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ARDS in patients with thermal injury

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Abstract *Objective:* To determine the time to onset of the adult respiratory distress syndrome (ARDS) in patients with thermal injury requiring mechanical ventilation. Secondarily, to consider the burn-related risk factors, demographics, incidence, and mortality for ARDS in this population.
Design: Retrospective chart review; ARDS defined according to the American-European Consensus Conference and the Lung Injury Severity Score definitions.
Setting: Regional, tertiary referral, adult burn unit in a university teaching hospital.
Patients and participants: Patients with thermal injury requiring mechanical ventilation, admitted between 1 January 1991 and 28 February 1995.
Interventions: None.
Measurements and results: Of 469 consecutive admissions, 126 (26.9 %) received intubation and mechanical ventilation. ARDS was defined according to the American-European Consensus and Lung Injury Severity Score (score > 2.5) definitions. The mean time to onset of ARDS from admission to the burn unit was 6.9 ± 5.2 and 8.2 ± 10.7 days when defined by the American-European Consensus and Lung Injury Severity Score definitions respectively ($p = 0.41$). Of the intubated patients, 53.6 and 45.2 % developed ARDS according to the American-European Consensus and Lung Injury Severity Score definitions, respectively ($p = 0.19$). Using multivariate logistic analysis, only age proved to be an independent risk factor for the development of ARDS ($p = 0.03$), although there was a trend toward an increased incidence of inhalation injury in patients with ARDS. Mortality was not significantly greater (41.8 vs 32.2 %) in those with ARDS compared to those without ($p = 0.27$).
Conclusions: According to the American-European Consensus Conference and the Lung Injury Severity Score definitions, ARDS is common in the adult burn population and has a delayed onset compared to most critical care populations. We found age to be a major predisposing factor for ARDS.

Key words Adult respiratory distress syndrome · Mechanical ventilation · Thermal injury · Burn · Inhalation injury · Incidence · Time to onset

Introduction

The adult respiratory distress syndrome (ARDS) was first described just over three decades ago [1] as a syndrome characterized by stiff lungs, hypoxemia, and bilateral infiltrates on chest X-ray. A number of physiological alterations and disease states are risk factors for the development of ARDS [2]. Among the less common

Table 1 Definitions of ARDS (*ARDS* adult respiratory distress syndrome, *PaO_2/FIO_2* arterial oxygen tension/fractional inspired oxygen concentration ratio, *PEEP* positive end-expiratory pressure, *PAWP* pulmonary arterial wedge pressure)

Definition	Criteria
American-European Consensus	1. Acute onset 2. $PaO_2/FIO_2 \leq 200$ (regardless of PEEP level) 3. Bilateral infiltrates seen on frontal chest radiograph 4. PAWP ≤ 18 (when measured) or no clinical evidence of left atrial hypertension
Lung Injury Severity Score[a]	1. Chest radiograph score (number of quadrants with alveolar consolidation from 0–4) 2. Hypoxemia score ($PaO_2/FIO_2 \geq 300$, 225–299, 175–224, 100–174, < 100) 3. PEEP score (≥ 5, 6–8, 9–11, 12–14, ≥ 15 cm H_2O) 4. Respiratory system compliance score (≥ 80, 60–79, 40–59, 20–39, ≤ 19 ml/cm H_2O)

[a] To calculate the Lung Injury Severity Score, a score from 0 to 4 is assigned to each criteria and then the individual scores are added. The aggregate sum is divided by the number of components used. ARDS is defined as a score > 2.5

predisposing factors are thermal injury and inhalation injury [3, 4, 5], which have accounted for 2.0–9.2 % of patients with ARDS in various studies [3, 4]. The percentage of patients with thermal and/or inhalation injury who go on to develop ARDS is somewhat controversial, varying from 1.8–17 % [3, 6, 7, 8, 9, 10, 11]. This controversy is in part due to the fact that most studies do not state explicit criteria for their definition of ARDS [6, 7, 8, 9, 10]. The time to onset of ARDS in most nonthermally injured populations is 12 to 72 h after admission to the intensive care unit (ICU) [3, 12, 13]. A delayed onset, however, has been observed in previous studies looking specifically at thermal injury as a risk factor for ARDS [7, 14].

