static compliance), required readings of PEEP and PaO2/FiO2, and measurements of pulmonary capillary permeability.

The aggressive open lung approach during the study, combined with ventilator settings to protect the lungs, makes the condition of the lungs less likely to be induced by the ventilator. We did not have a specific marker for assessing VILI but the airway plateau pressures and tidal volumes were kept as low as possible. It is still possible, however, that some of the findings of moderately-increased extravascular lung water, decreased oxygenation, and static pulmonary compliance were signs of VILI. The need for larger ventilatory volumes that are required by the increased metabolic rate increases the risk of VILI among patients with severe burns, as high tidal volumes and high airway pressures are sometimes inevitable. There were days in Study I when peak airway pressures were higher than 32 cm H2O among four patients who required high PEEP. There were also single days when tidal volumes were higher than 12 ml/kg BW among six patients, but the highest peak airway pressures were found on other days than when the tidal volumes were at their highest.

We used a score with a combination of clinical criteria to assess VAP, and only one of the 16 patients was diagnosed using the cut off of 6 and 8 score points as described by A’Court et al. It was difficult to reach this threshold for a diagnosis of VAP, particularly because, according to the scoring scale, the criteria of decreased PaO2/FiO2 should not be attributed to pneumonia in the presence of ARDS. In a recent study the score was compared with the results of quantitative cultures when trying to diagnose VAP among patients with burns. The sensitivity of the score was 0.3, and specificity 0.8, and the mean scores were almost on the same level (5.5 and 5.7) among the patients who had pathological quantitative cultures and those who had not, but bacteriological data do not increase the accuracy of a clinical diagnosis.

Sepsis, as classified in the study, was not considered to be a major factor in the development of ARDS, as there was no obvious sequential relation between sepsis and ARDS.
Acute kidney injury (paper II)

Incidence

We found that AKI, as assessed using the RIFLE classification, is common among patients with severe burns. We found AKI of 24% (31 of 127), which is similar to the 27% (81 of 304) reported in the first burn study that used the RIFLE classification and slightly lower than the 36% (45 of 126) reported in a letter at about the same time. This can at least partly be explained by the difference in age between the patients studied (mean 41 (SD 22.1) years in Study II compared with 49 (SD 19.2) years in the report by Lopes et al., but it cannot be explained by differences in TBSA%, as our study group had the largest extent of injury of the three studies (Study II 39% (SD 17.4) TBSA%, Lopes et al. 24% (SD 19.0), and Coca et al. 27% (SD 18.2)).

We based the RIFLE classification mainly on increases in plasma creatinine concentrations and we used the first recorded creatinine value as baseline. We also had the measurements of 24-hour urine output, but as oliguria paralleled the increased plasma creatinine concentrations this added little to the study. It is possible that a few more patients could have been classified as RIFLE-risk on transient reductions in urine output during resuscitation if we had recorded urine output 6-hourly instead of 24-hourly.

In a recent study AKI was reported among 109 of 221 (49%) in a group with similar age and TBSA% (mean age 42 years (SD 15.3) and 42% TBSA % (SD 18.9)), with 20% (44 of 221) overall mortality, which is not significantly higher than the 14% (18 of 127) overall mortality in our study (OR 1.51, 95% CI 0.83 to 2.74), or with an AKI mortality of 35.5% (38 of 62), which was the same as in our study (11 of 31). Even though the two study groups seem to be fairly similar (age, TBSA%, and mortality) the 49% incidence of AKI was twice as high as the 24% AKI found in our study (OR 3.01, 95% CI 1.86 to 4.89) The reported onset was early (compared with the median onset on day 7 in our study) as AKI was recorded during resuscitation among 28% of the patients. The patients who developed AKI during resuscitation had smaller urine outputs than those who did not, suggesting that there was a group of patients whose AKI were classified on the criterion of urinary output alone. A smaller fluid ratio (observed:expected) before admission was associated with early AKI. Fluid ratio before admission seems to be a promising variable for assessing AKI, and it has the potential to improve the acute phase of fluid treatment.
The potential selection bias from excluding the patients who died within 2 days (n=17), and those whose duration of stay was short (n=8) may have influenced the incidence of AKI in Study II. The finding that youth is a risk factor for early AKI can also be partly explained by this selection bias, as older patients with extensive burns are more likely to die.

**Outcome**

All the surviving patients in Study II recovered their renal function, defined according to RIFLE, which is consistent with findings reported from other studies in burned patients.\(^85,86\) The requirement for renal replacement in our Study II (3.1%) is in the range of the 2.5%-4.3% that has been reported in patients in ICU.\(^87-89\) The prognosis after burn-associated AKI seems to be better than that of patients in general intensive care. According to a multicentre long-term follow-up study, 3.4% (34 of 998) of the patients in ICU who required renal replacement while they were in hospital developed late endstage kidney disease.\(^90\)

Mortality increased with increasing RIFLE class. In Study II it was 5 of 6 (83%) among the patients classified as failures by RIFLE, similar to the results of other burn studies.\(^82,83\) Renal failure (requirement for renal replacement) has long been considered to be associated with poor prognosis and mortality in burns.\(^16\) Mortality in the ICU among patients classified as failures by RIFLE seems to be somewhat lower. Hoste et al. reported 26% mortality (397 of 1511) in the failure class among critically ill patients,\(^88\) and Lopes et al. found 55% mortality (20 of 36) in the failure class among patients with sepsis.\(^91\)

We do not know whether renal failure alone among patients with severe burns is more likely to be fatal than that among other patients in ICU, or if it is a more or less inevitable phase in the syndrome of multiple organ failure after severe burns when the syndrome ends in death. Another unanswered question is whether under-treatment and death would be a self-fulfilling prophesy resulting from the attitude that renal failure is such a poor prognostic sign that further treatment would be futile; this would further support the idea of a poor prognosis for renal failure in burns.

