

Is Interleukin 6 an Early Marker of Injury Severity Following Major Trauma in Humans?

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Hypothesis: Interleukin 6 (IL-6), a multifunctional cytokine, is expressed by various cells after many stimuli and underlies complex regulatory control mechanisms. Following major trauma, IL-6 release correlates with injury severity, complications, and mortality. The IL-6 response to injury is supposed to be uniquely consistent and related to injury severity. Therefore, we designed a prospective study starting as early as at the scene of the unintentional injury to determine the trauma-related release of plasma IL-6 in multiple injured patients.

Patients and Methods: On approval of the local ethics committee, 94 patients were enrolled with different injuries following trauma (Injury Severity Score [ISS] median, 19; range, 3-75). The patients were rescued by a medical helicopter. Subsets were performed according to the severity of trauma—4 groups (ISS, <9, 9-17, 18-30, and >32)—and survival vs nonsurvival. The first blood sample was collected at the scene of the unintentional injury before cardiopulmonary resuscitation, when appropriate. Then, blood samples were collected in hourly to daily intervals. Interleukin 6 plasma levels were determined using a commercial enzyme-linked immunosorbent assay test. The short-term phase protein, C-reactive protein, was measured to characterize the extent

of trauma and to relate these results to IL-6 release.

Results: As early as immediately after trauma, elevated IL-6 plasma levels occurred. This phenomenon was pronounced in patients with major trauma (ISS, >32). Patients with minor injury had elevated concentrations as well but to a far lesser extent. In surviving patients, IL-6 release correlated with the ISS values best during the first 6 hours after hospital admission. All patients revealed increased C-reactive protein levels within 12 hours following trauma, reflecting the individual injury severity. This was most pronounced in patients with the most severe (ISS, >32) trauma.

Conclusions: To our knowledge, this is the first study that elucidates the changes in the IL-6 concentrations following major trauma in humans as early as at the scene of the unintentional injury. The results reveal an early increase of IL-6 immediately after trauma. Moreover, patients with the most severe injuries had the highest IL-6 plasma levels. There is strong evidence that systemic IL-6 plasma concentrations correlate with ISS values at hospital admission. Therefore, IL-6 release can be used to evaluate the impact of injury early regardless of the injury pattern.

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INTERLEUKIN 6 (IL-6) is obviously one of the earliest and most important mediators of short-term phase response. Based on a recent review of the literature, Biffi et al¹ summarized the properties of IL-6 and characterized its response to injury. There are also clinical studies¹⁻¹³ that describe the IL-6 response to trauma, burns, and elective surgery. Although IL-6 is considered to be a mediator of the physiologic short-term phase reaction to injury, excessive and prolonged postinjury elevations are associated with increased morbidity.

In patients undergoing elective surgery, increased IL-6 levels were detected after skin incision¹² within 90 minutes, lasting for several hours.³ This cytokine release is related to the extent of the surgically induced trauma.^{4,10,14} Following accidental trauma, some researchers¹⁵⁻¹⁷

reported excessively increased plasma levels for many days and demonstrated some correlation with multiple organ dysfunction. Even in patients with an isolated head injury, an IL-6 response is reported.¹⁸

This study elucidates in patients (1) the early changes in IL-6 concentrations in the systemic circulation following major trauma, (2) whether the release and time course of IL-6 reflect the severity of injury, and (3) whether this mediator possesses any predictive value for survival as early as at hospital admission.

RESULTS

The patients (67 men and 27 women) were aged 18 to 70 years (median, 28.5 years). Seventy-six of these 94 patients survived the trauma. Eighteen patients (14 men and 4 women; median age, 39 years) died of severe head injury (n = 6) or major trauma

PATIENTS AND METHODS

PATIENT SELECTION

Following the approval of the All-University Ethics Review Board, 94 patients were enrolled in this study. Exclusion criteria were age younger than 18 or older than 70 years, urgent administration of major intravenous volume resuscitation before the first blood sample was obtained, pregnancy, any metabolic disorder, injuries secondary to acute heart attack or stroke, and the patient's withdrawn consent. No colloids were allowed before the first blood sampling. The resuscitation regimen was the same in all patients, consisting of crystalloids (contained in Ringer lactate solution) and hydroxyethyl starch solution (HAES 200/0.5), and did not differ from the commonly used therapeutic approach.