The Lung Injury Severity Score and the American-European Consensus definitions are generally accepted definitions of ARDS. The former, developed in 1988, is commonly used in the critical care setting [15]. The latter, developed in 1994, is considered to be the standard definition for future studies of ARDS, to facilitate comparison of data among centers [16]. To our knowledge, neither definition has been applied to studies of ARDS in patients with thermal injury. In light of these issues, this study was undertaken primarily to determine the time to onset of ARDS using these two definitions, and secondarily to identify risk factors, incidence, and mortality for ARDS in the adult burn population.

Materials and methods

Subjects

After approval from our institution's research ethics committee, we analyzed data from a database of 501 consecutive admissions to an adult regional burn center (Wellesley Hospital, Toronto, Ontario) between January 1991 and February 1995. From this database, we identified all patients who received intubation and mechanical ventilation. Patients were excluded if the charts were unavailable or the data were incomplete.

Measurements

The data extracted from the hospital charts included age, gender, hospital survival, the presence of inhalation injury, total body surface area burned (estimated according to the Rule of Nines [17]), and the presence of full thickness burn. The latter two were determined by the admitting physician. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score and the multiple organ dysfunction (MOD) score were measured on day 1 [18, 19]. Ventilation parameters [arterial blood gases, peak inspiratory pressure (PIP), positive end-expiratory pressure (PEEP), tidal volume (V_T), fractional of inspired oxygen (FIO_2), total respiratory system compliance (V_T/PIP-PEEP)] were recorded every 8 h. When available, pulmonary capillary wedge pressure (PCWP) was recorded. Daily chest radiographs were reviewed and divided into quadrants using a vertical line along the spinous processes of the vertebral column, and a horizontal line from the midpoint of the hilum to the chest wall, within each hemithorax. The number of quadrants containing alveolar and/or interstitial infiltrates was recorded. Inhalation injury was defined according to Shirani et al.'s multiple logistic equation, which takes into account age, presence or absence of facial burn, injury in a closed space, and total burn as a percent of total body surface area [20]. The formula determines a probability from 0.1 to 1.0 that a given patient has sustained an inhalation injury and has been shown to correlate well with bronchoscopy and/or ^{131}xenon lung scan in 1058 patients with thermal injury [20]. Using this formula, a priori we arbitrarily chose a probability of ≥ 0.85 to define inhalation injury.

ARDS was defined according to both the American-European Consensus definition and/or the Lung Injury Severity Score (Table 1). All components were required in order to define ARDS according to the American-European Consensus definition, and a score of > 2.5 was used to define ARDS according to the Lung Injury Severity Score [15, 16].

The primary endpoint was the time to onset of ARDS from admission to the burn unit. The secondary endpoints included (i) burn-related risk factors and demographics, (ii) incidence, and (iii) hospital survival.

Patient management issues

Patients admitted to our burn unit are treated with initial fluid resuscitation using intravenous Ringer's lactate solution, according to the Parkland formula [4 ml/kg per % total body surface area burned (TBSA)] [21]. Additional fluids are given as necessary to achieve a urine output of 0.5 ml/kg per h. Nutrition is provided us-

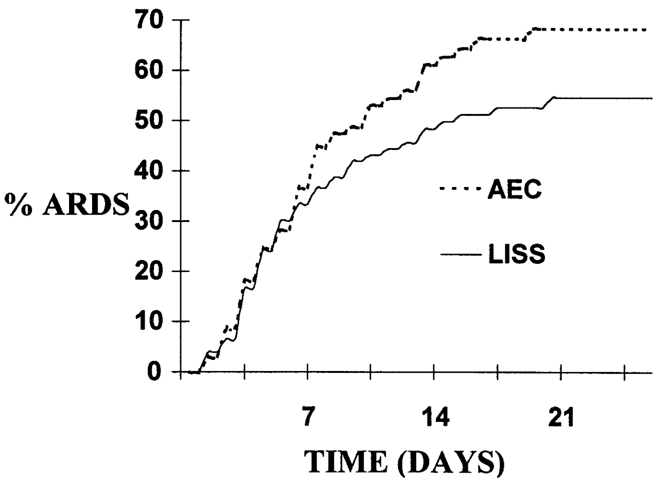

Fig. 1 Cumulative ARDS incidence for intubated patients with thermal injury using either the *AEC* American-European Consensus or *LISS* Lung Injury Severity Score