**Predisposing factors**

We found age, TBSA%, and FTB% to be predisposing factors for AKI. Coca et al. also found that age was associated with AKI,\(^82\) whereas others have found that TBSA% is associated with AKI, but not age.\(^21,92\)

We were unable to show that the severity of AKI was associated with age, TBSA%, and FTB%, most probably because of a lack of power as we studied too few patients.
We did not record and analyse the effects of pre-existing medical conditions in Study II. A recent study reported 26 of 62 (50%) comorbidity in the AKI group, compared with 33 of 159 (21%) among those without AKI (p<0.01) (comorbidity was defined by Charlson index >0).  

**Dysfunction of other organs and sepsis**

AKI after burns is closely paralleled by dysfunction of other organs. We found that it was preceded by lung dysfunction in almost all cases; 30 of the 31 patients with AKI required mechanical ventilation whereas only half of those without AKI required it. Cardiovascular dysfunction (SOFA) together with AKI were the ones that were associated with higher mortality.

AKI is associated with high mortality, and in many studies of burns it is thought to be caused by sepsis.  

Mosier et al. recently reported that the incidence of sepsis was higher in higher RIFLE classes. Chrysopoulo et al. have, however, reported that AKI among survivors was not the result of sepsis, as it preceded sepsis in their study.

In Study II we found sepsis among 27 of the 31 patients (87%) who developed AKI, which is similar to the results of some studies, and larger than those in other studies in burns.  

Severe sepsis was associated with AKI, but not all episodes of severe sepsis led to renal dysfunction, as we recorded episodes of sepsis even during the renal recovery period, which has not to our knowledge been reported previously. This indicates that at least some of the time-associated episodes of sepsis and AKI may be just time-related, rather than the result of cause and effect, which is not usually discussed in studies of burned patients.

**Scoring scales, SOFA, and RIFLE**

We have used SOFA and RIFLE for the assessment of renal function, two classifications with similar grounding that use the same markers to assess renal function (plasma creatinine concentration and urine output), but the difference is that SOFA is a static scale while RIFLE is dynamic, and this leads to differences between the two scales. The likely consequences of the choice between a static and a dynamic classification is shown in Table 21.
Table 21. The effect of some burn-related issues on classification of renal dysfunction using a static or a dynamic scale.

<table>
<thead>
<tr>
<th></th>
<th>SOFA</th>
<th>RIFLE</th>
<th>RIFLE burn adjusted for burns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma dilution</td>
<td>False negative</td>
<td>False positive</td>
<td>More sensitive</td>
</tr>
<tr>
<td>Fluid mobilisation</td>
<td>False positive</td>
<td>False positive</td>
<td>More sensitive</td>
</tr>
<tr>
<td>Increased total creatinine</td>
<td>False positive? (^a)</td>
<td>False positive? (^b)</td>
<td>(High demands are met) (^c)</td>
</tr>
<tr>
<td>Increased plasma creatinine concentration before the burn</td>
<td>False positive (^d)</td>
<td>False negative (^e)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\): False positive assuming that an adequate renal response to a burn is the ability to eliminate increased amounts of creatinine. \(^b\)-\(^c\): There would not be an increase in assessment (no AKI) with RIFLE if the burn-induced increase in glomerular function could meet the increased demands of elimination. \(^d\): Increased baseline values can be induced by the burn (true positive) but also caused by a pre-existing medical condition (false positive burn-induced renal dysfunction). \(^e\): A moderate increase in plasma creatinine concentration that would be classified as AKI among patients who had a low or normal baseline would not be classified as AKI among patients who had a high baseline, as the RIFLE classification is based on the increase in relation to baseline.

Not having a true baseline plasma creatinine concentration when using the RIFLE criteria is a problem. Estimated baseline concentration is an alternative, but it would give false-positive AKI recordings among patients with pre-existing but unobserved high values as these would be recorded as increases in relation to the estimated baseline. The initially low concentrations in plasma during resuscitation should, however, be of the same magnitude among burned patients as a group. Accordingly, the results of the RIFLE classification may be used to compare incidences of AKI between studies of patients with burns. The same problem is likely to occur among other groups of patients whose true baseline may be unknown and who are subjected to aggressive fluid resuscitation (such as patients with major trauma, and patients with severe sepsis).
Assessing physiological changes

The issue about the use of RIFLE, besides the difficulty of setting a valid baseline in injured patients, is that variations in plasma creatinine concentration during the first week can be caused by factors other than renal injury. The catabolic state after severe burns increases the amounts of creatinine that need to be eliminated, and the initial plasma dilution during resuscitation, followed by fluid mobilisation over the first weeks, can cause large variations in the plasma concentration. Although most patients studied after thermal injury present with low plasma creatinine concentrations during the first days after the burn, raised or high values during the end of the first week are not essential. When the physiological renal response after injury (increased glomerular vascular permeability, and increased renal blood flow as a result of increased cardiac index and the fluid required) is adequate, it is possible for the kidneys to eliminate increased amounts of creatinine. The glomerular filtration rate is increased among adult burned patients soon after injury.\(^{95}\)

Results from studies in burned children have suggested that elimination of creatinine after severe burns is not a problem for a young kidney. Serum creatinine concentration and creatinine clearance have been reported to be within the reference ranges during the acute phase after the burn, despite comprehensive signs of a pronounced pathophysiological response in inflammation, hormonal changes, hypermetabolism, and catabolism, including decreased lean body mass.\(^{38}\)

However, we need to know more about what an adequate glomerular filtration rate is, and what the RIFLE time-course curve should be among adult patients with major burns. The great advantage of the RIFLE is that it captures change, as the variations during the early period after burns are dynamic. Some of the issues with the SOFA are the same, including the fact that variations in plasma creatinine concentration during the first week can be caused by factors other than injury to the kidney.

