Role of Lung Contusions on Posttraumatic Inflammatory Response and Organ Dysfunction in Traumatized Patients

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Abstract

Background: Multiple trauma is often accompanied by lung contusion leading to secondary pulmonary inflammation and organ dysfunction. The particular role of lung contusions on the systemic inflammatory response remains unclear. Therefore, the aim of the present study was to compare the degree of lung contusion with markers of inflammation and multiple organ failure (MOF) in trauma patients.

Methods: According to the Injury Severity Score (ISS), 45 patients were assigned to a low (< 25 points) and a high ISS group (> 25 points), respectively. Both groups were subdivided into minor and major lung injury groups as defined by computed tomography (CT) scan. Plasma levels of interleukin 6 (IL-6), interleukin 8 (IL-8), tumor necrosis factor (TNF) receptors, C-reactive protein (CRP), and polymorphonuclear (PMN) elastase were assessed, as well as the Murray lung score (MLS) and the MOF score.

Results: Patients with low ISS present moderate activation of inflammation which is not influenced by the degree of lung contusion. In contrast, patients with a high ISS develop significant posttraumatic inflammation and MOF. Patients with high ISS and severe lung contusions present significantly higher MLS and MOF scores. Interestingly, patients of the high ISS group without severe lung contusions develop a similar degree of MLS and MOF only after 5 days following the traumatic insult. However, the initial plasma levels of IL-6 and IL-8 differ significantly in this group.

Conclusion: Our data show that severe lung contusions contributes to an immediate onset of posttraumatic inflammation in severely traumatized patients, resulting in MOF, while in severely injured patients without lung contusion, this development requires up to 5 days.

Key Words
Lung contusion · Multiple trauma · Multiple organ failure · SIRS · CT diagnosis · Respiratory dysfunction · Cytokines

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Introduction

The majority of patients suffering from multiple trauma exhibit a pattern of a generalized inflammatory response referred to as systemic inflammatory response syndrome (SIRS) [1]. Consequently, many patients develop dysfunction and failure of one or more organs, hence, defined as multiple organ dysfunction syndrome (MODS) or multiple organ failure (MOF) [2]. Several studies have shown the impact of thoracic trauma as one of the determining factors for posttraumatic organ dysfunction, in particular of the lung [3, 4]. In contrast, it has been shown that the overall degree of injury seems to be more important for the manifestation of MOF [5, 6]. Thus, the relevance of lung contusion with additional multiple trauma with respect to the manifestation of MOF remains unclear.

On admission, lung contusions cannot be reliably estimated by means of standard radiographs, since

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radiological signs on chest radiographs do not appear within the first several hours after blunt chest trauma [7]. Early positive chest radiographs, however, might be of prognostic significance [8]. It has been shown that chest CT scans allow for the early detection of all types of thoracic lesions after trauma, including lung contusion [9]. The short acquisition time of spiral CT facilitates the diagnostic of severely traumatized patients unless immediate bleeding control is required [10].

Posttraumatic SIRS is currently recognized as a complex process involving numerous humoral and cellular mediators, thus, leading to manifestation of temporary or permanent organ dysfunction (MOF) [11]. Despite the fact that the significance of plasma levels of inflammatory mediators remains obscure, some markers have been used to describe systemic inflammation and different patterns have been observed according to the manifestation of MODS [12]. The following parameters may, therefore, reflect the degree of systemic inflammation after trauma: (1) interleukin 6 (IL-6), a major determinant of the acute phase response [13]; (2) interleukin 8 (IL-8), which has a major importance for the recruitment of leukocytes during systemic inflammation and pulmonary complications [14]; (3) the 55-kD soluble tumor necrosis factor (TNF) receptor, which is associated with the degree of TNF release [4]; (4) C-reactive protein (CRP) as an accepted marker of inflammation and major acute phase protein; and (5) polymorphonuclear (PMN) elastase, as a leukocyte-derived protease roughly indicating granulocyte activity after trauma [15].

The aim of the present study was to evaluate the role of lung contusions assessed by spiral chest CT scans during admission on posttraumatic inflammation and organ failure. The impact of lung contusion was correlated with the overall degree of trauma (Injury Severity Score [ISS] < 25 vs. ISS > 25). Inflammatory markers, pulmonary function, and MOF were monitored for 14 days.

Materials and Methods

Patients

Forty-five consecutive patients were enrolled in this study. Inclusion criteria were: (1) age above 18 years; (2) clinical evidence of thoracic trauma with an Abbreviated Injury Scale (AIS) for thoracic injuries of at least 2 points or (3) multiple trauma with an ISS of at least 16 points [16]; (4) spiral chest CT performed on admission. Patients with acute hemorrhage requiring immediate operation were not included due to the missing chest CT scan.

