Serum angiotensin converting enzyme (serum ACE) levels and plasma fibronectin levels were measured daily in 46 septic patients during a ten day period. Thirty-eight patients developed ARDS; 28 survived (group 1), ten died (group 2), eight patients had no features of ARDS and survived (group 3). Sequential measurements of ACE and fibronectin levels were compared and plotted against indexes of respiratory impairment: PaO\textsubscript{2}/max, Qs/Qt, static compliance and V\textsubscript{D}/Va ratio. These indexes were taken as criteria of weaning from controlled ventilation. During ARDS (groups 1 and 2), serum ACE levels decreased and were closely correlated with the severity of lung injury. Persistently decreased levels after eight days were consistent with continuing injury or lack of endothelial repair. On the other hand, plasma fibronectin levels increased throughout the study in survivors (group 1 and 3) and decreased in the group with fatal ARDS only (group 2). These results indicate that serum ACE levels might be a good index of endothelial injury and repair during ARDS and fibronectin a better index for evolution of sepsis and vital prognosis.

Angiotensin-converting enzyme (ACE) is a dipeptidyl carboxypeptidase that converts angiotensin 1 to angiotensin 2 and inactivates bradykinin. Its highest activity is found in the lung capillary endothelial cells, where the enzyme is membrane bound. Therefore, it has been postulated that ACE serum levels could reflect endothelial injury. In several experimental models, paraquat, \textsuperscript{1} thiourea, \textsuperscript{2} and oleic acid-induced\textsuperscript{3} pulmonary edemas were consistent with an acute release of ACE from the endothelial cells. A dramatic increase in lung lavage and serum levels was observed which paralleled the decrease in lung ACE content. These changes occurred as early as five minutes after administration of the edemogenic agent. They were independent from any variation of hydrostatic pressure or colloid osmotic pressure.\textsuperscript{4}

In most cases of human acute lung injury and adult respiratory distress syndrome (ARDS), serum ACE levels were found to be low.\textsuperscript{5,6} Sequential measurements showed a biphasic evolution, with a decrease and return to normal ranges over a ten-day period.\textsuperscript{6}

These discrepancies between experimental and clinical data may have several explanations: (1) The initial decrease in serum ACE levels could be induced by hypoxemia alone, as suggested in experimental studies.\textsuperscript{7} (2) A decrease in serum ACE level might be a consequence of reduced pulmonary perfusion as described in patients undergoing cardiopulmonary bypass.\textsuperscript{8,9} (3) The inhibition of enzymatic activity of ACE could be due to the release of circulating proteases.

This mechanism was proposed to explain the decrease in ACE levels during septic ARDS.\textsuperscript{9} Furthermore, experimental injection of endotoxin was followed by a rapid fall in ACE level. This decrease might simply reflect the presence or the lack of continuing injury from toxins or mediators.\textsuperscript{10} (4) Finally, ACE serum levels might also reflect the depletion of lung ACE content during the early phase of ARDS. The more severe the endothelial injury, the deeper the initial decrease in serum level. The return to normal ranges might be taken as index of endothelial repair.

We tested the last hypothesis in this study. We compared sequential measurements of ACE serum levels with plasma fibronectin levels during the acute phase of severe sepsis and according to the occurrence of ARDS. Plasma fibronectin was taken as index of protease release and clearance; this protein is known to play a central role in the host defense system, where it acts as a nonimmunologic opsonin for the removal of different degradation products by the reticuloendothelial system. During severe sepsis, decrease in plasma fibronectin levels has been observed and seemed to be due to an acute consumption.\textsuperscript{11} This decrease might then extend the survival time of tissular or fibrinogen products with a possible deleterious effect on alveolar permeability.\textsuperscript{11,12} The impairment of fibronectin activity could also be produced by an imbalance between activated proteases (thrombin, plasmin neutrophil, or bacterial proteases) and circulating enzymatic inhibitors.\textsuperscript{13} In human studies, sequential measurements of plasma fibronectin levels were considered a reliable index for severity of sepsis and prognosis.\textsuperscript{14,15}

In this study, ACE and fibronectin levels were
compared to assess the specificity of changes in ACE levels during septic ARDS. Both indexes were plotted against different criteria of respiratory impairment and lung injury: PaO₂, Qs/Qt, static pulmonary compliance, VD/VA ratio.

