Inhalation injury assessed by score does not contribute to the development of acute respiratory distress syndrome in burn victims

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Abstract

Objective: To establish the incidence, mortality, and time of onset of acute respiratory distress syndrome (ARDS) in relation to extent of burn and inhalation injury in patients who required mechanical ventilation.

Design: Data about burn and inhalation injury were recorded prospectively whereas ARDS and multiple organ dysfunction were assessed by review of patient charts.

Setting: National burn intensive care unit at Linköping University Hospital, Sweden (a tertiary referral hospital).

Patients: Between 1993 and 1999, we studied all patients with thermal injury (n = 553) who required mechanical ventilation for more than two days (n = 91).

Measurements and results: Out of the thirty-six burn victims who developed ARDS (40%), 25 (70%) did so early post burn (in less than 6 days). Patients with ARDS had higher multiple organ dysfunction scores (mean 10.5) than those who did not develop ARDS (mean 5.6) (p < 0.01). The probable presence of inhalation injury as assessed by an inhalation lung injury score (ILIS) did not contribute to the development of ARDS. Mortality tended to be higher in patients who developed ARDS (14%) compared to those who did not (6%, p = 0.2).

Conclusions: In our burn patients the incidence of ARDS was high whereas mortality was low. We found no association between inhalation injury as assessed using the ILIS and development of ARDS. Our data support a multi-factorial origin of ARDS in burn victims as a part of a multiple organ failure event.

1. Introduction

Acute respiratory distress syndrome (ARDS) is a serious complication of various clinical conditions including sepsis, major trauma, and pneumonia. It is potentially lethal [1–3]. Burns have been thought to be less common triggers of ARDS, although burned patients often have characteristics that predispose to ARDS. However, a recent retrospective study showed that the incidence of ARDS that necessitated mechanical ventilation after major burns may be as high as 53.6% [4]. This is not surprising as the early complications of thermal injuries include respiratory and multiple organ failure and a massive systemic inflammatory response. The picture is complicated by pneumonia, multiple blood transfusions, inhalation injury, and high susceptibility to nosocomial infections [1,5,6]. Finally, mechanical ventilation in these patients can aggravate lung injury and multiple organ failure, particularly if injurious ventilation strategies are applied [2,7,8]. With this background it seems surprising that thermal injuries have not more commonly been described as triggers of ARDS [4].

The aim of our study was to investigate the time of onset, incidence, demographics, and mortality of strictly defined ARDS in burned patients who were mechanically ventilated. We also evaluated the impact of burn-related risk factors such as burn size (partial and full thickness burns) and inhalation injury on the incidence of ARDS.

Preliminary data from this investigation were presented at the 9th European Burn Association Meeting in Lyon, September 2001.

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2. Patients and methods

We studied prospectively all patients with burns who were admitted to our unit between January 1993 and December 1999, who were mechanically ventilated. The local ethics committee approved the study. Severely burned patients are operated on the first or second day and some patients have only temporary compromise of the upper airway. Those patients who were ventilated for fewer than 48 h were considered not to have been ventilated for primary pulmonary reasons and were excluded from further analysis. Patients who died within the first 2 days or were subject to “do not resuscitate” orders were also excluded. Age, sex, total body surface area burned (TBSA%, estimated by the rules of nines [9]), full thickness burn area (FTB%), duration of mechanical ventilation, PaO2:FIO2 ratios, and outcome were recorded in accordance with a protocol and were entered prospectively in the computerized database of our unit [10].

2.1. Burn treatment and supportive intensive care

Resuscitation was according to the Parkland formula, using 4 ml/kg/TBSA% if the TBSA% exceeded 10%. Diuresis (0.5–1.0 ml/kg h) and mean arterial pressure (>70 mmHg) were used as endpoints [11]. Intubation and mechanical ventilation were started if there was evidence of respiratory failure and hypoxemia, reduced level of consciousness, deep sedation and analgesia necessary for burn care, compromise of the airway, or circumferential burns of the neck or face. Mechanical ventilation included pressure cycled ventilation, PEEP of between 5 and 10 cm H2O, and peak inspiratory pressures of less than 35 cm H2O. All excisions and grafting operations were done within 24–36 h. Patients who did not seem to have deep burns at primary examination were re-evaluated daily and operated on if full thickness burns were identified. Wounds were covered by autologous grafts when available or for extensive burns by either heterologous grafts for temporary cover or in special cases by cultured keratinocytes.