Table 2 Clinical characteristics of all 126 intubated patients with thermal injury. Patients were identified as having ARDS if they fulfilled either the LISS or the AEC definition (*AEC* American-European Consensus Conference, *LISS* Lung Injury Severity Score, *% TBSA* percentage total body surface area burned, *% FTB* percentage of patients with a full thickness burn, *% ILI* percentage with inhalation lung injury, *APACHE II* Acute Physiology and Chronic Health Evaluation score on day 1, *MOD* multiple organ dysfunction score on day 1)

Variables	All patients ($n = 126$)	ARDS ($n = 67$)	No ARDS ($n = 59$)	p value
Age (years)	46.9 ± 17.9	50.2 ± 16.9	43.2 ± 18.4	0.03
% female	27.0	23.9	30.5	0.40
% TBSA	37.3 ± 25.8	38.6 ± 21.5	35.9 ± 30.1	0.57
% FTB	61.9	59.7	64.4	0.59
% ILI	34.9	40.3	28.8	0.18
APACHE II	17.7 ± 9.0	17.6 ± 7.9	17.8 ± 10.2	0.91
MOD	4.5 ± 2.8	4.4 ± 3.2	4.5 ± 2.4	0.95

ing either oral or enteral feeding. Thermal injury wounds are dressed and treated with topical antimicrobials: silver sulphadiazine, mafenide (alpha-amino-p-toluene sulfonamide monoacetate) or polysporin (polymyxin B sulfate and bacitracin) two to three times per day. Surgical excision of the eschar occurs within 2 to 5 days following the thermal injury. Autografts are used to cover excised wounds. Biobrane (synthetic bilayer with bovine collagen) is used for temporary wound coverage. Finally, donor sites are dressed with scarlet red (oil impregnated fine mesh).

Intubation and mechanical ventilation are provided if the patient has at least one of the following: hypoxemia or respiratory failure; reduced level of consciousness; large sedation or analgesia requirements for burn care; upper airway compromise on admission; circumferential neck or extensive facial burn; and/or a large burn area (> 30 % TBSA). Patients may also receive intubation as a safety measure prior to transfer to the burn unit if a large burn wound is present.

Statistical analysis

Statistical techniques included Student's t-test for continuous variables (i.e., age, length of stay), chi-squared analysis of categorical data (i.e., gender, inhalation injury, presence of full thickness burn), and Kaplan-Meier curve with log rank test for incidence and time of onset of ARDS. Multivariate logistic analysis was performed for burn and demographic-related predictors of ARDS, using age, sex, percentage of total body surface area burned, APACHE II score, MOD score, and the presence of full thickness burn and inhalation injury at day 1 as the independent variables.

Results

Of the 501 patients admitted to the burn unit, 26 charts were unavailable and 6 charts had incomplete data. Of the remaining 469 patients, 126 (26.9 %) received intubation and mechanical ventilation.

The mean time to onset of ARDS was 6.9 ± 5.2 and 8.2 ± 10.7 days from admission to the burn unit, according to the American-European Consensus and the Lung Injury Severity Score definitions, respectively; the difference was not statistically significant ($p = 0.41$). Figure 1 shows the cumulative incidence of ARDS according to each definition. The slopes of both curves are virtually identical and are steepest during the first 7 days of admission.

Table 2 details the age, gender, presence of full thickness burn and inhalation injury, and APACHE II scores at day 1 for the total population, as well as for those with and without ARDS. Of these variables, age was the only independent risk factor for ARDS ($p = 0.03$). Although not statistically significant, there was a trend toward a greater incidence of inhalation injury in patients who developed ARDS (40 vs 29 %, $p = 0.18$).

Sixty-seven patients (14.3 % of the total population and 53.2 % of intubated patients) developed ARDS, according to either one or both definitions. In intubated patients, the percentage of patients who developed ARDS was not different irrespective of which definition for ARDS was used (53.6 vs 45.2 % for the American-European Consensus and the Lung Injury Severity Score definitions, respectively; $p = 0.19$).

Of the 126 intubated patients, the APACHE II score on day 1 was 17.6 in those who developed ARDS compared to 17.8 in those who did not ($p = 0.9$). One hundred and four patients had sufficient data for calculation of MOD score on day 1 and the difference between those who did and did not develop ARDS was not statistically significant (4.4 vs 4.5, respectively, $p = 0.95$).