TRAUMA SCORE

The severity of injury was assessed by the Injury Severity Score (ISS), based on the Abbreviated Injury Scale (AIS).¹⁹ For these post hoc calculations, the ISS assessment was based on the final diagnosis of each patient. To elucidate whether increased IL-6 production is related to the severity of trauma (regardless of the location of the injury itself), patients were divided into 4 groups according to the ISS:

1. Values less than 9, which indicate minor injury (n = 11; 10 men and 1 woman) provided that no AIS value exceeded 2 points (ISS median, 3; range, 2-8).
2. Values from 9 to 17, which indicate medium injury (n = 29; 20 men and 9 women), covering a maximum of 2 AIS values of 3 points (ISS median, 11; range, 9-17).
3. Values from 18 to 30, which indicate severe injury (n = 38; 26 men and 12 women), consisting of a maximum of 2 AIS values of 4 points (ISS median, 27; range, 18-30).
4. Values greater than 32, which indicate the most severe injury (n = 16; 11 men and 5 women) (ISS median, 45; range, 32-75).

PLASMA IL-6 ASSAYS

For IL-6 measurements, 2 mL of peripheral venous blood was collected at the scene of the unintentional

injury, immediately at hospital arrival, at 30 minutes after hospital arrival, at every other hour during the first 12 hours, and at 24, 72, 120, and 240 hours thereafter. Blood was drawn into ammonium-heparinate-coated syringes (Sarstedt, Nümbrecht, Germany). The first sample from the scene of the unintentional injury was immediately processed in the helicopter using an expedition centrifuge (model EBA 6S; Hettich, Tuttlingen, Germany) and stored on ice during the flight. The following samples were spun at 2500g in a refrigerated 4°C centrifuge (model 3K12; Sigma-Aldrich Corp, St Louis, Mo). The plasma was separated, fractionated, and immediately frozen (-70°C) until the time of assay.

Circulating IL-6 levels were measured using a random access chemiluminescence-immunoassay system (IMMULITE IL-6; DPC Biermann GmbH, Bad Nauheim, Germany). The duration of processing was approximately 70 minutes, and the sensitivity was 1 pg/mL (range, 2-2000 pg/mL; reference values, 1-11 pg/mL). The test was standardized according to National Institute for Biological Standards and Control and World Health Organization protocol 89/548.

The plasma concentration of the C-reactive protein (CRP) was measured to estimate the extent of trauma impact on each individual.²⁰ A turbidimetric method was used (Hoffmann-LaRoche, Grenzach Whylen, Germany). Reference values in healthy individuals are below 4 mg/mL.

STATISTICS

All results are presented as mean ± SD or SEM if not indicated otherwise. A nonparametric Friedman 2-way analysis of variance was performed to evaluate differences between groups or in a variable over time. The Wilcoxon signed rank test was used to analyze differences between 2 periods of measurement, and the Mann-Whitney rank sum test indicated specific group differences. An α adjustment according to Bonferroni-Holm was applied when appropriate. Significance was accepted at the 95% confidence level ($P \leq .05$). In addition, the results were analyzed using linear or exponential regression formulas.

(n = 12; thoracic and abdominal injuries with irreversible hemorrhagic shock) within 36 hours of the unintentional injury. The median ISS of the nonsurvivors was higher (37.5 points; range, 25-75 points) than the median ISS of the survivors (17 points; range, 2-48 points).

An analysis of the mean circulating IL-6 plasma levels according to the ISS classification revealed a clear difference between the groups (**Figure 1**). Immediately at the site of the unintentional injury, there were elevated IL-6 concentrations in all 4 subsets, more pronounced in patients with an ISS higher than 18. Patients with minor injuries had a slightly lower IL-6 release compared with patients with severe injuries. Patients with severe and most severe trauma impact displayed continuously increasing plasma levels throughout the first 6 hours of the observation period.