Study Groups

Patients were grouped according to their lung injury and the severity of trauma. Multiple trauma with risk of MOF was assumed if the ISS was equal to or higher than 25 points, as described previously [17]. Severe lung contusion was considered if more than seven segments showed signs of contusion, which is reflected by a CT-based Lung Injury Score (CT-LIS) of greater than 4 points. Thus, the following groups were established as shown in table 1: group 1 (ISS < 25 and CT-LIS < 4), group 2 (ISS < 25 and CT-LIS ≥ 4), group 3 (ISS > 25 and CT-LIS < 4), group 4 (ISS > 25 and CT-LIS ≥ 4).

Clinical Monitoring

In all patients, standard diagnostic procedures, including anterior-posterior chest radiographs, as well as primary surgical treatment and intensive care therapy, were performed according to the institutional standards. During a follow up of 14 days, laboratory evaluations and clinical assessment, including the Murray lung score (MLS) and the MOF score according to Goris, were performed [18, 19]. In addition, plasma samples were taken every morning and frozen at –80°C for the assessment of cytokines. On admission to the intensive care unit (ICU), the ISS was assessed.

Radiographic Evaluation

In all patients, spiral chest CT scans were performed within 2 h after admission on a Siemens Computerto-

Table 1 Study groups. The 45 patients were divided into four groups based on the Injury Severity Score (ISS) and the computed tomography (CT)-based Lung Injury Score (CT-LIS). The number of patients, age, CT-LIS, ISS, and non-survivors are given as mean ± standard error of the mean (SEM).

Group	Patients (n)	Age (years)	CT-LIS (points)	ISS (points)	Death (n)
1 (ISS < 25; CT-LIS < 4)	11	40.6 ± 5.8	1.6 ± 0.25	15.6 ± 1.5	0
2 (ISS < 25; CT-LIS ≥ 4)	8	41.6 ± 5.6	4.9 ± 0.23	18.4 ± 1.5	0
3 (ISS > 25; CT-LIS < 4)	7	37.9 ± 4.9	2.0 ± 0.45	33.0 ± 5.8	0
4 (ISS > 25; CT-LIS ≥ 4)	19	41.1 ± 3.9	5.2 ± 1.39	40.6 ± 2.35	5

Table 2 Spiral chest CT-LIS. On the basis of Murray et al. [18], a simplified CT-LIS was used. Lung injury was defined by points from 0 to 4 for each lung side independent of the CT-evaluated number of contused segments.

Score points	Number of segments with contusion
0	No contusion
1	1–2 segments
2	3 segments
3	4–7 segments
4	> 7 segments

mograph (Somatom plus). Spirals of 25 s duration were performed in all patients, allowing to investigate 25 cm of the thorax. Chest CT scans were printed immediately for clinical use and saved onto a laser disc for later off-line evaluation by a radiologist. The images of the patients were presented in a random sequence to ensure that the radiologist was blinded to the identity and the clinical status and diagnosis of the subject. Lung contusion was classified according to the number of lung segments showing signs of traumatic injury, e.g., disruption of the parenchyma, hemorrhage, or atelectasis. Hence, a CT-LIS was calculated in order to describe the overall degree of lung contusion (Table 2). According to this specification, maximal lung contusion was established with 4 points for each side.

Laboratory Evaluations

Plasma samples were taken daily and stored at –80°C for later analysis. The sampling of plasma probes and the determination of additional inflammatory markers was approved by the local Ethics Committee.

PMN elastase and CRP were determined using the Hitachi 717 Autoanalyzer. PMN elastase was measured using the IMAC immunoassay (Merck, Darmstadt, Germany). In brief, the formation of aggregates of serum elastase with antibody fragments against human PMN elastase and horseradish peroxidase was tested. The peroxidase catalyzes the reaction of detectable quinoneimine dye formation. CRP was tested using the Time Quant kit (Boehringer, Mannheim, Germany) measuring CRP antigen-antibody complexes.

