Increased serum concentrations of procollagen type III peptide in severely injured patients: An indicator of fibrosing activity?

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Objectives: **To determine the serum concentrations of procollagen type III peptide in severely injured patients with different outcomes and to evaluate the relationship between serum procollagen type III peptide concentrations, sources of increased posttraumatic fibrotic activity (wounds, lung, liver, kidney), and decreased elimination of procollagen type III peptide (liver).**

Design: **Prospective study.**

Setting: **Surgical ICU, university hospital.**

Patients: **Fifty-seven patients (mean injury severity score: 38.5 points, range 13 to 75 points), between 16 and 70 yrs of age, treated in our institution within 6 hrs after the accident.**

Measurements: **Serial measurements were started on admission and continued on a 6-hr basis. After 48 hrs, the monitoring interval was extended to 24 hrs until recovery (but at least until day 14) or death. At each point of evaluation, pulmonary and circulatory function parameters and chest radiographs (once a day) were evaluated, the results were recorded, and blood samples were drawn to determine procollagen type III peptide, total bilirubin, creatinine, γ-glutamyl transferase, polymorphonuclear elastase, and other parameters. Statistic evaluation was done with the Wilcoxon test, Spearman rank correlation, and a multiple regression model.**

Results: **Mean procollagen type III peptide serum concentrations (± SD) were significantly different in patients who died (8.0 ± 3.8 U/mL) compared with those patients who survived with organ failure (2.7 ± 1.3 U/mL) or without complications (1.4 ± 0.5 U/mL), respectively. Significant correlations of procollagen type III peptide concentrations with the serum bilirubin concentrations (r = .7), days with need of mechanical ventilation (r = .64), Pao_2/Fio_2 ratio (r = –.6), polymorphonuclear elastase (r = .6), serum creatinine concentrations (r = .55), and injury severity score (r = .33) were observed. There was a tendency toward higher serum procollagen type III peptide concentrations in patients with severe skeletal injuries.**

Conclusions: **Serum procollagen type III peptide concentrations in severely injured patients may be considerably increased in correlation with injury severity and outcome. Procollagen type III peptide serum concentrations seem to reflect the sum of increased collagen formation from wound healing and fibrogenesis of mediator-related organ damage (especially lung) and decreased procollagen type III peptide excretion due to impaired liver function. Further data are necessary to evaluate the role of hepatic elimination in these patients. (Crit Care Med 1993; 21:240–247)**

KEY WORDS: **procollagen; multiple organ failure; multiple trauma; adult respiratory distress syndrome; liver fibrosis; respiratory failure; accidents and trauma; wound healing; critical illness; hepatic failure**

Collagen synthesis is a main feature of the proliferative phase of wound healing. Increased quantities of collagen have been found not only in the healing surgical or traumatic wound (1) but also in a variety of fibrosing tissues (liver, lung, kidney, heart) that have been injured from inflammatory or other destructive

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processes (2). The direct quantification of collagen production depends on tissue biopsies that usually are not available in the clinical setting. However, in the course of collagen biosynthesis, collagen-derived peptides are deposited in the extracellular matrix and released into the circulation. Procollagen type III peptide is cleaved from the aminoterminal end of procollagen type III, one of the predominant types of collagen being produced during wound healing and contributing to the composition of lung connective tissue. Procollagen type III peptide can be measured in serum samples by commercially available radioimmunoassays and provides an estimate of collagen type III biosynthesis and turnover. Increased levels of procollagen type III peptide have been found locally in wounds (1) and in bronchoalveolar lavage fluid from patients with fibrotic pulmonary disease (3) and the adult respiratory distress syndrome (ARDS) (4) as well as in serum samples of individuals after surgery (5), with chronic fibrotic liver disease (6–8), myocardial infarction (9), renal insufficiency (10), severe wound infection (5), and ARDS (10, 11).