2.2. ARDS

ARDS was diagnosed in each patient using the American-European consensus conference criteria (acute onset, bilateral infiltrates on chest radiographs, absence of clinical evidence of left atrial hypertension, PaO2:FIO2 ratio < 200 mmHg) [1]. Arterial blood gases were recorded at least every 8 h in all patients. Chest radiographs were taken at initial examination and repeatedly during further treatment if there were ventilatory problems or insertion of central venous catheters.

2.3. Multiple organ failure score

Multiple organ dysfunction scores (MODS) were calculated 3 times a week as described by Marshall et al. [12]. Laboratory and clinical data were recorded according to a preset clinical protocol and thereafter extracted from patient charts. The worst score during the treatment period was used for the calculations. Unfortunately, the Glasgow coma scale, which is necessary for evaluating neurological dysfunction for calculation of MODS, is not used in our country. Considering that most patients were deeply sedated at least temporarily, patients with no neurological deficit before they were intubated or after they had been weaned from mechanical ventilation were given the score 0 for neurology [12].

2.4. Inhalation injury

There is no consensus about the diagnosis of inhalation injury [13,14]. We used a simplified score in which we included the most important indicators of inhalation injury that have been described by several investigators [5,15,16]. The inhalation lung injury score (ILIS) was calculated from data at the time of admission. The following variables were scored and given one point each: (a) burn occurring indoors; (b) facial burn; (c) visible soot in the airways or a substantial mucosal inflammatory reaction noticed during either tracheal intubation or bronchoscopy; (d) raised concentrations of carbon monoxide (COHB) or cyanide in the blood. The maximum score was four points.

2.5. Statistical analysis

Data are presented as mean or median and range. Risk factors were identified using logistic regression with ARDS (development, early/late onset) as the dependent variables. Independent factors examined were TBSA%, FTB%, MODS, ventilator days, ILIS, age. Chi-squared analysis was used for nominal data. Statistical analyses were made by Statistica™ software (Statsoft, Tulsa, OK, USA). The level of significance was p < 0.05.

3. Results

Between 1993 and 1999, 553 patients with burns were admitted to our unit. Mean TBSA% was 13.3% and median 7.0%. FTB% was 4.8% (mean) and 0.5% (median). A total of 137 patients were mechanically ventilated. Forty-six failed the inclusion criteria and were not further considered. In the remaining 91 (Tables 1 and 2) the mean TBSA % was 31% (median 26%) and 80 patients had full thickness burns with a mean FTB % area of 15% (median 9%). Eight patients died (9%). The mean duration of mechanical ventilation was 14 days (range 3–74).

Thirty-six patients (40%) developed ARDS. Their mean PaO2:FIO2 ratio was 118 mmHg at onset of ARDS. Patients with ARDS stayed longer on ventilatory support (24 compared with 9 days, p < 0.001). A correlation was found between ARDS and MODS (p < 0.01), whereas age did not
correlate \((p = 0.14)\). Mortality tended to be higher in the ARDS group (14\% versus 6\%; \(p = 0.20\)).

The mean ILIS was not different comparing patients with and without ARDS \((p = 0.56)\). The mean time to onset of ARDS was 6.5 days (median 3.5). Most \((n = 25, 70\%)\) of the patients developed ARDS within 6 days, but it could develop up to 30 days after the burn (Fig. 1). We did not find any striking differences between early and late ARDS (Table 3).

