Serum concentration of 7S collagen and prognosis in patients with the adult respiratory distress syndrome

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Abstract

Background – 7S collagen, an N-terminal peptide of type IV collagen, is a primary constituent of the basement membrane. To evaluate whether the serum concentration of 7S collagen reflects the severity of inflammatory lung disease, the serum concentration of 7S collagen was measured in patients with adult respiratory distress syndrome (ARDS) and idiopathic pulmonary fibrosis (IPF).

Methods – A radioimmunoassay was used for the measurement of 7S collagen. Gas exchange abnormality was expressed as the arterial oxygen tension (P_{aO_2}) divided by the fractional concentration of inspired oxygen (F_{iO_2}).

Results – The mean (SD) concentration of 7S collagen was 2.7 (0.9) ng/ml in 10 healthy subjects, 5.0 (1.5) ng/ml in 11 patients with IPF, and 14.8 (9.7) ng/ml in 13 patients with ARDS. Significant differences were observed between the patients with ARDS and both healthy subjects and the patients with IPF. In the patients with ARDS serum concentrations of 7S collagen were strongly related to P_{aO_2}/F_{iO_2} ($r = -0.61$). Moreover, the mean (SD) serum concentration of 7S collagen in the eight patients with ARDS who died (19.5 (10.2) ng/ml) was considerably higher than that of the five who survived (7.1 (2.1) ng/ml).

Conclusion – These results suggest that serum levels of the 7S fragment of type IV collagen may have some prognostic value in ARDS.

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damage to the pulmonary basement membrane. In this study serum concentrations of 7S collagen were measured in patients with adult respiratory distress syndrome (ARDS) and those with idiopathic pulmonary fibrosis (IPF), and the use of 7S collagen in assessing the severity of these diseases was evaluated.

Methods

PATIENTS

Thirteen patients (12 men and one woman) with ARDS diagnosed according to the criteria of Pontoppidan *et al.*⁵ and 11 patients (nine men and two women) with IPF were studied. None had evidence of liver disease based on their past histories and blood chemistry data.

The mean age of the patients with ARDS was 62 years (range 17-88). Five patients survived and eight died of ARDS. At the time of diagnosis of ARDS, other organ failure coexisted in six patients, all of whom died. Multiple organ failure was defined by the criteria of Dorinsky *et al.*⁶ Some details of the patients with ARDS are summarised in the table. The blood samples for assay of P_{aO_2} and concentration of 7S collagen were taken on the same day in each patient.

The mean age of the 11 patients with IPF was 61 years (range 48-73). Seven patients had clinically active and four had clinically stable disease. Active disease was defined by increased erythrocyte sedimentation rate, elevated serum levels of lactate dehydrogenase, a rapid fall in P_{aO_2} , and rapid radiographic changes such as worsening pulmonary infiltration.

Also included in this study were 10 healthy men. Each subject agreed to have blood samples taken.

ASSAY FOR 7S COLLAGEN

The samples were measured by duplication. For the measurement of 7S collagen a radioimmunoassay (Double Antibody Collagen Type IV-7S kit, Nippon DPC, Tokyo) was used. Following the procedure specified in the package insert, 200 μ l of serum from each patient was pipetted into the prepared tubes. After addition of 100 μ l collagen type IV-7S anti-serum (diluted 30 000 fold in buffer) the tubes were incubated for 24 hours at room temperature and 100 μ l iodine-125 labelled collagen type IV-7S was then added. After two hours incubation at 37°C 1.0 ml of cold precipitating

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Type IV collagen is a major constituent of all basement membranes where it forms a network structure, partly because of interactions between the N-terminal domains of adjacent molecules. These domains, known as 7S collagen,¹ are known to be comparatively resistant to proteases. It has therefore been proposed that serum concentrations of 7S collagen reflect degradation or synthesis of the basement membrane, or both.²⁻⁴

As type IV collagen exists in the basement membrane of pulmonary capillaries and alveoli, we hypothesised that serum concentrations of 7S collagen in patients with inflammatory lung disease may reflect the extent of

Clinical characteristics of patients with adult respiratory distress syndrome (ARDS)