Although many single measurements have been reported up to now, very few serial measurements of procollagen type III peptide concentrations are published, and little is known about the fluctuation of circulating procollagen type III peptide concentrations in patients with severe accidental injuries. Since trauma not only leads to direct damage of connective and skeletal tissue but also of other organs via the inflammatory response (whole body inflammation [12]), we hypothesized that procollagen type III peptide levels might be of value in estimating the "whole body wound." To test this hypothesis, we determined serum procollagen type III peptide concentrations in severely injured patients.

MATERIALS AND METHODS

We performed a prospectively designed study to evaluate the release of procollagen type III peptide into the circulation of patients suffering from severe traumatic events. Patients were enrolled if the following criteria were met: a) clinically important injuries of at least two body regions (head/brain, thorax, abdomen, skeletal system) or three major fractures; b) age between 16 and 70 yrs; and c) treatment in our hospital within 6 hrs after the accident. All injuries were documented, and the injury severity score was calculated. Severe injuries of the skeletal system comprised above-knee amputations, uni- or bilateral femur fractures, and complex fractures of the pelvic girdle. Serial measurements were started on admission and continued on a 6-hr basis. After 48 hrs, the monitoring interval was extended to 24 hrs (0700 hrs) until day 14. If the patient was still in a state of organ dysfunction at that time, the measurements were continued until clinical recovery or death. At each evaluation point, the type of ventilation, FIO_2, PaO_2, positive end-expiratory pressure, chest radiograph, and a variety of other circulatory and pulmonary function parameters as well as diagnostic and therapeutic interventions were recorded. Furthermore, blood samples were drawn for measurement of circulating procollagen type III peptide, bilirubin, creatinine, polymorphonuclear elastase concentrations, and other laboratory parameters. After centrifugation, serum samples were stored at –80°C until assay.

Organ failure was defined as follows: respiratory failure (need for mechanical ventilatory therapy plus PaO_2/FIO_2 ratio of <280 or positive end-expiratory pressure of ≥8 cm H_2O); ARDS (respiratory failure plus chest radiograph with bilateral interstitial edema); liver failure (serum bilirubin concentration of >3 mg/dL [>51 μmol/L] of at least 48-hrs duration); and renal failure (serum creatinine concentration of >2 mg/dL [>177 μmol/L] of at least 48 hrs duration).

Total bilirubin, creatinine, γ-glutamyl transferase and alkaline phosphatase concentrations in serial serum samples were determined according to routine procedures. Polymorphonuclear elastase in complex with α-1-proteinase inhibitor was measured by a commercially available ELISA test kit (Merck, Darmstadt, FRG). Procollagen type III peptide in serum was determined with a new version of the radioimmunoassay RIAgnost® PIIIP (Behringwerke, Marburg, FRG) using the principle of a two-stage sandwich technique as outlined by the manufacturer. The lower detection limit is about 0.1 units of procollagen type III peptide/mL. The monoclonal antibodies used in the kit are highly specific for the procollagen type III peptide, the complete aminoterminal peptide consisting of 3 conformationally distinct domains (col 1–3) (MW 45,000 daltons). The possibility of a cross-reaction with other basal membrane proteins occurring in the concentration ranges that are physiologically relevant can be virtually ruled out. The normal range of RIAgnost PIIIP has been determined using serum samples from 158 healthy men and women. By calculating the 5th and 95th percentile, a normal range of 0.3 to 0.8 U/mL has been established (information given by the manufacturer). We considered values of >1.0 U/mL as increased. One unit of procollagen type III peptide/mL corresponds to about 15 ng/mL quantified by the original version of the assay (13) (personal communication of the manufacturer). To allow a comparison of results obtained by the tests of Behringwerke and Farmos Diagnostica (Finland) used by other authors (5, 7, 9, 14),

an approximate conversion rate was calculated by using the normal ranges of both tests, and assuming that they represent the same concentrations of procollagen type III peptide. Therefore, we estimated that 1 U/mL (Behringwerke) amounts to 6 ng/mL (Farmos).