### 4. Discussion

Our results confirm the findings of Dancey et al. [4] who reported that ARDS is common in patients with burns, and leads to longer periods requiring ventilatory support. The new findings of the present study are that ARDS emerged rather early (70\% in fewer than 6 days and median 3.5 days after the burn). ARDS seems to be not, or only partially related to the TBSA\%, FTB\% or age. In agreement with the data of Dancey et al. [4], we found no association between ARDS and inhalation injury. Contrary to their data, we found a strong correlation between development of ARDS and multiple organ failure. Despite this correlation, mortality of ARDS was low in our study (14\%), which contrasts the findings of Dancey (42\%). Furthermore, only 25\% of their patients developed ARDS before day 6 [4].

Little is known about the pathogenesis of human ARDS in burns. We assume that the massive inflammatory reactions that occur as a result of severe burns are a major reason for the development of ARDS, presumably together with infection and sepsis [2,5,16–21]. Massive pulmonary infiltration of leukocytes, interstitial and intra-alveolar...
edema, intra-alveolar hemorrhage, and severe destruction of the alveolar structures are important responses to peripheral burns even without smoke [22–24]. The injured endothelial–epithelial barrier is an important prerequisite for ARDS. Increased permeability causes alveolar flooding, inactivation of surfactant, increased alveolar surface tension and, finally, reduced compliance of the respiratory system [2,25]. Loss of epithelial integrity promotes bacterial translocation, bacteremia, and sepsis [26]. Thus, a multi-factorial etiology of ARDS in burn patients with probable promoters such as systemic inflammatory response possibly together with effects of inhalation injury and, at a later stage, pneumonia, other infections and ventilator-induced complications seems plausible.

4.1. Inhalation injury

We examined the correlation between inhalation injury and ARDS. There is strong evidence particularly in animal models that inhalation injury results in increased oxygen demands, increased extravascular lung water from increased microvascular permeability, and increased fluid transport across the endothelial–epithelial barrier [17,27]. In sheep, Alpard et al. [28] found a correlation between the incidence of ARDS and increasing doses of inhaled smoke in combination with cutaneous burns.

A problem with inhalation injury as a predictor of clinical outcome is its poor definition. Many methods have been suggested for confirming the diagnosis but so far there is little uniformity in the measurements or definitions used. Among other diagnostic features bronchoscopy together with biopsies has been suggested as superior in the prediction of respiratory complications [13]. In our unit, we did not subject every patient to fiberoptic bronchoscopy and no patients had biopsies. Our patients had an estimation of a probable inhalation injury using the ILIS. The variables used add to the probability of inhalation injury and the most significant factors in previous scores were chosen for this study [5,15,16]. However, there is a potential drawback of this score as carbon monoxide or cyanide may be falsely too low when the patient arrives late at the hospital (patients with the most extensive burns are often referred from long distances) or because of aggressive oxygen treatment during transport. This may partly explain why we did not find significantly higher inhalation injury scores in the patients that developed ARDS. Our findings, however, support the results of Dancey et al., [4] who also were unable to identify a correlation between ARDS and inhalation injury.

It is sometimes assumed that the combination of large burns and inhalation injury would elicit ARDS, which, however, could not be confirmed by our results. In this respect, it seems important to stress that there were patients that had four points in ILIS and very large TBSA% that did not develop ARDS. A similar finding is presented in the study of Masanes et al. [13] who used bronchoscopy to diagnose inhalation injury. They reported that fewer than 50% of the patients with the diagnosis of inhalation injury developed ARDS. In those who did develop ARDS, mortality was 19%, which is in the range of our findings.

It also parallels our clinical impression that pulmonary complications and ventilatory problems resulting from inhalation injury can be predicted only to a limited extent for the individual patient by risk factors as used in this study.

4.2. Multiple organ failure

Multiple organ failure was a more common finding in the ARDS group. Surprisingly, incidence of multiple organ failure did not differ in early versus late ARDS. Early mortality from ARDS is commonly attributed to the underlying disease, whereas ARDS patients dying later frequently suffer and die from multiple organ failure [29]. Therefore, we initially expected an association between multiple organ failure and late ARDS. Interestingly, the increase in organ failure scores paralleled the development of ARDS, i.e., occurred early postburn. It was astonishing that ARDS developed so early postburn, reducing the likelihood of overt infection and sepsis (which was hardly ever experienced at this early stage in our patients) as possible origins of ARDS. In view of these observations, we hypothesize that the early emergence of ARDS as part of a multiple organ failure scenario could have the burn injury as a common trigger, rather than secondary events such as infection.