There were group-specific differences concerning the maximum IL-6 production too. Within the first hours af-

ter trauma (from immediately at the site of the unintentional injury to 6 hours later), patients with severe and most severe injury showed clearly increasing plasma levels of IL-6 (eg, for time points immediately at hospital arrival vs 2, 4, and 6 hours later, the ISS was 9-17 vs >32; $P = .03$). In contrast, patients with minor or medium injuries revealed lower IL-6 levels during the first day. Thereafter up to the third day after admission, there was a decrease of IL-6 concentrations in all groups (data not shown).

At hospital admission and 6 hours later, IL-6 plasma levels were related to the individual severity of trauma, expressed as ISS values (**Figure 2**, top and bottom). Because of too few complete data sets of the nonsurvivors, we did not do a correlation analysis in this group so as to differentiate between survival and nonsurvival.

In **Figure 3**, the mean IL-6 plasma levels of the first 12 hours were set against the corresponding ISS values. As outlined before, there is a positive linear relation

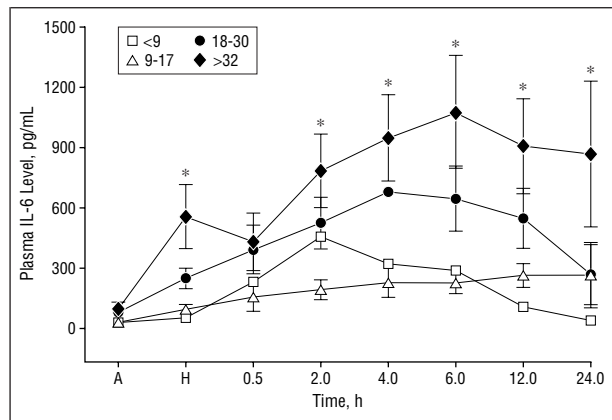


Figure 1. Plasma concentrations (mean \pm SD) of interleukin 6 (IL-6) in 94 patients allotted to 4 groups according to the different trauma impact. The severity of injury was assessed using the Injury Severity Score (ISS): an ISS less than 9 indicates minor injury; an ISS of 9 to 17, medium injury; an ISS of 18 to 30, severe injury; and an ISS greater than 32, most severe injury. The more severely the patients were traumatized, the higher the IL-6 values throughout the observation period. After 4 hours following hospital admission, there is a clear distinction between the 4 groups, with lowest values in patients with minor injuries and maximum concentrations in patients with the most severe trauma. A indicates at the scene of the unintentional injury; H, at hospital arrival; and asterisk, $P = .03$ for the most severe and severe injuries vs medium and minor injuries.

($r = 0.61$) between both variables in survivors during this period. Again, there was no time-dependent correlation analysis performed for the nonsurvivors.

Following major trauma, mean IL-6 concentrations of the surviving patients (ISS, >9 ; $n = 65$) differed from those of nonsurviving individuals ($n = 15$) (Figure 4). In this analysis, minor injuries ($n = 11$) were excluded since there is no risk of any unintentional injury-related death in these patients. The data of another 3 survivors were removed from this analysis because of missing values. At the site of the unintentional injury and during the first 2 hours afterward, we found quite similar IL-6 plasma levels, irrespective of the fate of these patients. Between the 4th and 12th hour after admission, however, differences became statistically evident ($P = .02$). This group difference sustained until death.

Interleukin 6 induces the hepatic synthesis of short-term phase proteins (eg, CRP). C-reactive protein is known to be released in relation to the extent of the tissue damage.²⁰ Regardless of the severity of injury, all subsets revealed an increase in CRP plasma levels starting as late as 6 hours after the injury. The concentration did depend on the ISS values, with the highest levels in the most severely injured patients (Figure 5).

To elucidate if the IL-6 release may be a (very) early and, therefore, better variable to estimate the extent of tissue damage, we set the highest IL-6 concentrations reached during the first 6 hours against the maximum CRP values of the first day after trauma challenge. We found a positive exponential correlation ($r = 0.55$) between both variables. Again, the data of nonsurviving patients were excluded in this analysis (Figure 6).