Renal dysfunction seems to follow a course similar to that of other dysfunctioning organs, as the time delay between different organs can be marker-specific rather than organ-specific. The impact on the kidneys is likely to be before the increase in plasma creatinine concentration has reached the classification threshold. Markers of proximal tubular dysfunction (such as 24-hour urinary N-acetyl-beta-D-glucosaminidase activity) can be almost doubled on the first day after injury among patients with severe burns, and may increase further during the first week.\(^{96}\)
Pathophysiology of renal dysfunction in burns

The reasons for AKI among patients with severe burns may be multifactorial, as its onset was preceded by the initial inflammatory response (SIRS) and pulmonary dysfunction. This, together with its early onset, suggests that it is the burn and resuscitation rather than infective complications that are responsible for the dysfunction. It has been suggested that pulmonary dysfunction may promote pathogenic inflammation and the development of multiple organ failure after trauma.\(^{69}\) In Study I we also found that ARDS developed soon after injury, and that renal dysfunction was more common among the patients with the most severe respiratory dysfunction.

**Sex-related difference in mortality (paper III)**

**Expectations of a survival advantage for women**

We found no evidence of a sex-related difference in survival after thermal injury. The number of deaths among patients in the age group 16 -49 years, when hormonal differences would be most influential, was too small (n = 12) to evaluate the potential of the protective properties of female sex hormones fully. The mean age for the natural menopause in Sweden is 50 years, and two SDs (capturing 95.5\%) give an interval between 42.4 years and 58.0 years of age. The ages of four of the women who died were within that interval, leaving one female death (aged 21) in the group of young women who were most likely to be fertile.

In a number of studies young women have been reported to survive better than men after severe trauma.\(^{97-99}\) The mechanisms behind female advantage are not fully understood, but the protective properties of female sex hormones have been supported by results from animal burn studies (trauma-haemorrhage in animal studies,\(^{100}\) and hormonal effects on inflammatory regulation and cardiac function after experimental burns\(^{51}\)).

Another possible physiological mechanism that favours a female advantage is the genetic explanation (the expression of the female X chromosome mosaic is favourable as women would be less affected by an unfavourable X-linked genetic polymorphism).\(^{101}\) We think that if there had been a relevant difference for genetic reasons we could have found a survival advantage for women, because the total number of deaths was 67.

Study III was relatively large, and more than 1000 patients admitted to one burn unit were included. The entire group was exposed to similar treatment protocols, data were recorded prospectively, and there was no difference in mortality over the years. We tried to
Discussion

handle the shortcoming of a single-centre investigation by multivariate adjustments for factors that are well known to affect outcome after burns. The overall model had a high (0.47) pseudo R² which supports the strength of the statistical model used. This confirms our hypothesis that there does not seem to be a sex-related difference in mortality after thermal injury. The conclusion is, however, hampered by the restricted number of deaths, particularly among younger adults.

Survival advantage of male patients with burns

Studies that have investigated sexual dimorphism in mortality after burns have produced mixed results. There seems to be no difference in mortality between boys and girls with burns,¹⁰²,¹⁰³ but most studies of adult patients including large datasets have reported that men have a survival advantage.⁶,¹⁰²,¹⁰⁴,¹⁰⁵ A recent analysis from the National Burn Repository (USA) for variables predictive of mortality found that sex did not contribute to the predictive model.⁷ Adjustments have been made for a number of variables (including age, race, cause of burn, TBSA%, presence of inhalation injury, mechanical ventilation, coexisting medical conditions, coexisting trauma, pneumonia, and body weight) in burn studies.⁶,⁷,¹⁰²,¹⁰⁵,¹⁰⁶ The absence of experimental data to our knowledge that support the findings of male survival advantage after burns raises the question of whether there are other factors (such as genetic or gender-related factors) of importance for mortality that were not recorded in these studies.

Genetic polymorphism (carriage of the CD14-159 C allele) has been shown to be associated with an increased risk for sepsis and for mortality among patients with severe burns, while sex was not associated with mortality.¹⁰⁷ This was reported from a study with a much smaller dataset than the studies that found a male survival advantage. Sepsis-associated mortality is also higher among women than men in general intensive care.¹⁰⁸

There are studies that have reported more interventions (such as mechanical ventilation, vasoactive medication, renal replacement, and invasive procedures) among men in general intensive care, and also that the mortality adjusted for severity of illness and age did not differ between the sexes,¹⁰⁹ but we do not know if a more equal number of interventions would have been beneficial enough to give a survival advantage to the women that were studied.

Men as a group have been compared with women more prone to be exposed to burns (Figures 1-2), including men in almost all age groups, and work-related burns that are mainly found among men. This predominance of men is true in most cultures even though examples of the opposite can be found. The reported predominance of young women in fire-related
Deaths in India have been attributed to kitchen accidents, self-immolation, and domestic violence.\textsuperscript{110}

**Potential limitations**

We did not evaluate the presence and impact of pre-existing medical conditions, though how important their effects are in the perspective of sex-related mortality in burns may be controversial. Burned women have been reported to have more extensive medical histories than age-matched and TBSA-matched burned men.\textsuperscript{111} McGwin et al. found that such illnesses did not contribute to their predictive model for mortality among burned patients.\textsuperscript{7}

Another view is that the model we used was adjusted for age. Substantial co-existing medical conditions are most likely to contribute to outcomes in older age groups, and it is possible that the main effect that age has on mortality is the effect of the increasing number and severity of co-existing medical conditions. It is important that the life expectancy of men is shorter than that of women, which is reflected in the larger number of women among the group of elderly people who are exposed to burns, and that crude mortality is higher among women, as we found in Study III.