Patients and Methods
The study took place from September 1982 to September 1983 on the patients admitted for a documented sepsis; 46 patients entered the study, 42 had positive blood cultures, and four had a viral influenza seroconversion with immediately positive sputum cultures.

Thirty-eight patients fulfilled the criteria for diagnosis of ARDS—diffuse bilateral infiltrates on chest roentgenograms, normal or low capillary wedge pressure, severe hypoxemia (Qs/Qt>20 percent), and low pulmonary compliance. Of these, 28 survived at least ten days and composed group 1 (nonlethal ARDS). The ten other patients died before the tenth day after admission and composed group 2 (lethal ARDS). The eight remaining patients had sepsis without ARDS and composed group 3 (control).

All patients in groups 1 and 2 needed controlled ventilation with PEEP. Fluid management and antibiotic therapy were used as required. Intermittent mandatory ventilation (IMV) was not used. The respiratory functional assessment was performed under controlled ventilation using a previously described device,17 which allows measurement and monitoring of quasistatic compliance (normal ranges 50 to 60 ml/cm H₂O) and of Vₚ parallel/Vₐ ratio (normal under 0.10). The best arterial pressure of oxygen (PaO₂ max) was measured after 45 minutes of breathing of pure oxygen under controlled ventilation with PEEP. The increase in shunt fraction was calculated with standard equations, using O₂ contents of mixed venous and arterial blood during pure oxygen administration.

The weaning from controlled ventilation was systematically attempted when PaO₂ max was over 300 mm H₂O, static compliance over 30 ml/cm H₂O, and the Vd/Vₐ ratio under 0.30. Complete weaning and extubation were done after a 24-hour period of continuous positive airway pressure (CPAP) in spontaneous ventilation if the patient had no hypercapnia and a respiratory rate under 30/minute.

Biologic Methods
The ACE activity was measured according to the method of Cushman and Cheung, modified by Lieberman.18 Normal values in healthy control subjects are 20 to 35 U/ml. Plasma fibronectin was measured according to the method of Pott et al.19 Normal values in healthy control subjects are 200 to 400 mg/L. Statistical comparison used analysis of variance and Student's t test. Means are expressed with SD, and statistical significance was considered when p<0.05.

Results
Group 1: Nonlethal ARDS
In this group the weaning was successful in 15 patients during the ten days of the study. Group W+ included patients who were weaned; group W− included the 13 patients who were not able to be weaned after ten days of controlled ventilation. These 13 patients needed controlled ventilation during an average of 18 days (range 13 to 28 days).

Since the weaning was done according to the results of respiratory functional assessment, the 15 patients of group W+ were dispatched according to the date of this weaning. Four patients could be weaned at day 5 (group W+ 5), 5 patients at day 7, and 6 at day 9 (groups W+ 7 and W+ 9). The results of the respiratory functional assessment were compared between each of the four groups—W+, W+ 7, W+ 9, and W−. At admission, PaO₂, Qs/Qt, static compliance, and Vd/Vₐ ratios were not different among the groups. These four indexes became significantly different from the third day after admission between groups W+ 5 and W−, groups W+7 and W−, and groups W+5 and W+9. The results were not different between groups W+9 and W−

ACE levels: For the whole group 1, sequential measurements of ACE showed a diphasic evolution of mean levels, with an initial decrease from day 1 to day 3 and a later increase from day 5 to day 9 (Fig 1). The SDs of these mean levels were very wide (±20 percent).

FIGURE 1. Evolution of ACE levels (n = 28 M ± SD).

FIGURE 2. Comparison of ACE levels in group W+ vs W− at day 10.
There was a significant difference between groups W+ and W− as early as the first day after admission (p<0.05) (Fig 2), but the ACE level had no predictive value for the success of weaning. The comparison, according to the date of weaning, is shown in Figure 3. In group W+ 5 the diphasic evolution of ACE levels was not observed, and all the patients had values over 20 U/ml with no significant variations. Starting from day 3, the levels measured in this group were significantly higher than in any of the other groups (p<0.01). The diphasic evolution was observed in groups W+ 7 and W+ 9. The initial decrease had the same magnitude, but the nadirs of the curves were delayed according to the date of weaning. In group W−, ACE levels remained low. Mean levels were not different in groups W+ 9 and W− (Table 1).