The IL-6 and IL-8 levels were measured by an enzyme-linked immunosorbent assay (ELISA), as described earlier [20]. Briefly, micro titer plates were coated overnight with mouse antibodies (IL-6: 5E1, IL-8: 3H7) in different solutions with phosphate-buffered saline (PBS) for each ELISA. For saturation, PBS and 1% bovine serum albumin (BSA) was used. International standards for IL-6 and IL-8 were obtained from the National Institute for Biological Standards and Control of the WHO (IL-6: recDNA HUMAN TYPE Code 89/548; IL-8: recDNA HUMAN TYPE Code 89/520; NIBSC, Hertfordshire, UK). The incubation time was 2 h for both assays. As a secondary antibody, biotinylated rabbit antibodies were applied with an incubation time of at least 1 h. Next, streptavidin peroxidase, the anti-rabbit conjugate, was added and incubated for 1 h at room temperature. For the substrate, equal volumes of 3,3′,5,5′-tetramethylbenzidine (TMB)-peroxidase and peroxidase solution B were used. After 5 min, the color reaction was stopped by adding 1 M H_2SO_4. The absorption was measured at 450 nm, blank with air, using the Dynatech MR5000 photometer (Dynatech GmbH, Denkendorf, Germany). Circulating cytokines and soluble TNF-α receptors were determined bulkwise from frozen plasma samples applying ELISA techniques on 96-well Immuno MaxiSorp plates (Dynatech MR5000 photometer, Rückersdorf, Germany): TNF-R1 and TNF-R2 were quantified as described by Leeuwenberg et al. using either mAB MR1-1 (anti-TNF-R55) or mAB MR2-2 (anti-TNF-R75) to cover the immunoassay plates (25). After adding the plasma samples, incubation with specific biotin-labeled rabbit anti-sTNF-R antiserum followed. Further analysis was analogous to the above described quantification of IL-6 and IL-8. The detection limit for both receptors was 100 pg/ml.

Statistical Analysis

All data are expressed as mean ± standard error of the mean (SEM). The Shapiro-Wilk test of normality and Levene's test for the homogeneity of variances were performed. The Kruskal-Wallis test and analysis of variance (ANOVA) post-hoc tests were applied to test significant differences between groups. Significant differences were considered at a p-value < 0.05.

Results

Patients and Clinical Course

Forty-five patients were enrolled in this study. The mean age of the patients was 40.5 ± 2.5 years, ranging from 18 to 73 years. The average ISS of all of the patients included was 29.1 ± 2 points, and the mean CT-LIS was 3.7 ± 0.3 points. The patients were allocated into the four subgroups according to their ISS and CT-LIS as indicated in table 1. The 28-day survival rate was 89% and all of the five non-survivors were of group 4 with the highest ISS and CT-LIS scores.

Pulmonary Function

The MLS indicated significant elevation during the first several days after trauma in severely injured patients with lung injury (group 4) compared to the patients without lung injury (groups 1 and 3) or less severe injury (groups 1 and 2). During the whole observation period, the MLS was not relevantly elevated in groups 1 or 2. However, in patients with ISS > 25 without relevant lung injury (group 3), the MLS increased during the first few days after trauma. After day 3, no significant difference between groups 3 and 4 could be observed (Figure 1).

Multiple Organ Failure

The mean MOF scores in groups 3 and 4 were significantly elevated during the first week of the observation period compared to groups 1 and 2. Severely injured patients with high CT-LIS (group 4) started with high MOF scores, which subsequently declined during the observation period. However, in severely injured patients with low CT-LIS (group 3), the MOF score showed a tremendous increase after day 3 and started to decrease during the second week of the observation period (Figure 2).

Markers of Posttraumatic Inflammation

IL-6 and IL-8 levels were substantially elevated during the first few days after trauma, as depicted in figures 3 and 4. In particular, the values of IL-6 and IL-8 were significantly higher in patients with an ISS ≥ 25 and high CT-LIS (group 4) on day 1 of the observation period. Subsequently, the values of group 3 reached normal to slightly increased values from day 2 onwards. In contrast, the average IL-6 as well as IL-8 values revealed a clear secondary increase during the end of

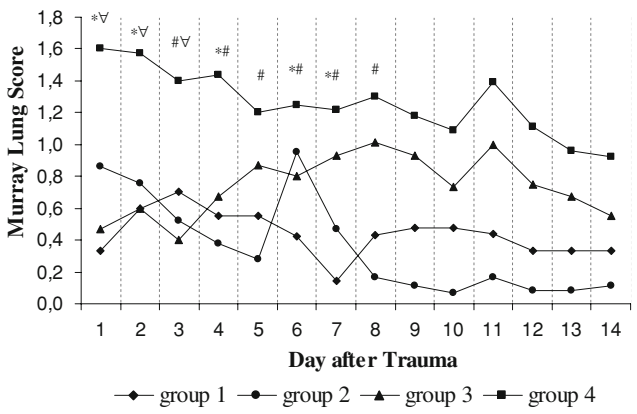

Figure 1. Time course of the Murray lung score (MLS). The *asterisks* denote a significant difference between groups 1 and 4, the *diamonds* denote a significant difference between groups 1 and 3, the *hash symbols* denote a significant difference between groups 2 and 4, the *double dagger symbols* denote a significant difference between groups 2 and 3, and the ∀ symbols denote a significant difference between groups 3 and 4.