We used the variable “mechanical ventilation” as an indicator of pulmonary dysfunction or inhalation injury. It may be a limitation that we did not have a reliable indicator of inhalation injury to use in the model instead, but findings from a recent study suggested that respiratory dysfunction (early mechanical ventilation) and not inhalation injury was associated with mortality.\textsuperscript{6}

When we compared the characteristics of our study group with data about patients from the study by Kerby et al. who reported a survival advantage for men after burns,\textsuperscript{102} we did not find any obvious differences between their study group and ours that could explain the different conclusions. There was no difference in overall TBSA\% (13.6\% compared with 13.1\% in our study), or overall mortality (5.3\% compared with 6.0\% in our study, \( p = 0.3 \)), but the tendency to higher mortality can be explained by the older mean age in our study (29.6 years compared with 33.4, \( p = 0.001 \)), and the fact that we excluded all patients who had non-thermal burns, because mortality from flame injuries is higher than overall burn mortality.
Liver function (paper IV)

Assessing early burn-induced effects on liver function

We have studied dynamic liver function among patients with thermal injury using the rate of disappearance of indocyanine green from plasma (PDR$_{ICG}$). This is, to our knowledge, the first time this has been done together with measurement of static liver function tests, variables of the central circulation, and detailed recording of organ dysfunction. We found that the PDR$_{ICG}$ seems to give a comprehensive assessment of liver function after severe burns.

Early transient liver dysfunction, as assessed by the PDR$_{ICG}$, was common, and the PDR$_{ICG}$ measurements were associated with TBSA% and plasma C-reactive protein concentration in a multiple regression model that included (adjusted for) age, cardiac index, and plasma bilirubin concentration. This supports the hypothesis that there is a burn-induced effect on liver function that can be recorded by that method, and that the course of deterioration and recovery of hepatic function can be monitored.

The findings of low and decreasing PDR$_{ICG}$ values among patients who died supports the argument that the effects on the liver that were measured by PDR$_{ICG}$ are relevant. Signs of liver necrosis and fatty infiltration of the liver are common findings at necropsy among children with large burns.\cite{112} We do not know from the results of our study if decreasing liver function measured by PDR$_{ICG}$ before death is a marker of imminent acute liver failure or just a sign of the dying process.

Our study median PDR$_{ICG}$ of 18.3 %/minute on day 1 was in between results from other studies. Mean values between 12-17 %/minute have been reported among critically ill patients,\cite{113-115} while patients having elective surgical procedures present with mean values within the reference range (18 %-25 %/minute) suggested by the LiMON manual.\cite{116}

The fact that high values (PDR$_{ICG}$ values that were above the reference interval, >25.0 %/minute) were found in Study IV even when cardiac index was not increased suggests that inflammation and hypermetabolism were important factors in the hepatic “hyper”-function. All the patients had signs of inflammation (increased plasma C-reactive protein concentrations). The genes encoding the basolateral hepatocyte ICG transporters have been shown to be upregulated by inflammatory stimulation, which can increase the rate of ICG uptake into hepatocytes.\cite{113} The highest value found in Study IV was 49.6 %/minute (in two patients), which is similar to the peak values that have been found among critically ill patients,\cite{117} but values up to 43 %/minute have also been found among individual healthy patients before elective surgery,\cite{116} suggesting that the normal variation can be substantial.
We found age to be a major factor for liver function assessed by PDR$_{ICG}$, not surprisingly as age can influence liver function by a number of mechanisms. An age-related decline in liver volume of 20% across a lifespan of 20-80 years age has been reported.$^{118}$ The mass of functional hepatocytes is reduced in elderly patients, with decreased liver function (as measured as retention rate 15 minutes after injection of indocyanine green) as a consequence.$^{119}$ Hepatic metabolic capacity (MEGX, lignocaine metabolite production) and the hepatic acute phase response are reduced after major surgery among elderly patients when compared with adult but not elderly patients.$^{120}$ The magnitude of the early systemic inflammatory response after burns has been shown to be age-dependent.$^{53}$

Our data suggest that the hepatic “hyper”-function response is more pronounced among young adults. The median age was 38 years (range 19-67) among the six patients (6 of 17) who had high PDR$_{ICG}$ measurements on day 14, which was close to the mean age (29 years) in a study in which albumin synthesis was found to be increased at the end of the second week after injury.$^{121}$ It is also in line with findings from a study of eight young (median age 39 years) patients who showed an increased elimination rate of ethanol after burns compared to healthy controls.$^{122}$

Median age among the remaining patients in Study IV was 65.5 years (min-max 20-85).

Liver dysfunction, static tests

Our findings of abnormal liver function (common occurrence and early onset) based on PDR$_{ICG}$ have not to our knowledge been previously reported in adult burned patients, but they are in line with the findings of early and high initial release of hepatic enzymes from studies in children with more serious injuries compared with our patients.$^{33,38}$

We found an overall association between plasma bilirubin concentration and PDR$_{ICG}$, and PDR$_{ICG}$ seems to be more sensitive to liver dysfunction than plasma bilirubin, which is in line with previous findings among critically ill patients.$^{113}$

Increased concentrations of plasma bilirubin during the first days after injury can be caused by haemolysis from capillaries in the burned skin, and by decreased hepatic excretory function. We did not find increased plasma bilirubin concentrations on day 1 among the patients with the largest TBSA%, including deep burns, or a parallel with PDR$_{ICG}$ values above the upper reference limit. Concentrations can theoretically be within the reference range after a burn both if the burn is deep enough (coagulation of capillaries) to prevent perfusion of haemolysed blood in to the central circulation, and if the liver has sufficient excretory func-
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A new and important finding is that liver dysfunction among adult patients with severe burns seems to be as common as dysfunction in any other organ. We interpret these effects on liver function as part of a multiple organ dysfunction syndrome that is primarily induced by the burn. However, this needs to be investigated further.

We found early changes in a number of other organ systems that could be classified as dysfunction or failure, which suggests that the changes we found in liver function also reflect a state of dysfunction. We did not, however, find significant associations in the regression model between variations in the SOFA organ dimensions and the PDR$_{ICG}$ measurements. It is possible that a timely delay as a result of differences in the progression pattern between variables can have counteracted such a parallel. Whether this was the result of a different pattern of dysfunction or of the choice of markers cannot be established from our results.