The mortality for intubated patients was 37.3 % ($n = 47$). The difference in mortality between patients who developed ARDS compared to those who did not was not statistically significant (41.8 vs 32.2 %, respectively, $p = 0.27$).

Discussion

Our results suggest that according to the American-European Consensus and Lung Injury Severity Score definitions, there is a delay in the onset of ARDS in patients with thermal injury. This is in contrast to the majority of studies examining ARDS incidence from all causes, which generally report a mean onset between 12 and 72 h after admission to the intensive care unit [3, 12, 13]. A delay in the onset of ARDS in thermally injured patients has previously been reported. Pruitt et al. found an onset occurring at 5 to 6 days and Tranbaugh et al. at 4 to 24 days [7, 14]. The definitions of ARDS used in these studies varied from the current definitions, thus we felt it was necessary to confirm these findings based on standard definitions in use today.

The reason for this delay in ARDS onset after admission to the ICU is not entirely clear. A potential explanation may be that thermal injury is an indirect cause of ARDS, likely resulting from a systemic inflammatory process which develops over several days. A possible explanation for an apparent delay in onset is that patients with thermal injury are admitted to the ICU at the time of insult. In patients with sepsis, however, the initiating event may occur several days before admission, with ARDS developing soon thereafter. Although we do not have data to rule out confounding causes of ARDS in our patients, complications such as sepsis, aspiration, or pneumonia do occur in patients with thermal injury. The time to develop these complications may create an apparent delay in ARDS onset attributed to thermal injury. For example, in Shirani et al.'s population of 1058 patients with thermal injury, 201 developed pneumonia an average of 11 days after admission [20]. Tranbaugh et al.'s study of 14 patients with thermal and inhalation injuries showed that 4 of 5 cases of ARDS developed as a result of burn wound or pulmonary sepsis, 4 to 24 days after the initial injury [14]. ARDS may develop 12 to 72 h after these complications develop [12], but this can be much later in the course of an admission for thermal injury.

It is interesting that the time to onset of ARDS according to the American-European Consensus and Lung Injury Severity Score definitions were virtually identical. The incidence of ARDS, however, was slightly higher when using the American-European Consensus definition. This difference may be important when ARDS is used as part of the inclusion criteria or outcomes in studies involving patients with thermal injury. In addition, the delay in onset and high incidence in this population may provide a unique opportunity to study treatments that attempt to prevent ARDS. Likewise, this population may be useful in studies attempting to find early markers of ARDS.

Using either definition, we observed an overall ARDS incidence of 14.3% in our patients with thermal injury and 53.2% in the subgroup of patients requiring intubation. Most studies examining the incidence of ARDS in patients with identifiable risk factors have not included burn cases [12, 13, 22]. Garber et al. reviewed 83 articles, examining the incidence and risk factors for the development of ARDS from a variety of causes [5]. Out of 7 articles published using burn injury and/or smoke inhalation as predisposing factors, only 2 articles contained definitions for ARDS, one of which contained just 2 patients with inhalation injury who developed ARDS [3, 11]. The incidence in these 7 articles varied from 1.8 to 17%. Varying or lack of ARDS definitions makes these studies difficult to compare and may explain the discrepancy in the observed incidences.

For example, in 529 consecutive patients with thermal injury (mean total body surface area 26.5 ± 3.4%; mean age 29.3 ± 4.3), Hollingsed et al. found 14 (2.6%) of the patients developed ARDS, with a mortality of 50.0% [11]. They defined ARDS as hypoxemia [arterial oxygentension (PaO_2) < 60 mm Hg with $FIO_2 > 0.60$, or a $PaO_2/FIO_2 < 150$] with PEEP > 10 cm H_2O and diffuse, bilateral interstitial infiltrates on chest radiograph. In another study, Fowler et al. reviewed 993 patients with at least one risk factor for ARDS, which included 87 patients with burn injury (no patient demographics were provided) [3]. The authors found that only 2 burn patients (2.3%) developed ARDS, which was defined as follows: acute respiratory failure requiring mechanical ventilation, a sudden onset of bilateral pulmonary infiltrates on chest radiographs, a PCWP ≤ 12 mmHg, a total static pulmonary compliance of ≤ 50 ml/cm H_2O, and an arterial to alveolar partial pressure of oxygen ratio of ≤ 0.2. In this study, the mean time to onset of ARDS after the initial burn was 6 h, and, similarly, the mortality was 50.0%. Although these studies have many similarities, it is difficult to form many conclusions since different definitions of ARDS were used.