COMMENT

The patients in this study were classified according to the extent of injury severity, based on the AIS values. The

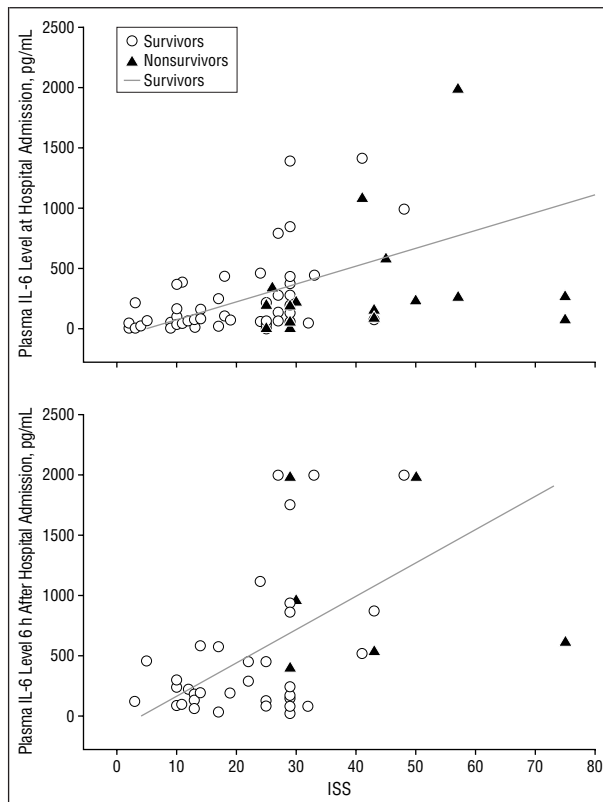


Figure 2. Individual plasma concentrations of interleukin 6 (IL-6) related to the Injury Severity Score (ISS) classification (definitions given in the legend to Figure 1) at hospital admission (top) and 6 hours later (bottom). There is a linear correlation (top: $y = 14.8x - 71.7$, $n = 64$, $P < .001$, $r^2 = 0.27$; bottom: $y = 27.7x - 112.6$, $n = 47$, $P < .01$, $r^2 = 0.25$) between the individual ISS and the IL-6 plasma concentration at either time point in surviving patients.

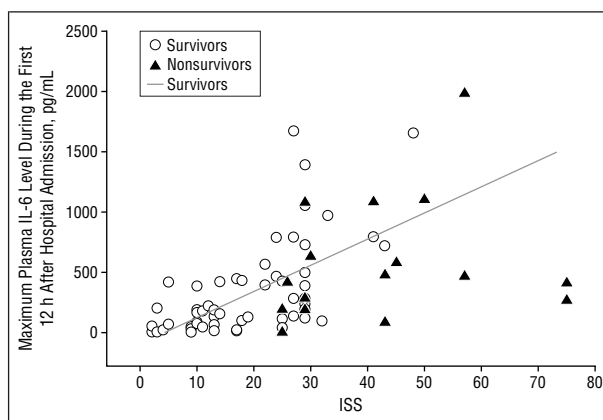


Figure 3. Mean interleukin 6 (IL-6) plasma levels vs the corresponding individual Injury Severity Score (ISS) values during the first 12 hours after hospital admission. There is a positive relation ($r = 0.61$, $y = 21.6x - 95$, $n = 64$, $P < .001$, $r^2 = 0.37$) between the severity of trauma (ISS) and IL-6 release in survivors.

ISS (group) limits were set at 1×3^2 , 2×3^2 , and 2×4^2 points.