Resuscitation

We did not find significant associations between resuscitation indicators (day 1) and liver dysfunction (lowest PDR$_{ICG}$ measurement during the study period), which suggests that the liver dysfunction recorded was not the result of shortcomings in resuscitation.

There can, however, have been local shortcomings in liver resuscitation as the indicators for resuscitation were measured in the central circulation. It is also possible that we have missed recording periods of severe hypoperfusion and acidosis, as not all resuscitation variables were monitored continuously. Ischaemia and reperfusion during the resuscitation phase are probably important mechanisms for the variations in liver function seen in the present study, whether or not there were shortcomings in resuscitation. All the patients required large volumes to maintain adequate central circulation.

Liver function is dependent on adequate perfusion and oxygen delivery. Experimental haemorrhagic shock with hypovolaemia has been shown to induce depletion of adenosine triphosphate (ATP) and pericentral necrosis in the liver, and liver function (as assessed by ICG clearance) can remain reduced to 60% of baseline after 5 hours’ resuscitation, whereas tissue ATP is restored by the resuscitation.\textsuperscript{123}

Studies of burns in animals have shown that there is a decrease in hepatic blood flow (both in the hepatic artery and portal venous blood flow) and in hepatic oxygen delivery
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ing the first two hours after a burn. Reports of recovery vary among studies, from completely recovery to baseline after 18 hours (blood flow and oxygen delivery) and partial recovery of hepatic blood flow to 75% of baseline after 24 hours. While there is also a decrease (down to 70% of baseline) in plasma clearance of ICG within the first hour after a burn, the dysfunction in hepatic excretory function seems to develop more slowly. It is still decreasing after 24 hours to 57% of baseline, indicating that changes in plasma clearance of ICG early after the burn cannot be explained just as changes in perfusion.

It is not possible from the results of Study IV to discern which specific mode of injury or cellular changes caused the variations that were found in the PDRICG measurements. Several mechanisms can theoretically cause liver damage after thermal injury, such as ischaemia-reperfusion injuries immediately after the burn, the inflammatory response leading to increased concentrations of proinflammatory cytokines and other signals of apoptosis, and possibly fatty changes in the hepatocytes and hepatic oedema.

An interesting finding is that the severe, persistent, and decreasing low PDRICG values were not accompanied by increased plasma ALT activity. Our data suggest that the hepatic dysfunction we found soon after injury was of another level of severity, or caused by other mechanisms than those that cause acute liver failure, as for example an acetaminophen-(N-acetyl-para-aminophenol)-induced liver injury. However, we do not know if the recorded dysfunction should be seen as a mild stage of liver failure that recovered, or whether it is merely a physiological response to a burn.

Dose and reference range

We used a dose of ICG 0.5 mg/kg bodyweight. Sakka et al. compared two doses of ICG (0.5 mg/kg and 0.25 mg/kg) and showed that PDRICG values below 10 %/minute were about 1 %/minute lower with the dose 0.25 mg/kg, while PDRICG values of 15 %/minute or more were about 2 %/minute higher with the dose 0.25 mg/kg, although the range varied between subjects by >4 %/minute. If we had chosen to use the lower dose of ICG this could have further lowered the values among the patients with persistent liver dysfunction (without affecting the overall result); it could have shifted roughly three of the seven patients with transient liver dysfunction to the group of single PDRICG below reference value (18 %/minute); and it could have shifted four of the six patients with single PDRICG below the reference value to no PDRICG below reference value.

It is limiting that we do not know the clinically relevant reference range for PDRICG among patients with major burns, or different age groups. It is a reasonable assumption that
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high PDR$_{ICG}$ values should be expected during the hypermetabolic and “hyper”-circulatory phase of a severe burn, and that “normal” PDR$_{ICG}$ values may be pathological, or at least seen as signs of an aged or otherwise decrepit liver, that may or may not have the ability to meet the increased demands after injury. It is therefore possible that we have underestimated the incidence of liver dysfunction in Study IV.

However, as we adjusted for age-related changes by including age in the regression model, we do not think that it interferes with our conclusion.

General discussion

Selection of patients

We chose to study patients with severe burns who were likely to develop organ dysfunction, and found that it is an early and common phenomenon. Burn-induced effects on organ function were recorded for all patients, as were different degrees of dysfunction with a variable expression in each of the separate organs (studies I, II, and IV). We have used a 20% TBSA% limit for inclusion (except for study III), which is in line with most studies of adult burns, as patients with severe burns are more likely to develop organ dysfunction than patients with smaller TBSA%. This model seems to be reproducible, as the results are congruent between studies (early onset and the development of organ dysfunction and sepsis; age and TBSA% are important independent variables for dysfunction and outcome). It would, however, be interesting to study organ dysfunction as thoroughly among all patients with thermal injury who are admitted, to examine the assumption that dysfunction is uncommon and mild in this group. It is possible that a systematic assessment would show dysfunction in some organs that remained undetected as we examined only larger burns.

General limitations

The one-centre approach with results generated from a relatively small study group is a limitation that makes it difficult to generalise the results, but one advantage of such a study is that the population is less heterogeneous and the effects of different treatments and regimens are reduced. This advantage is further supported by the strict protocol for the treatment of burns at the unit, which can strengthen the value of the results.

The clinical perspective largely depends on indirect signs of physical conditions and processes that are often interrelated, which can make it difficult to study organ dysfunction
and the interplay between dysfunction of several organs. Using well-known techniques and scores can increase the value of the results, as the findings can be compared between studies.

**TBSA% and pre-existing medical conditions**

An underlying assumption in the present thesis is that age and TBSA% are important factors for patients with burns. We used them as independent variables in all the studies, and found that they were important for the development of organ dysfunction and for mortality after burns, in line with previous findings.\(^2,^3,^6,^7,^8\) It is possible, however, that these two variables are indicators of other important factors that we not have examined.