All factors were tested for normal distribution with the chi-square test for goodness of fit: days of respirator therapy and injury severity score were normally distributed; serum procollagen type III peptide levels, bilirubin, creatinine, and Pao_2/Fio_2 ratios followed a log-normal distribution ($p > .1$). The log-transformed values were only used for the stepwise variable selection in a multiple regression model. All other estimations were assessed with nonparametric tests (Wilcoxon test for two samples, Spearman rank correlation). The application of the Spearman rank correlation analysis yields a correlation coefficient "rho" that is indicated by "r" throughout the manuscript. Statgraphics version 4.0 (STSC and Statistical Graphics) was used for all statistical calculations.

The study was carried out in accordance with the Ethical Committee of the Ludwig Maximilians-University of Munich.

RESULTS

Serum procollagen type III peptide concentrations of 57 multiple-injured patients were determined during a 14-day period beginning immediately after trauma. The study population consisted of 44 male and 13 female patients with a mean age of 38.3 yrs (range 17 to 70). The mean injury severity score was 38.5 points (range 13 to 75). In 11 patients with a prolonged state of organ dysfunction, measurements were continued for a maximum of 35 days until clinical recovery or death.

Nine patients (mean injury severity score 43.3) died, all (except one) from multiple organ failure with a median survival time of 18 days (range 10 to 39). Organ dysfunctions were survived by 31 patients (mean injury severity score of 41.5), whereas 17 subjects (mean injury severity score of 30.5) recovered without complications. The course of the mean serum procollagen type III peptide concentrations of these three patient groups is illustrated in Figure 1. At the beginning, all patients (except for one patient with tourniquet's syndrome of the right lower limb after laceration of the femoral and popliteal artery and multiple open fractures of the femur, knee, and tibia showed a serum procollagen type III peptide concentration of 2.8 U/mL already in his first serum sample) had procollagen type III peptide serum concentrations within the normal range. After the second day, however, an increase with significant differences between these three groups

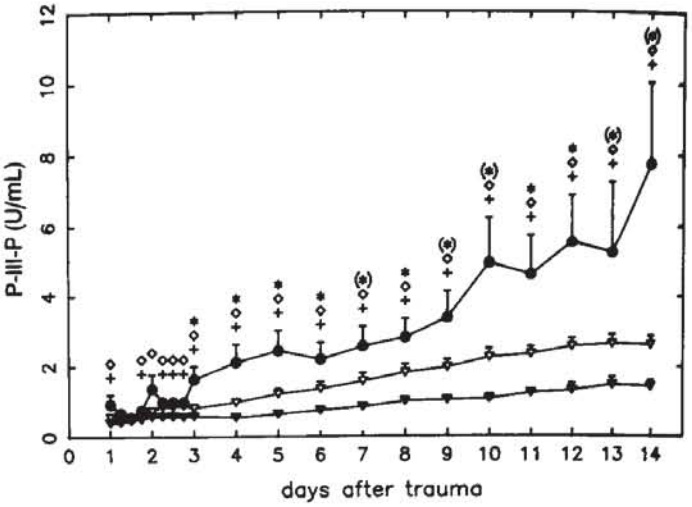

Figure 1. Mean concentration (± SEM) of procollagen type III peptide (*P-III-P*) serum concentrations of nonsurvivors (n = 9, *closed circles*), survivors with organ failure (n = 31, *open triangles*), and survivors without organ failure (n = 17, *closed triangles*). $^*p < .05$ for nonsurvivors vs. survivors with organ failure; $(^*)\,p < .05$, with one patient omitted from the group of nonsurvivors who had late adult respiratory distress syndrome with an increase of procollagen type III peptide to 4.4 U/mL starting only after 2 wks. $^\circ p < .05$ for nonsurvivors vs. survivors without organ failure; $^+p < .05$ for survivors with organ failure vs. survivors without organ failure.

could be observed for the remainder of the study period. Patients with lethal outcome reached a mean (± SD) maximum procollagen type III peptide level of 8.0 ± 3.8 U/mL, which was significantly ($p < .001$) higher than the mean maximum procollagen type III peptide level of survivors with organ failure (2.7 ± 1.3 U/mL) or of patients without complications (1.4 ± 0.5 U/mL). The difference in the mean maximum procollagen type III peptide concentration of the latter two groups was also highly significant ($p < .001$).