However, these anatomically based scores (eg, ISS) merely describe the injury severity from an anatomical point of view and do not necessarily reflect the amount of tissue destruction following major trauma. On the other hand, the magnitude of damage to the tissue governs the inflammatory response²¹⁻²⁸ and thus may be an impor-

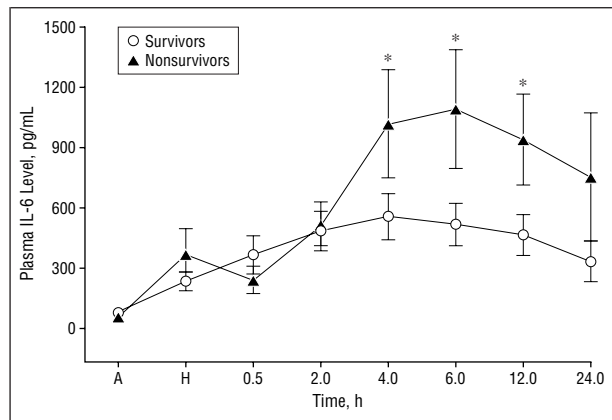


Figure 4. Immediately after trauma, there was no difference between the mean \pm SEM interleukin 6 (IL-6) concentrations in surviving (only those patients with an Injury Severity Score [ISS] >9) and nonsurviving ($n = 15$; median ISS, 43) individuals (definitions given in the legend to Figure 1). Four hours following hospital arrival, a steep increase in IL-6 concentration was observed in nonsurviving patients. The difference was sustained until death. Asterisk indicates $P = .02$ for nonsurvivors vs survivors.

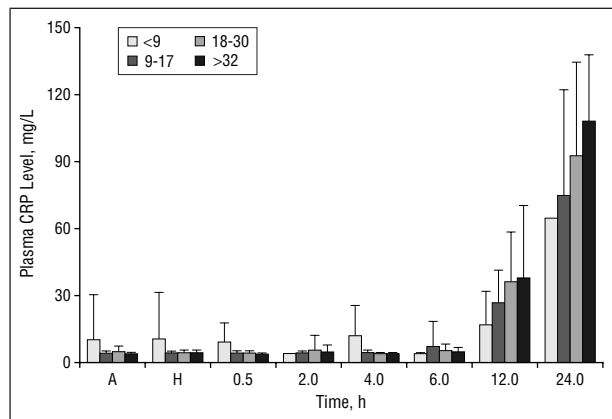


Figure 5. Plasma concentrations (mean \pm SD) of C-reactive protein (CRP) related to the Injury Severity Score (ISS) classification (definitions given in the legend to Figure 1). The CRP plasma levels increased in all patients later than 6 hours after the challenge. The individuals most severely traumatized (ISS, >32) reached the highest concentrations. A indicates at the scene of the unintentional injury; H, at hospital arrival.

tant determinant of the (clinical) outcome of each individual. Therefore, any mediator representing the extent of damaged tissue should be a useful instrument in defining injury severity.

From studies^{3,4,6,12,13,29-31} in elective surgery, we have learned that IL-6 plasma levels may reflect the extent of surgical trauma since the circulating IL-6 levels could be related to the underlying tissue damage. This is in line with the results of our study on accidental trauma (Figure 1). Moreover, the released IL-6 levels correlated positively with the final (definitive) ISS assessment as early as at hospital admission and during the first 6 hours thereafter (Figure 2, top and bottom). This relation persisted up to the first 12 hours after the injury (Figure 3). The ISS values were based on the final assessment of each patient during the first day following trauma. Our results strongly support the hypothesis that IL-6 level is an early variable that is able to describe the degree of tissue injury. From the earliest point acquirable following major trauma (at the scene

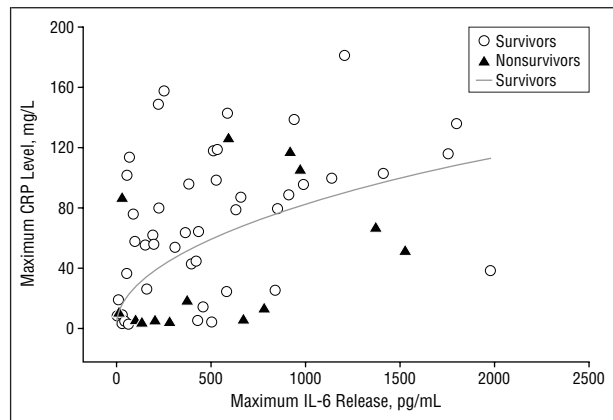


Figure 6. There is a positive exponential correlation ($r = 0.55$, $y = 3.26x + 0.47$, $n = 64$, $P < .001$, $r^2 = 0.30$) between the highest interleukin 6 (IL-6) release and the maximum values of C-reactive protein (CRP) reached during the first 24 hours after injury.

of the unintentional injury), there is clear differentiation between minor and major injuries.