It is also possible that the variable “full thickness burns” (FTB%), indicating the depth of the injury, would give a result different from that of the total extent of injury (TBSA%) in a larger series. We have not found that FTB% adds anything to the information the TBSA% contributes. The two have been strongly inter-related, and they have contributed in a similar way and extent. When using a model for inclusion that excludes patients with mainly superficial burns (patients who not require invasive lines or monitoring), TBSA% and FTB% are likely to be inter-related.

Another factor that we suspect is important is pre-existing medical conditions, although we did not examine their influence until the last study (study IV). It is a reasonable assumption that a large proportion of the effects of any pre-existing medical condition have been reflected in our results as effects of older age. There are also recent studies in burns that have not found coexisting illness to be a predictor of mortality after adjustment has been made for age and TBSA%.\(^7\) We used it in a dichotomous fashion (present/not present), which is probably not optimal, and it was not associated with variations in PDR\(_{ICG}\) in a regression model. This is in line with the results of another study in which the presence of coexisting illness was not associated with AKI or mortality in an adjusted multivariate analysis.\(^8\) The challenge remains to find a useful form of this variable, graded according to its possible impact on organ function and mortality after severe burns.

**Sequence and time of onset: possible relations**

It is a reasonable assumption that organ dysfunction develops on a clinical continuum, and that patients have mild to severe expressions of the syndrome. The insensitive nature of the markers of organ function can impair our detection of dysfunction early in its course. One example, mentioned above, is the use of biomarkers for detecting kidney injury earlier.\(^9\)
The sequence of organ dysfunction is one of the features that was described in the first reports of the syndrome. It is an observation made on the basis of data gathered with markers that are often used at the time in concurrent studies, giving some information about differences and similarities between centres and groups of patients. Whether or not there is an operative sequence we do not know. It would, however, be interesting from a clinical perspective to find out if organ dysfunction of later onset can be prevented by supporting organ function early after injury.

Our findings of the order of onset (Tables 10 and 12) are in line with the results from a recent paper from a burn centre using similar resuscitation volumes. We found that early organ dysfunction was common; first onset was detected on the first day after injury in some organs (SOFA respiratory, SOFA cardiovascular, SOFA hepatic, and PDRICG); during the first week in other organs (SOFA coagulation, SOFA renal, RIFLE); and a few (enteral dysfunction) were detected during the second week after injury. This temporal order may be a truly sequential order if there are different mechanisms or a different susceptibility for dysfunction in different organs. It could also be an illusion because of the marker used to detect dysfunction, as there can be a delay of days before the marker reaches the set threshold for dysfunction (for example, plasma creatinine concentration). This being so, patients with more severe burns and organ dysfunction are more likely to be classified as having developed organ dysfunction, and the threshold will be reached earlier than for patients with moderate burns and organ dysfunction. A possible example of this is the early and high initial release of hepatic enzymes among children with extensive burns.

The physiological response to thermal injury

The magnitude of the physiological response to thermal injury varies, and this can be because of age, extent of injury, pre-existing medical conditions, or other individual features (genetic). Burn care (including resuscitation, and excision and grafting) and sepsis are also important factors. The adequacy of the response is suggested as follows: dysfunction always indicates inadequate organ function, and it is likely to have secondary injurious effects on the function of other organs. Function (within general reference limits) can be adequate or inadequate, depending on whether the degree of function is sufficient to meet the increased demands - for example, after injury. “Hyper”-function can be adequate or exaggerated, depending on whether it is a physiological response to a “hyper”-demand induced by injury, or an over-reaction leading to uncontrolled “hyper”-function of the organ. Even if “hyper”-function
can be an adequate response, there is a possibility that toxic byproducts can be generated, and these could cause secondary tissue injuries (Figure 10).

Figure 11 shows another way to outline different degrees of organs’ responses to thermal injury. It suggests that different responses can be found in different ranges of age and TBSA%. “Hyper”-function can be a normal and adequate response among young adults with severe burns, while normal function can be the adequate response among young adults with moderate burns. Dysfunction is often found among older adults, even among patients with moderate burns, suggesting an interplay between age and organ dysfunction, and a linked association with mortality.

Figure 10. Effects of thermal injury on organ function. An outline of different degrees of responses and how they can affect organ function. Some of the effects of the burn, including the initial hypovolaemia and reperfusion, have a direct injurious effect on organs. It is a physiological consequence after the injury, but the consequences for organ function may also be harmful.
**Good prognosis despite multiple organ failure among burned patients**

The recorded organ dysfunction was transient, with organ function recovering among survivors, and the prognostic relevance of early organ dysfunction was small. In study IV we found that 12 of 17 developed multiple organ failure according to the SOFA score during the study period, and that the mortality in this subgroup was 3 of 12. These three patients did not die until 3 to 8 weeks after the first recording of multiple organ failure.

The prognosis of organ dysfunction among patients with severe burns is better than among patients treated in a general intensive care unit (ICU), possibly because the underlying reason for being there among patients with burns is physical trauma not a progressive disease, and because the patients are younger than general ICU patients. Mortality has been reported to be 8% (11 of 142) in a group of children with severe burns, whereas 21% (30 of 142) developed multiorgan failure. The main issue for managing organ dysfunction among burns is to treat the underlying mechanism, which is the burned skin, and the problems with organ dysfunction resolve as the skin heals.

Multiple organ failure was the major cause of death, and it was not surprising that we found that death was associated with persistent and advanced dysfunction. It is difficult to distinguish at what point the phase of organ dysfunction ends and the dying process begins, or
if the start of organ failure is the first step on the path to death. Organ failure can be considered as an inevitable part of the dying process, and perhaps there should be a time limit for recording organ dysfunction before death, when the dysfunction can no longer be considered a consequence of the burn and is irreversible.