We elected to use more standardized definitions, which to our knowledge have not been evaluated in thermally injured patients, and which may explain why our observed incidence is somewhat higher. As in all studies involving patients with ARDS, the population base must be considered. Compared to Hollingsed et al.'s population, our patients had similarly large burn areas but were much older (mean age 47 years compared to 29 years in Hollingsed et al.'s population) [11]. In our patients, the presence of comorbid illnesses may have predisposed them to longer admissions and to infectious complications, both of which may have impacted on the development of ARDS. We are unable to verify this as data on comorbidities were not obtained. However, the incidence of ARDS in our population using Hollingsed's and Fowler's definitions increased to 19.4 and 25.3%, respectively. These incidences are higher than what we observed, implying that these earlier definitions are somewhat less strict and supports the contention that our patients were sicker and hence more prone to ARDS.

We found only a trend toward inhalation injury being present more often in those patients who acquired ARDS. This may represent a Type II error as a result of our relatively small sample size. However, our findings in relation to inhalation injury need to be interpreted cautiously. To date, there is no gold standard definition for inhalation injury and many different technologies have been tested and reported to have a role in its diagnosis [23–29]. Bronchoscopy and/or ^{131}xenon perfusion scanning are generally considered useful, although both have limitations [23, 30]. We generally perform bronchoscopy for diagnosis of inhalation injury, but retrospectively we were unable to ensure the methodology was standardized. For this reason, we elected to use a previously validated multiple logistic equation that defines inhalation injury [20]. We are uncertain about its sensitivity and specificity in our population. In addition, we arbitrarily defined inhalation injury as a probability ≥ 0.85, which has not been validated. However, the incidence of inhalation injury did not change significantly when we performed a sensitivity analysis using cutoff probabilities from 0.50 to 1.0.

Of the burn-related risk factors and demographics evaluated in our study, only age proved to be an independent predictor of ARDS. Both age and increased burn size have been described as risk factors for ARDS [6, 31, 32], and both have recently been shown to be independent predictors for mortality in patients with burn injuries [33]. By contrast, Hollingsed et al. were unable to show either age or burn size as risk factors, although a trend was seen [11]. Older patients may be more susceptible to ARDS because of comorbid disease causing impaired organ function. Saffle et al. studied 529 patients with thermal injury and observed that the number of organs failing increased dramatically from 28.6 % in patients less than 40 years of age to 68.8 % in those over 40 years of age [32]. The lungs were the most common system to fail, and severe multiple organ failure was frequently seen.

Based on standard definitions of ARDS [15, 16], we found no significant impact of this syndrome on mortality. Given that multiple organ failure has been shown to impact significantly on mortality, and lungs are the most common organ failing, it is interesting that ARDS did not significantly increase mortality in our patients [19]. Similar mortality rates have been reported in other studies of burn patients with ARDS, but without comparison to those without ARDS [11, 34]. For example, Hollingsed et al. reported a mortality of 50 % in patients with thermal injury and ARDS [11]. In patients with respiratory failure (defined as multiple episodes of pneumonia; intubation for at least 10 days or tracheostomy; $FIO_2 > 0.60$; or ARDS) the mortality increased from 3 to 40 %. In studies of ARDS from a variety of causes, it has been shown to have a significant impact on mortality [13, 22]. For example, Hudson et al., in a study of 695 patients admitted to an intensive care unit, reported a mortality of 62 and 19 % ($p < 0.005$) in those with and without ARDS from all causes, respectively. However, the mortality varied according to the etiology of ARDS. When associated with sepsis, for example, the difference between those with and without ARDS decreased to 69 vs 49 %, respectively [13]. When ARDS from all causes is considered, it is uncommon for patients to die from respiratory failure; most die as a result of multiple organ failure [22]. This may partly explain why ARDS did not significantly impact on the mortality of our patients. In support of our finding, Darling et al. have reported that patients with thermal injury most commonly die as a result of multiple organ failure, rather than solely from respiratory failure [35].

Based on the American-European Consensus and the Lung Injury Severity Score definitions of ARDS [15, 16], we found that in mechanically ventilated, thermally injured patients, ARDS is quite common and its onset is delayed, occurring approximately 1 week after the initial injury.

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