Patients who died early after major trauma also showed higher values of IL-6 for several hours. Although it was possible to differentiate between survivors and nonsurvivors as early as 4 hours after hospital arrival (Figure 4), the data did not allow a prediction of the individuals' further fate based on the mean IL-6 plasma values. This was because of the few complete data sets, foiling exact statistical analyses. However, no survivor developed subsequent sepsis or multiple organ failure. Multiple organ failure and related death, on the other hand, appear to be associated with significantly elevated IL-6 levels from the second day.¹⁶

The CRP level is known to reflect the impact of trauma on the body²⁰ and is associated with the tissue damage. The time course of trauma-induced CRP production in general goes along with a gap of several hours. As a consequence, elevated CRP levels were not detectable in our study during the first 6 hours after trauma (Figure 5). After the period of primary hepatic short-term phase reaction, an increase in the CRP concentrations occurred, which was most pronounced in the patients with most severe injury. This result clearly corroborates the literature-based hypothesis of an association of CRP with the severity of tissue damage and the correctness of our primary classification of trauma extent that had lead to 4 subgroups.

The time course of IL-6 release evidently precedes the equivalent production of CRP by at least 12 hours (Figure 1).

There was a positive correlation between the highest IL-6 release and the maximal generation of CRP during the first day (Figure 6).

We failed to demonstrate long-lasting elevations of circulating IL-6 that have been described elsewhere.^{15,32} In our study, the IL-6 concentrations decreased after 6 to 12 hours following hospital admission. In patients with minor to severe injuries, low levels were reached latest on the third day after trauma (data not shown). We are unable to explain this discrepancy to the findings of others.^{15,32} There are, however, recent publications^{30,31} that support our findings of a steady decline in IL-6 concen-

trations after an initial elevation. Although these results were based on (elective) surgical trauma—either in carcinoma-bearing patients³⁰ or in patients who underwent cholecystectomy³¹—the time course of the IL-6 release is in line with our results. Moreover, these researchers^{30,31} reported a significant relation between late CRP levels and IL-6 concentrations. There are different findings in patients with short-term spine injuries, in whom no changes in systemic IL-6 levels were present whereas the CRP level regularly (infection driven?) was high.³³ Unlike the latter results, IL-6 plasma concentrations were elevated in patients with long-term spinal cord injury.¹¹

With the test system that was used in this study, IL-6 plasma levels are available within approximately 70 minutes after sample collection. Therefore, an early characterization of the injury severity is possible before exact diagnostic data or a final assessment of the patient is available. In addition, IL-6 plasma levels sufficiently predict trauma severity on hospital admission up to 6 hours after the injury. Our results corroborate the suggestion of IL-6 as an early characteristic descriptor of the overall trauma extent, a hypothesis already outlined by Biffi¹ and Patrick³² and their colleagues.

Since IL-6 has been identified as one of the most consistently cytokine reactant of postinjury complications, this mediator's response is expected to be more than a simple instrument to measure injury severity. Although an early (4 hours following trauma) and marked increase in IL-6 release appeared to be associated with nonsurvival in our trauma study, we do not recommend IL-6 as an indicator of outcome, especially because no patient in our study population had any (late) septic event or developed any multi-organ dysfunction syndrome or even multiple organ failure. Any predictive value of IL-6 for survival has to be estimated in further, much larger, prospective studies.

Based on our data, we suggest that the IL-6 level definitely provides an early variable of the extent of injury and may, therefore, be an important factor for defining initial treatment steps in trauma surgery.³⁴ It may, therefore, be a useful tool in early trauma management.

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