**Mechanisms: inflammatory engines**

Translocation of gut-derived toxic and inflammatory factors is a suggested mechanism for progression of the multiple organ failure syndrome. Experimental ischaemia gives a dose-dependent increase in gut permeability, and the permeability can be increased about five times over the initial measurement after 60 minutes. A burn study in animals reported findings of a more than threefold increase in gut epithelial apoptosis after burn-induced gut hypoperfusion when it was compared with hypoperfusion without burns. Sequestration of neutrophils into the intestinal tissue is a possible cause of the increased gut permeability after thermal injury. Burn studies in animals have also shown that the increase in permeability was significant on the first day after the injury, and further doubled on the third day, while it was entirely inhibited in neutrophil-depleted animals.

Our findings that the first onset of sepsis was detected on median days 3-4 after injury, while the onset of dysfunction was detected on median days 1-2 in most of the other organs, is congruent with the gut-lymphatic hypothesis. Our data suggest that patients with severe burns who are resuscitated according to the principles of modern burn care, do not as a group present with the clinical signs that give rise to suspicions of sepsis during resuscitation. The sepsis classification (according to the International Sepsis Conferences 1991 or 2001) does capture the inflammatory state (SIRS) that develops almost immediately after injury among patients with severe burns, while signs that give rise to suspicions of systemic infection generally develop after a few days (such as low SVRI and high body temperature), together with evidence of bacteria in the central circulation (documented infection).

Although patients with severe burns are thought to develop dysfunction of the gut barrier soon after the burn, plasma endotoxin concentrations found within the first 24 hours after the burn have been found to be within the same range as controls. Another study showed that the increase in intestinal permeability on day 2 after the burn was more pronounced among patients who developed serious clinical infections during the first 2 weeks than among those who did not. Some of the studies that have used selective decontamination of the gastrointestinal tract to prevent translocation of gut-derived toxic and inflammatory factors after
burns have showed promising results, such as attenuation of burn-induced myocardial contractile dysfunction and inflammatory signaling,\textsuperscript{134} and decreased mortality.\textsuperscript{135}

In paper IV we reported that enteral dysfunction was the least common, and the latest to develop, and in all cases it was detected after the first onset of sepsis, but it is a reasonable assumption that it must develop over days before enteral feeding has to be interrupted, and that enteral dysfunction and sepsis are parallel processes with adverse effects on each other. It is also possible that the intestinal integrity can have been compromised among these patients long before the enteral symptoms were obvious, with prolonged bacterial translocation from the gut eventually leading to sepsis, to the use of antibiotics, and to a progression of the already impaired gut barrier.

According to the gut-lymphatic hypothesis, the lung would be the first major vascular bed to be exposed to gut-derived toxic and inflammatory factors. A number of studies have reported that it is one of the first organs to become dysfunctional,\textsuperscript{16,24,25,128} and we also found that the early respiratory dysfunction was severe enough to require life support (mechanical ventilation) even in the absence of a diagnosis of smoke inhalation. This supports the idea of the lung as an inflammatory engine for the progression of multiple organ dysfunction.

The liver also showed signs of early dysfunction, but the dysfunction was transient except in a few patients in whom hepatic dysfunction was persistent and advanced.

**Mechanisms: “two-hit”**

Animal studies have shown that the effect of a second hit on the hepatic circulation is more pronounced than the initial effects of the burn.\textsuperscript{124} Some of the variables studied (Study IV) suggest a “two-hit” course over the study period, taking the onset of sepsis on day 4 as the second trigger. This “two-hit” course was not as apparent from the PDR\textsubscript{ICG} measurements, as we found both decreasing (n=5) and increasing (n=5) values after the onset of sepsis. Sepsis was common, and its onset was not reflected in variations in the results of static liver function tests in all patients.

Dehne et al. who monitored several markers (IL-2, IL-6, IL-8, IL-10, IL-13, procalcitonin, and C-reactive protein) of the inflammatory response to thermal injury over a period of four weeks in two groups of patients (TBSA of more and of less than 30%) found that there had already been a parallel proinflammatory and anti-inflammatory activation at the time of admission. It was more pronounced and more extended among the patients with larger burns, and it correlated with a higher incidence of multiple organ dysfunction syndrome and SIRS.\textsuperscript{136}
Mechanisms: microcirculatory hypotheses

The transient disseminated intravascular coagulation syndrome (DIC) has been suggested as another systemic cause of multiple organ dysfunction in burns, the theory being that diffuse deposition of fibrin formations in the microvasculature could have a pathological role in the development of organ dysfunction. A recent study has found that 91% (41 of 45) of patients with severe burns had DIC soon after injury, and that overt DIC was associated with multiple organ dysfunction and mortality. We did not assess coagulation as comprehensively as in the study cited above, but we found (Study IV) that coagulation dysfunction, as assessed by plasma prothrombin complex, was early, complete (17 of 17), and severe, but not as persistent as described above.

Central nervous system

The fact that we decided not to use the SOFA neurological dimension because of difficulties in scoring the intubated and ventilated patients correctly does not mean that we do not think that it is important and interesting to study neural dysfunction after burns. The close interactions, anatomical and functional, between the central nervous system and the immune system are important for mediation of the inflammatory response after injury, and there are a number of factors after a severe burn that can have adverse effects on cognitive and other functions of the brain. The large amount of drugs given during the period of intensive care can be mentioned as one example, and disturbances in the coagulation system and periods of central hypoperfusion or vasoconstriction are others.

Skin dysfunction

When skin grafts do not take to the wound bed and do not heal, it is an interesting aspect of skin dysfunction after burns, but it is difficult to obtain objective records. Duration of hospital stay can be used as a surrogate variable for healing after burns, as the required degree of wound care mainly governs the need for in-hospital care. We have chosen not to use duration of hospital stay as a marker for skin dysfunction in the regression models, however, because of its generality.