No.	Age	Sex	Causes of ARDS	Pao ₂ /Fio ₂	Outcome	Concentration of 7S collagen (ng/ml)
1	63	M	Sepsis	74	Deceased	32.8
2	21	M	Lymphoma	77	Deceased	29.6
3	50	M	Sepsis	93	Deceased	29.9
4	62	F	Aspiration	96	Deceased	20.0
5	54	M	Sepsis, SLE	106	Deceased	15.0
6	17	M	Sepsis	116	Survived	9.4
7	50	M	Lymphoma	127	Deceased	5.4
8	88	M	Bacterial pneumonia	145	Survived	7.4
9	48	M	Bacterial pneumonia	158	Survived	4.4
10	55	M	Bacterial pneumonia	165	Survived	5.5
11	75	M	Shock, DIC	180	Deceased	9.9
12	77	M	Sepsis	224	Survived	8.9
13	46	M	Leukaemia	250	Deceased	13.7

SLE = systemic lupus erythematosus; DIC = disseminated intravascular coagulation.

solution was added. Tubes were centrifuged for 15 minutes at 2000 *g*. The supernatant was decanted and the precipitate counted for one minute with a gamma counter. The intra-assay and interassay coefficients of variation were 4.3% and 4.7%, respectively.

STATISTICAL ANALYSIS

Data were analysed by analysis of variance (ANOVA). Fisher multiple comparisons were used to test for statistically significant differences among the three groups. The unpaired *t* test and the regression coefficient were used for the other analyses.

Results

The mean (SD) serum concentration of 7S collagen in the 10 healthy subjects was 2.7 (0.9) ng/ml with an upper limit of 4.5 ng/ml. The mean serum concentration of 7S collagen was significantly greater in patients with ARDS (14.8 (9.7) ng/ml) than in healthy sub-

Mean serum concentration of 7S collagen in healthy subjects, patients with idiopathic pulmonary fibrosis (IPF), and those with adult respiratory distress syndrome (ARDS). The mean (SD) serum concentration of 7S collagen was significantly greater in patients with ARDS (14.8 (9.7) ng/ml) than in healthy subjects ($p < 0.01$) and those with IPF (5.0 (1.5) ng/ml; $p < 0.01$).

jects ($p < 0.01$) and those with IPF (5.0 (1.5) ng/ml; $p < 0.01$) (figure). There was no significant difference between the mean value in the patients with IPF and the healthy subjects. The mean serum concentrations of 7S collagen in the eight patients who died of ARDS was 19.5 (10.2) ng/ml, whereas in the five surviving patients it was 7.1 (2.1) ng/ml.

The serum concentration of 7S collagen in the patients with ARDS revealed a significant correlation with the value of Pao₂/Fio₂ ($r = -0.61$; $p < 0.01$). In ARDS patients with multiple organ failure the mean serum concentration of 7S collagen was 17.3 (9.5) ng/ml, and in those without multiple organ failure it was 12.6 (10.1) ng/ml. In patients with clinically active and clinically stable IPF the mean serum concentrations of 7S collagen were similar (5.2 (1.8) ng/ml and 4.9 (0.5) ng/ml, respectively).

Discussion

In inflammatory lung disease non-specific alveolar septal injury is observed histologically.⁷ In patients with ARDS an increase in neutrophils was observed in the lung parenchyma⁸ and also in the bronchoalveolar lavage fluid.⁹ The elastase present in the neutrophils can cleave type IV collagen.¹⁰ We therefore speculated that the serum concentration of 7S collagen might increase with diffuse destruction of the lung basement membrane during an inflammatory process, and the degree of pulmonary matrix damage (the severity of ARDS) might be related to its concentration in the serum.

Since only the serum concentration of 7S collagen was measured, the question arises as to whether this reflects the amount of damage to the pulmonary basement membrane. In the patients with ARDS who died, two had no other organ failure and their concentrations of 7S collagen were both over 20 ng/ml.

On the other hand, the mean serum concentration of 7S collagen in the patients with IPF was not particularly high. This might be partly because of the small number of patients in the study, and partly because of the relatively slow destruction of the alveolar septa in those patients.

In conclusion, these results suggest that the serum concentration of 7S collagen could reflect the degree of pulmonary basement damage and may, therefore, have some prognostic value in ARDS.

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