The kinetics of procollagen type III peptide release in the individual subjects were similar to the graphs of the mean plots. Setting off with normal values, there was a more or less pronounced increase beginning 2 to 4 days after trauma with a maximum usually around days 10 to 17, followed by a plateau and a gradual decline. Patients who died showed a continuous increase up to 13.7 U/mL until death.

From the whole study population, 11 patients presented with procollagen type III peptide concentrations within the normal range during the whole observation period. They had injuries of mild severity (except for one with lethal brain damage), no severe injuries to the skeletal system (except for one with a fracture of the acetabulum), and rarely, respiratory failure or dysfunction of other organ systems (Table 1). In the groups with increasing procollagen type III peptide levels, the frequency of these entities increased. This concomitant increase of procollagen type III peptide peak levels with

organ failure and injury severity could be further substantiated by a correlation analysis, using the Spearman rank correlation (Table 2). The highest correlation became evident for serum bilirubin values and procollagen type III peptide concentrations (0.70), whereas the correlation of procollagen type III peptide with the injury severity score was much weaker. In a multiple regression model with stepwise variable selection (after logarithmic transformation of log-normally distributed variables), the highest bilirubin, highest creatinine, days of respirator therapy and lowest Po_2/FIO_2 ratio after 7 days (in that order) contributed significantly to the variability of procollagen type III peptide, explaining 73% of the variation in procollagen type III peptide levels. No correlation was found between procollagen type III peptide levels and indicators of cholestasis (γ-glutamyl transferase, alkaline phosphatase).

Nine patients developed renal failure, of whom five needed continuous arteriovenous hemofiltration. In three cases, procollagen type III peptide increases preceded the increase in serum creatinine, three patients showed a simultaneous increase, and in three individuals, the increase in procollagen type III peptide concentrations followed the increase in creatinine with a lag of several days. In one patient, procollagen type III peptide values remained low despite high serum creatinine concentrations. During hemofiltration, the serum concentrations of procollagen type III peptide increased substantially, whereas creatinine concentrations remained stable.

The presence of severe skeletal injuries (bilateral above-knee amputations, bilateral and unilateral fractures of the femur, complex fractures of the pelvic girdle) led to significant ($p < .01$) increases of mean procollagen type III peptide levels from 2.6 ± 2.6 (SD) to 3.5 ± 2.9 U/mL. When the mean procollagen type III peptide concentrations are controlled for bilirubin (Table 3), however, only a tendency toward higher serum concentrations of procollagen type III peptide due to skeletal trauma could be found in the low but not the high bilirubin group. The presence of severe thoracic injury (abbreviated injury scale 3) did not significantly influence procollagen type III peptide levels (3.8 ± 3.2 vs. 2.7 ± 2.5, $p > .05$).

In patients with overt ARDS, respiratory failure without ARDS, and without pulmonary impairment, the mean maximum procollagen type III peptide concentrations were 7.6 ± 3.5, 3.3 ± 2.5, and 1.6 ± 0.7 U/mL, respectively. The mean procollagen type III peptide concentrations over time of these three groups are depicted in Figure 2. The relationship of serum bilirubin concentrations and respiratory function is analyzed in Table 4. In addition to the correlation of bilirubin concentrations with procollagen type III peptide concentration in serum, the presence of respiratory failure adds significantly to the procollagen type

Table 1. Mean injury severity score; rate of serious injuries to the skeletal system; rate of organ failure (total); rate of respiratory, liver, renal failure and adult respiratory distress syndrome (ARDS) as well as the mortality rate in relation to different concentrations of procollagen type III peptide given as percentage of patients (number of patients in parentheses)