Burning the largest immune organ is another perspective of skin dysfunction, which can explain why the extent of TBSA% burned is associated with virtually all the variables of physiological morbidity that are used in different studies.
Conclusions

Respiratory dysfunction (paper I)

Our data suggest that the respiratory dysfunction that is seen after burns appears early as a result of burn-induced ARDS and inhalation injury. The early onset of ARDS, together with the changes in white blood cell count and organ dysfunction, suggest a syndrome in which the respiratory distress is mediated by an inflammatory process induced by the effect of the burn rather than being secondary to sepsis. These conclusions should be adopted with caution as the study group was small and the diagnoses overlapped.

Acute kidney injury (paper II)

The incidence of AKI after major burns was 0.11/100,000 people/year. Our data suggest that AKI is common among patients with severe burns, and that it develops soon after the burn and parallels dysfunction in other organs. Although AKI recovered in all survivors, in those with more severe acute kidney injury and those with cardiovascular dysfunction as well, it correlated with mortality.

Age, TBSA%, and the extent of full thickness burns (FTB) was higher among the patients who developed AKI. Thirty of the 31 patients with AKI required mechanical ventilation whereas only half (51 of 96) of the with no AKI required mechanical ventilation. Pulmonary dysfunction and SIRS developed before the onset of AKI was recorded. Sepsis was a possible aggravating factor in AKI in 48% (15 of 31). We could find no support for the idea that AKI of late onset is associated mainly with sepsis.

Sex-related difference in mortality (paper III)

Our data suggest that there is no relevant sex-related difference in survival after thermal injury. The conclusion is, however, tempered by the restricted number of deaths in our study group, particularly among the younger adults.

Liver function (paper IV)

Our data suggest that early liver dysfunction, as assessed by the PDR_{ICG}, is common, and that it is associated with TBSA%, plasma C-reactive protein, age, cardiac index, and plasma bilirubin concentration. This supports the hypothesis that there is a burn-induced effect on liver function that can be recorded by the PDR_{ICG} method, and that the course of deterioration
and recovery of hepatic function can be monitored accordingly. The PDR_{ICG} seems to be more sensitive to liver dysfunction than the isolated plasma bilirubin concentration.

We found a large number of high PDR_{ICG} measurements and our results indicate that the burn-induced inflammatory and hypermetabolic state has a substantial role in high PDR_{ICG} values. Our data suggest that the hepatic "hyper"-function response is more pronounced among young adults, so it is possible that we have underestimated the occurrence of liver dysfunction in the present study as we do not know the clinically relevant reference range for PDR_{ICG} among patients with major burns. Liver dysfunction among adult patients with severe burns seems to be as common as dysfunction in any other organ. We interpret these effects on liver function as a part in a multiple organ dysfunction syndrome that is primarily induced by the burn. However, this needs to be investigated further.

**General conclusions**

We found that organ dysfunction is an early and common phenomenon among the patients who were studied, suggesting that the selection of patients with a 20% TBSA limit for inclusion is useful. The model seems to be reproducible as the results are congruent between studies. The one-centre approach with results generated from a relatively small study group, however, makes it difficult to generalise the result.

Our data suggest that the prognosis of organ dysfunction among patients with severe burns is good, with recovery of organ function among survivors. This may be because the underlying cause among patients with burns is physical trauma, not a progressive disease. Multiple organ failure was, however, the main cause of death in this group.

Sepsis, as classified in the study, was common. Our data suggest that patients with severe burns who are resuscitated according to protocols of modern burn care do not present with the clinical signs that give rise to suspicions of sepsis during resuscitation.

The findings of respiratory dysfunction of early onset and a delay in signs of sepsis are congruent with the gut-lymphatic hypothesis, and the idea of the lung as an inflammatory engine for the progression of multiple organ dysfunction.

Our data further suggest that clinical strategies to improve burn care further should be focused on early interventions, interesting examples of which include: selective decontamination of the gastrointestinal tract to prevent translocation of gut-derived toxic and inflammatory factors; optimisation of fluid replacement during the first 8 hours after injury by goal-directed resuscitation; and possible improvement in the fluid treatment given before admission.
I Sverige vårdas cirka 12/100 000 invånare per år på sjukhus för brännskador, och bara ett fåtal av dem har stora brännskador. Bland de som har de svåraste brännskadorna, och speciellt de som avlider på sjukhuset, är det vanligt att funktionen i olika organ påverkas negativt vilket har stor betydelse för hur sjuka de blir, och för risken att avlida. Det faktum att både storleken på skadan och tidpunkten för när skadan skedde är kända är en stor fördel för studier av organfunktion, och det gör att brännskadepatienter är ideala för studier inom detta område. Organfunktion och mortalitet bland brännskadade patienter studerades i denna doktorsavhandling med en deskriptiv explorativ metodik (ingen intervention eller kontrollgrupp) av konsekutiva patienter som vårdades vid ett nationellt brännskadecentrum i Sverige.


Organfunktion är ett tidigt fenomen och det är vanligt efter svåra brännskador. Våra resultat tyder på att prognosen är god bland brännskadepatienter, med återställd funktion bland de som överlever. Multipel organsvikt var dock den vanligaste dödsorsaken. Att den respiratoriska dysfunktionen kom tidigt i förloppet medan tecken på blodförgiftning kom några dagar senare överensstämmer med "gut-lymphatic" hypotesen för utveckling av organsvikt, och med idén att lungan kan fungera som en inflammatorisk motor för vidare sjukdomsutveckling. Att organfunktion utvecklades tidigt efter skadan talar för att en inflammatorisk process orsakad av effekterna av brännskadan snarare än blodförgiftning skulle vara orsaken.

Våra resultat pekar på att kliniska strategier för att förbättra vården av stora brännskador bör fokuseras på tidiga insatser. Det kan vara strategier såsom: selektiv dekontaminering av mag-tarmkanalen för att minska utflödet av bakterier och inflammatoriska faktorer; optimering av de intravaskulära vätskevolymerna under de första 8 timmarna efter skadan genom målstyrd vätskebehandling; och att försöka optimera den prehospitala vätskebehandlingen.
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