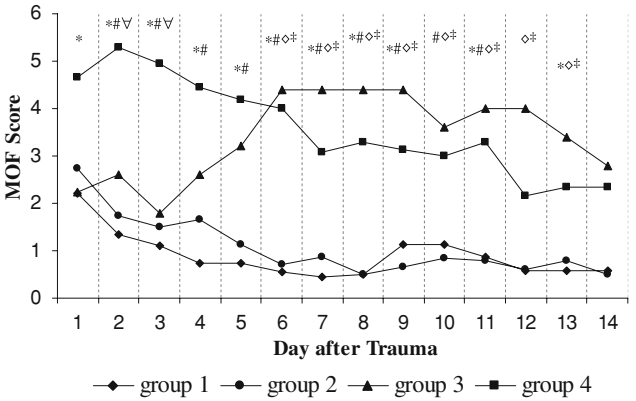

Figure 2. Time course of the MOF score. For definitions of the symbols, see Figure 1.

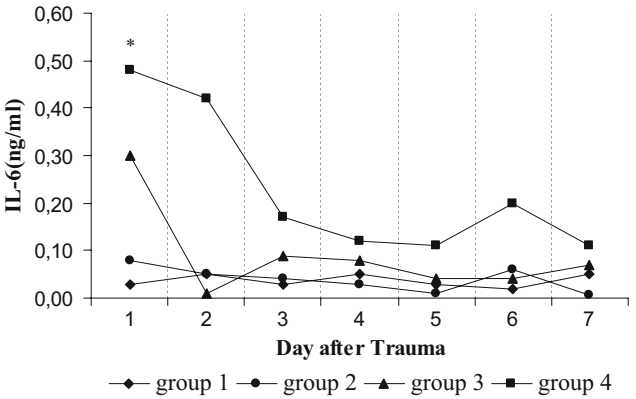

Figure 3. Time course of IL-6 serum levels within the four study groups. For definitions of the symbols, see Figure 1.

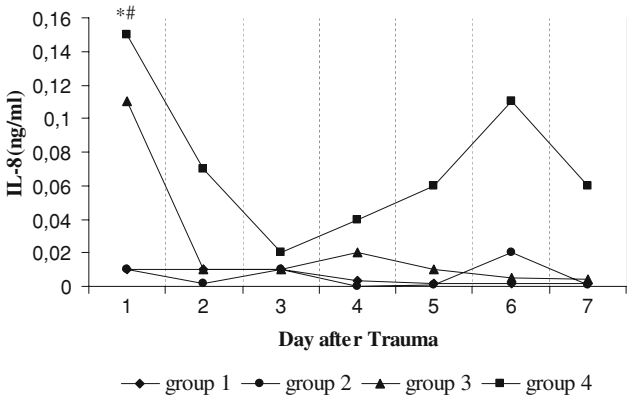

Figure 4. IL-8 time course. For definitions of the symbols, see Figure 1.

the first week in the heavily injured patients when additional lung contusions were present (group 4). In the low ISS groups, only a trend to initially higher IL-6 values due to additional lung contusions (group 2) was noted.

Concerning CRP, elastase and TNF receptors, no significant difference was observed between the groups. The CRP increased in all groups during the first several days, whereas elastase and TNF receptors showed an initial increase and then declined during the first week.

Discussion

Spiral Chest CT and Primary Trauma Management

The purpose of this study was to evaluate the impact of lung contusions on posttraumatic inflammation and organ failure. Since the typical signs of lung contusions on standard anterior-posterior radiographs appear only after several hours following trauma, we employed spiral chest CT scans in all patients on admission to assess lung contusion immediately after admission. The superiority of a conventional chest CT as compared to standard radiographs in respect to the diagnosis of pulmonary injuries such as hemato- and pneumothorax, aspiration, or parenchymal injuries has been described in recent years in a variety of studies [7, 9].