	Maximum Concentration of Procollagen Type III Peptide (U/mL)			
	<1.0	1–2	2–5	>5.0
Number of patients	11	16	21	9
Injury severity score	31.8	35.5	42.9	41.6
Skeletal injuries (%)	9 (1)	56 (9)	76 (16)	56 (5)
Total organ failure (%)	36 (4)	50 (8)	90 (19)	100 (9)
Respiratory failure (%)	27 (3)	38 (6)	67 (14)	100 (9)
ARDS (%)	0	0	10 (2)	56 (5)
Liver failure (%)	18 (2)	38 (6)	76 (16)	100 (9)
Renal failure (%)	0	0	14 (3)	67 (6)
Mortality (%)	9 (1)	0	5 (1)	78 (7)

Table 2. Correlation coefficients and p values using the Spearman rank correlation between procollagen type III peptide (maximum) serum concentrations and markers of organ function or injury severity

Variable 1	Variable 2	Correlation Coefficient	p Value
Procollagen Type III peptide	$Bilirubin_{max}$	0.70	<.001
	$Creatinine_{max}$	0.55	<.001
	Po_2/FIO_{2min} [a]	–0.60	<.001
	Po_2/FIO_{2min} [b] (after 1 wk)	–0.56	<.001
	Respirator days	0.64	<.001
	Injury severity score	0.33	<.05
	γ-GT	0.02	>.5
	Alkaline phosphatase	0.03	>.5

Max, maximum; Min, minimum; γ-GT, γ-glutamyl transferase.
[a]Lowest Po_2/FIO_2 ratio during the whole study period; [b]lowest Po_2/FIO_2 ratio between day 8 after trauma and the end of the observation period, thus excluding patients with respiratory failure of short duration immediately after trauma.

Table 3. Dependency of procollagen type III peptide levels on serum concentrations of bilirubin in patients with and without severe injuries to the skeletal system. Procollagen type III peptide values (U/mL) are given as mean ± SD. The Wilcoxon test for two samples was used for comparison of patients with and without skeletal injuries within each range of bilirubin concentrations (number of patients in parentheses)

	Bilirubin ≤3 mg/dL (≤51 μmol/L)	Bilirubin >3 mg/dL (>51 μmol/L)
Skeletal injury	1.9 ± 0.8 (9)	4.2 ± 3.2 (22)
No skeletal injury	1.5 ± 0.9 (16)	4.4 ± 3.5 (10)
p Value	<.1	>.5

III peptide concentrations in patients with serum bilirubin concentrations >3 mg/dL (51 μmol/L). In patients without liver failure (bilirubin ≤3 mg/dL (≤51 μmol/L), there is only a tendency toward higher procollagen type III peptide concentrations due to respiratory failure.

Polymorphonuclear elastase, which is released from neutrophil granulocytes, was used as an indicator of the inflammatory response to trauma. There was a significant correlation between the highest procollagen type III peptide values and polymorphonuclear elastase levels ($r = .60, p < .001$).

DISCUSSION

This study has demonstrated that procollagen type III peptide serum levels are increased in many patients suffering from severe trauma.

The kinetics of procollagen type III peptide increasing over time are similar in almost all patients, starting off with normal values, increasing to a broad maximum, followed by a gradual decline over a period of 2 to 3 wks. This decrease was only observed in surviving patients, whereas expiring subjects showed a steady increase of procollagen type III peptide levels until death. The latter finding may be partly explained by the fact that many of the nonsurvivors died too early (median surviving time 18 days) to observe a decline of procollagen type III peptide levels. Apart from 11 patients with normal values throughout the observation period, the normal range was not reached again within 2 wks after trauma in surviving patients with initially increasing procollagen type III peptide serum concentrations. Others (5) have observed similar patterns of procollagen type III peptide release after abdominal or orthopedic surgery. They (5) saw peak procollagen type III peptide concentrations days after major abdominal and 60 days after orthopedic surgery with values returning to normal not before 6 months in the latter group. These data imply that serial measurements are necessary to interpret procollagen type III peptide values, whereas detached determinations may be misleading. Although procollagen type III peptide is supposed to be eliminated primarily via liver endothelial cells with a half-life of minutes (15), changes in procollagen type III peptide serum concentrations seem to be relatively slow in our patients. Thus, determination of procollagen type III peptide every, or every other, day may be sufficient to record the fluctuations accurately enough.