The early fulfillment of ARDS criteria may be suggestive of an effect of the permeability changes seen early postburn and/or a consequence of edema formation in the lung from the fluid resuscitation regimen used. However, this seems less likely as it has been shown that pulmonary edema is extremely rare during the resuscitation period even when larger fluid volumes are used [30,31]. The fact that we had no patients with preexisting cardiac failure in the group (medical charts reviewed) is further reducing the likelihood of pulmonary edema. Moreover, during the last 2 years of our study the PiCCO system (Pulsion, Munich, Germany; the same as used by Holm et al., [31]) was used without identifying a single patient with increased extravascular lung water early postburn. Another argument is that there was no correlation between the TBSA% and the development of ARDS, which should be the case if the acute respiratory failure was due to pulmonary edema as a result of the fluid overload rather than ARDS. Furthermore, a fluid overload would hardly induce or explain the multi-organ failure.

4.3. Outcome

Another important finding of our study is that mortality in patients with ARDS was only 14% and not significantly higher than in those without ARDS. This is in contrast to other studies, which showed that both inhalation injury and ARDS carry high mortalities. Dancey et al. [4], for example, found a mortality of 42% in patients with ARDS.
Contributing to these differences may be that we excluded patients on “do not resuscitate” orders. However, this should be of minor importance when considered against the fact that mean burn size in the group studied by Dancey et al. [4] was almost identical to ours and the FTB% were even higher in our study.

The favorable outcome of our study is in line with outcome data from other trauma patients with ARDS. Recent data have suggested that the mortality of patients with ARDS depends on the underlying disease rather than the ARDS itself [29,32,33]. Consequently, it may be hypothesized that burn and other trauma patients have a lower mortality from ARDS whenever they survive the initial “shock event”, because they subsequently benefit from the more “curable nature” of their ARDS triggering illness.

4.4. Mechanical ventilation

We found a strong correlation between the duration of ventilatory support and the development of ARDS. This is not surprising as ARDS usually necessitates ventilatory support. Furthermore, mechanical ventilation itself may further complicate lung injury. Ventilator associated pneumonia (VAP) is one of the most common complications of mechanical ventilation, and burned patients are at even higher risk of VAP than patients with neurological diseases or trauma [6,34]. Maintenance of sufficient oxygenation and alveolar ventilation in burned patients often requires increased minute ventilation because of the injured endothelial–epithelial barrier, respiratory mechanics, and the hypermetabolic state, which increases CO₂ production. Increased ventilation has been traditionally achieved by large tidal volumes and high peak pressures, which further aggravate lung injury. [2,7,8]. Newer studies have shown that mechanical ventilation with small tidal volumes and lower peak airway pressures significantly improves the outcome of patients with ARDS [8,35]. However, mechanical ventilation in our unit has always been used according to prevailing international guidelines, so we do not think that factors related to mechanical ventilation have biased our results. Furthermore, an important finding in the present study was that ARDS developed early (median 3.5 days). This finding significantly reduces, at least from the theoretical perspective, the risk that the ARDS development was an effect of the ventilatory strategy.

4.5. Limitations of our study

One major limitation of this single center study is the relative small number of patients examined. Tendencies towards correlation between ARDS and clinical variables such as TBSA%, FTB% and age may have reached significance if a larger patient population had been accessible.

5. Conclusions

In conclusion, ARDS is common among patients with thermal injury who require mechanical ventilation and usually occurs early (median 3.5 days). The mortality is low and pathogenesis is still not clear. Our findings, however, support a multi-factorial etiology. An intense systemic inflammatory response to the burn injury, possibly augmented by infection, sepsis, and genetic predisposition, seems plausible to us. Although our findings do not support inhalation injury as a significant trigger of ARDS, further studies, more precisely diagnosing inhalation injury, should be conducted to clearly define its role in the development of ARDS.

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