Lung Contusion and Severity of Trauma with Respect to Pulmonary Dysfunction and Multiple Organ Failure

Increased MLS, thus, indicating deteriorated pulmonary function, may be either directly due lung injury or indirectly due to the development of acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) [21]. The data of this study clearly indicate the involvement of both mechanisms in severely traumatized patients leading to lung failure. In group 3 with a high ISS and moderate lung contusion, MLS increased during the first few days after trauma according to the development of a posttraumatic systemic inflammatory process [22]. When substantial lung contusion was part of the trauma (group 4), the MLS was already elevated from the first day after trauma. The trend to a slow recovery of this directly traumatic-induced pulmonary dysfunction towards day 5 was then stopped by the manifestation of ALI or ARDS, similar to the course of MLS in group 3 (Figure 1). Thus, the combination of high ISS and lung contusion caused immediate and lasting alterations of the respiratory function in this particular injury pattern. Group 3, with high ISS but without direct lung contusion, showed a secondary MLS increase after 3 days, thus, demonstrating the inflammatory-based pulmonary dysfunction.

In contrast, the groups with low ISS indicated only moderate early alterations of the MLS with slight secondary deterioration of the MLS. The MLS in group 2 with low ISS and lung contusion showed a rapid decline within a short time period, thus, demonstrating the potential of rapid recovery of lung dysfunction. Hence, as demonstrated in figure 2, isolated lung injury is not a relevant cause for the development of secondary organ dysfunction when the overall degree of injury is below 25 ISS points.

According to the study of Sauaia et al. [17] and Harwood et al. [23], an ISS value of 25 points is associated with a higher risk of development of MOF. The results of this study strongly support this differentiation, indicating significantly higher MOF scores in the groups with high ISS scores. Moreover, the participation of severe lung contusion in the trauma pattern (group 4) led to an increase of the average MOF score compared to severely injured patients without relevant lung contusions (group 3), which was, however, only significant during the first three days, probably due to the direct thoracic trauma. However, minor overall injury severity combined with lung contusion (group 2) did not result in a significant increase of MOF, suggesting that lung contusion does not have a specific influence on the overall manifestation of posttraumatic organ dysfunction [24].

Lung Contusion, Severity of Trauma, and Inflammatory Response

Trauma is understood as a combination of insults which cause a local or generalized inflammation. Severe trauma is often accompanied by whole-body ischemia due to hemorrhagic shock, tissue destruction with necrosis and hypoperfusion, fractures, and organ contusion. This regularly causes local activation of inflammatory processes in order to repair tissue injuries [22]. Major activation of humoral and cellular mediator cascades due to severe injury possibly leading to a systemic inflammatory process contributing to remote organ failure [12]. In this study, PMN elastase, CRP, IL-6, and IL-8, as well as the 55-kD soluble TNF receptor were determined as markers of inflammation and patients developed for all of these parameters a measurable posttraumatic inflammatory response. However, only IL-6 and IL-8 initially showed a significant increase in the severely injured group with lung contusion (group 4), followed by a slight increase at the end of the first week. IL-6, showing a similar pattern of elevation as IL-8, has been established as a posttraumatic

marker of inflammation and has also been related to injury severity and complications [25]. The changes of plasma levels of IL-6 and IL-8 were comparable to those reported by others in trauma patients [4, 26]. Indeed, the initial and secondary high level of IL-8 is consistent with the understanding of the induction of secondary pulmonary failure due to a systemic accumulation of inflammatory cells [27].

While CRP shows an increase in all groups during the first week, elastase and TNF receptors R1 and R2 start with an initial elevation that declines during the first few days after trauma. The systemic concentration of these inflammatory markers was not related to the injury severity and the degree of lung contusion, which are probably also due to the limited number of patients in the group. However, there is evidence that a large amount of the inflammatory mediators is produced by local cells like alveolar macrophages and the endothelium and systemic measurements represent only a vague estimation of the pulmonary injury induced [28–30]. As a consequence, the local state of organ dysfunction and the actual damage might be difficult to estimate, relying on systemic measurements even more, as a number of other factors such transfusion, operation procedures, and individual trauma patterns influence the result. Still, the tremendous impact of severe trauma combined with lung contusion is clinically obvious as five patients died in this group (group 4). To explain the pathophysiological mechanisms, local humoral and cellular interactions need further investigation.

Conclusion

The results of this study indicate that the degree of traumatic injury as expressed by the Injury Severity Score (ISS) is a major determinant of posttraumatic inflammation and organ dysfunction. The presence of a substantial lung contusion involving more than seven lung segments seems to cause immediate respiratory dysfunctions, as well as inflammation-related respiratory dysfunction during the subsequent traumatic course. In patients without relevant lung contusion, pulmonary dysfunction needs up to 5 days to be clinically manifest, indicating the inflammatory origin of the pulmonary dysfunction. When the overall degree of trauma is moderate, however, the presence of lung contusion does not induce a relevant systemic inflammatory response. The severity of injury and the presence of lung contusion seem to be related to organ failure and outcome.

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Conflict of interest statement

The authors declare that there is no actual or potential conflict of interest in relation to this article.

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