One well-known cause of procollagen type III peptide release is wound healing in fractures and following orthopedic operations (5). Therefore, we investigated the influence of severe trauma of the skeletal system in our patients. Although procollagen type III peptide concentrations were higher in patients with severe fractures, this difference was reduced after breakdown of the data, accounting for the major correlating factor (bilirubin). Yet, for low concentrations of bilirubin there remained a tendency toward higher procollagen type III peptide levels in patients with skeletal injuries. These findings are not in contrast to the data of Haukipuro et al. (5) who reported a correlation of procollagen type III peptide concentrations with the

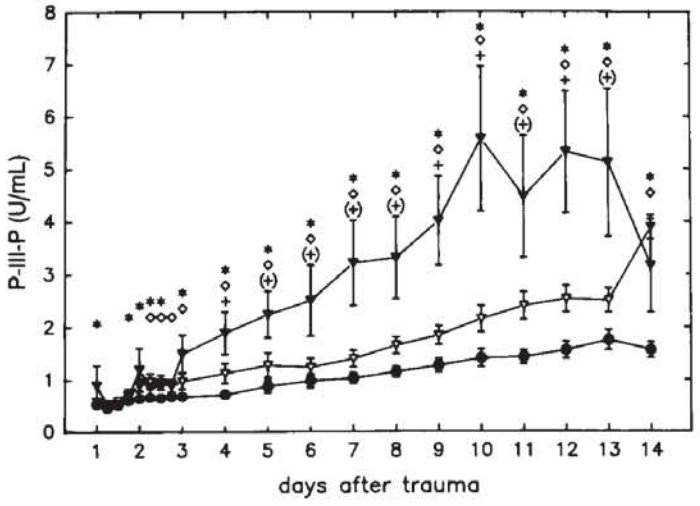

Figure 2. Mean concentration (± SEM) of procollagen type III peptide (*P-III-P*) serum concentrations of patients with adult respiratory distress syndrome (ARDS) (n = 7, *closed triangles*), acute respiratory failure without ARDS (n = 24, *open triangles*), and those patients with normal respiratory function (n = 26, *closed circles*). $^{*}p < .05$ for ARDS vs. acute respiratory failure without ARDS; $^{(*)}p < .05$, with one patient omitted from the group with ARDS who had late ARDS with an increase of procollagen type III peptide to 4.4 U/mL starting only after 2 wks. $^{\diamond}p < .05$ for ARDS vs. no acute respiratory failure; $^{+}p < .05$ for acute respiratory failure without ARDS vs. no acute respiratory failure.

Table 4. Relation of maximum procollagen type III peptide levels with bilirubin in patients with and without respiratory failure. Procollagen type III peptide values (U/mL) are given as mean ± SD. The Wilcoxon test for two samples was used for comparison of patients with and without respiratory failure within each group of bilirubin concentrations (number of patients in parentheses)

	Bilirubin Serum Concentrations		
	≤3 mg/dL (≤51 μmol/L)	3–10 mg/dL (51–170 μmol/L)	>10 mg/dL (>170 μmol/L)
No respiratory failure	1.4 ± 0.6 (16)	1.4 ± 0.6 (6)	2.5 ± 0.5 (4)
Respiratory failure	2.0 ± 1.2[a] (9)	3.5 ± 2.4[a] (12)	7.3 ± 3.5[b] (10)
p Value	> .1	< .01	< .01

[a]Including one patient with acute respiratory distress syndrome; [b]including five patients with acute respiratory distress syndrome.

type of surgery and tissue damage. Only one of our 11 patients with consistently low concentrations (≤1.0 U/mL) of procollagen type III peptide sustained a major fracture, whereas the other patients with increased serum procollagen type III peptide usually had major skeletal trauma. Furthermore, in Haukipuro's patients, the mean maximum value was about 1.3 U/mL (for conversion rate, see Results), which corresponds with the procollagen type III peptide peak levels of our patients without complications (1.4 U/mL) but is much lower than in our more severely injured subjects. Therefore, the effects of wound healing, which reach statistical significance in their study, seem, in absolute terms of procollagen type III peptide concentration, rather low as compared with those effects of other major influencing factors in our patients. We conclude that procollagen type III peptide release due to healing of skeletal injuries contributes to the total procollagen type III peptide concentration in serum, but may be concealed by other dominating factors in severely injured patients.

These other determinants may be "wounds" of a different entity, namely of tissue damage not caused by direct mechanical trauma but mediated by biochemical effectors of the inflammatory response, hypoxia, and others. Such wounds and their healing have been described using procollagen type III peptide as a marker of collagen formation in acute viral hepatitis (16), in chronic active cirrhosis (postviral, alcoholic) (7, 16), after myocardial infarction (9), in fibrotic lung disease (3) in man, and in kidney damage in animals (17).

The liver from patients with chronic fibrosing liver affections is thought to be a major source of procollagen type III peptide production. Procollagen type III peptide concentrations, comparable with the concentrations found in our patients, have been noticed frequently, and a significant correlation between histologically confirmed hepatic fibrosis and procollagen type III peptide concentrations was reported (6, 7, 16). However, the influence of posttraumatic or septic liver failure on procollagen type III peptide concentrations is not known. In one study, highly increased procollagen type III peptide serum concentrations in patients with posttraumatic multiple organ failure (liver failure always present) have been reported (11). Yet, these authors could not differentiate, whether these high procollagen type III peptide concentrations were due to fibrotic processes or to the impairment of procollagen type III peptide extraction via liver endothelial cells, the main pathway of procollagen type III peptide elimination from the circulation (14, 15).

Our data might suggest a dependence of procollagen type III peptide serum concentrations on liver function in trauma patients, since we found the highest correlation of all parameters for procollagen type III peptide concentrations with bilirubin. Similar correlations have been observed in studies dealing with primary liver disease (7). Since intact procollagen type III peptide is mainly degraded in the liver (14) and a decreased biliary excretion was suggested to take place during severe liver damage (6), it may be deduced from the comparison of the procollagen type III peptide concentrations with those values of bilirubin in our patients that at least in subjects with lethal organ failure the rapid increase of procollagen type III peptide concentrations reflects in part dysfunction of procollagen type III peptide elimination via the liver. It is not clear, however, whether a decreased rate of elimination of procollagen type III peptide via the liver is really a main cause for increased procollagen type III peptide concentrations in serum. Despite very high bilirubin values, a two- to threefold increase in biliary excretion of procollagen type III peptide into bile was observed in humans with liver cirrhosis compared with healthy controls (8), indicating that the mechanism of procollagen type III peptide elimination may not be seriously disturbed in such patients. Recently, however, it has been shown that biliary excretion does not contribute significantly to the hepatic extraction of circulating procollagen type III peptide in the normal liver (18). Therefore, the correlation of procollagen type III peptide concentrations with serum bilirubin concentrations might not indicate the impairment of a common mechanism of hepatic elimination. Furthermore, no correlation of procollagen type III peptide serum concentration with the hepatic extraction ratio could be observed in another study (14), implying that decreased extraction may be only one mechanism to increase serum procollagen type III peptide. Thus, many authors (6, 7, 16) claimed that increased procollagen type III peptide concentrations in serum are caused by an increased production due to fibrogenesis in many forms of liver disease. Although we cannot directly confirm fibrotic activity in the livers of our trauma patients with high procollagen type III peptide, there is evidence that in severe posttraumatic liver failure, necrosis and fibrosis (and thus, fibroblastic activity) take place in the liver (19). No correlation of procollagen type III peptide with circulating liver enzyme values could be verified in our patients, excluding posthepatic cholestasis.

Besides a high correlation of procollagen type III peptide with serum bilirubin concentrations, a good correlation with renal function was observed in our patients. A slight increase of procollagen type III peptide has been described in patients with renal failure (10). It is known that some procollagen type III peptide

degradation products are excreted via the urine (8, 13, 14). However, the results of most investigations demonstrate that the renal pathway of excretion of intact procollagen type III peptide (Col 1-3 peptide) is much less important than the liver's role (8, 14). On the other hand, damage of the kidney in an experimental model led to an increased release of a collagen synthesis-stimulating factor (17). Thus, fibroblast activity during repair of posttraumatic kidney damage might be a contributor to increased procollagen type III peptide formation.

Very high levels of procollagen type III peptide have been reported in eight patients with ARDS (10). Jochum et al. (11) found similar high procollagen type III peptide serum concentrations in trauma patients with ARDS and multiple organ failure (n = 12) which were, however, only somewhat (but not significantly) higher than in patients without ARDS (n = 12) but suffering from other posttraumatic organ dysfunctions. We have measured comparably high values in our patients with ARDS. Furthermore, we found a high correlation of procollagen type III peptide with respiratory function (Pao_2/Fio_2 ratio, total days of respirator therapy). ARDS is the most severe manifestation of respiratory failure, but the pathogenetic factors underlying ARDS and respiratory failure without ARDS may be qualitatively the same. Therefore, we would expect fibroblast activity not only in (radiologically) overt ARDS but also in milder forms of pulmonary dysfunction. An increase of procollagen type III peptide found in all patients with respiratory failure may indicate that such an increased collagen synthesis actually takes place. The increase of procollagen type III peptide concentrations in patients with respiratory failure seems to be independent of liver function since the presence of pulmonary dysfunction exerts a significant influence on procollagen type III peptide concentrations within patient groups with similar bilirubin concentrations.

Since neutrophil granulocytes are thought to play a major role in the inflammatory destruction of lung connective tissue (20), thus indirectly causing reparative processes such as fibrosing activity, polymorphonuclear elastase levels were determined to indicate neutrophil activity. The high correlation of procollagen type III peptide concentrations with polymorphonuclear elastase concentrations suggest some relationship between the posttraumatic inflammatory response (and its sequelae) and the secondary increase of procollagen type III peptide concentrations. Whether there is a causality between mediator release (e.g., polymorphonuclear elastase), tissue destruction, reparative fibrosing activity, and procollagen type III peptide concentrations remains speculative.

Although the highest procollagen type III peptide values of all have been observed in ARDS patients, respiratory function was only the third most important determinant of procollagen type III peptide variability in a multiple regression model, indicating that pulmonary fibrosis is not the sole or main contributor to procollagen type III peptide formation. Although ARDS is not an isolated entity but usually part of multiple organ failure (21), Entzian and co-workers (10) supplied no detailed information on liver and renal function in their ARDS patients, but at least three of them had multiple organ failure, indicating that other mechanisms for the procollagen type III peptide increase may have been present in their patients. Thus, procollagen type III peptide cannot be used as a specific marker for ARDS or fibroblastic lung processes in these patients.

In summary, increased procollagen type III peptide serum concentrations seem to represent increased collagen formation in severely injured patients as well as decreased excretion of procollagen type III peptide via the liver. Moreover, they do not reflect the damage to a single organ but are the integral of reparative activities from the whole body. Healing of traumatic and surgical wounds as well as the reactions in restoring organ integrity after destruction by proteases, oxygen radicals, and other mediators in the wake of the traumatic shock seem to contribute to procollagen type III peptide release. Therefore, monitoring of procollagen type III peptide serum concentrations in severely injured patients might be of value in estimating the "whole body wound" that has been inflicted on the organism by direct tissue damage and inflammatory mediator-induced trauma. However, as long as the role of hepatic extraction of procollagen type III peptide is not completely defined, such an interpretation of increased procollagen type III peptide concentrations has to be considered with caution, not only in the trauma patients but also in other severely ill subjects. Independently from the discussion about the pathobiochemistry, procollagen type III peptide serum concentrations may serve as an indicator of injury severity and prognosis.

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