Fibronectin levels: Sequential measurements of fibronectin groups levels tended to be higher but the ACE levels were of no predictive value. The evolution was shown in Table 1. The ACE levels were correlated with the PaO2/FIO2 ratio (r = 0.72) and with the pulmonary vascular resistances (r = −0.63). In our study there was an evident correlation between ACE levels and the results of pulmonary functional assessment (PaO2,max, static compliance, and VD/VA ratio). ACE levels remained high, and the diphasic evolution was not observed in group W+ 5 (early weaning). ACE levels remained low when the respiratory impairment was long-lasting (group W+). The decrease in ACE levels paralleled the delay in respiratory improvement. Furthermore, the comparison between group 1 (nonlethal ARDS) and group 3 (sepsis without ARDS) shows that the decrease in ACE levels is better linked with the lung endothelial injury than solely with the sepsis.

The comparison of sequential measurements of plasma fibronectin brings new information about the specificity of the ACE decrease. The possibility has

![Figure 3. Evolution of ACE according to the date of weaning.](image-url)

Table 1—ACE and FN Levels

<table>
<thead>
<tr>
<th>Group</th>
<th>W+ 5</th>
<th>W+ 7</th>
<th>W+ 9</th>
<th>W−</th>
</tr>
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<tbody>
<tr>
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<td>21±5</td>
<td>17±3</td>
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<td></td>
<td>318±83</td>
<td>318±83</td>
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</tbody>
</table>

Comments

We tested the hypothesis that sequential measurements of ACE levels could be useful as an index of endothelial injury and repair during ARDS. Some results confirm previously published data:

1. Serum ACE levels decrease during ARDS. Sequential measurements are consistent with a diphasic evolution—initial decrease during the first three days and return to normal ranges within seven to ten days.

2. ACE levels do not simply reflect the severity of hypoxemia. No correlation could be found between ACE and PaO2. All patients underwent controlled ventilation and had a PaO2 within the normal ranges.

3. The discrepancy between the results of clinical and experimental studies might be explained by the usual delay between the acute enzymatic depletion (increased serum levels five minutes after experimental injury) and the time of admission and blood sampling in human ARDS (decreased serum levels after at least 24 hours).

4. The decrease in ACE levels is well correlated with the severity of lung injury. Osamu et al. found an early significant correlation of ACE levels with the PaO2/FIO2 ratio (r = 0.72) and with the pulmonary vascular resistances (r = −0.63). In our study there was an evident correlation between ACE levels and the results of pulmonary functional assessment (PaO2,max, static compliance, and VD/VA ratio). ACE levels remained high, and the diphasic evolution was not observed in group W+ 5 (early weaning). ACE levels remained low when the respiratory impairment was long-lasting (group W−). The decrease in ACE levels paralleled the delay in respiratory improvement. Furthermore, the comparison between group 1 (nonlethal ARDS) and group 3 (sepsis without ARDS) shows that the decrease in ACE levels is better linked with the lung endothelial injury than solely with the sepsis.

The comparison of sequential measurements of plasma fibronectin brings new information about the specificity of the ACE decrease. The possibility has
been considered in several studies that plasma fibronectin might be a reliable index of lung endothelial

injury. Fibronectin acts as a nonspecific opsonin for the clearance of degradation products by the reticuloendothelial system. Fibronectin might, as collagen and elastin, be destroyed by proteases during the acute pulmonary leukostasis and activation of PMNs. In human ARDS, the initial decrease in fibronectin level was proposed as a prognostic index, and therapeutic replacement has also been done with enriched cryoprecipitates in some patients. In our study fibronectin levels in group 1 increased throughout the study. No difference was observed according to the initial severity of lung injury or the rapidity of improvement. The sequence was the same in group 3 (nonlethal sepsis without ARDS). On the contrary, in group 2 (lethal ARDS) fibronectin levels decreased from day 1 to day 5 and were then significantly lower (80 44 vs 285 82 mg/L, p<0.01).

These different findings indicate that sequential ACE levels are well correlated with the initial extent and prolongation of lung injury during ARDS. During the first days of clinical evolution, the lack of decrease might be valuable for prediction of respiratory improvement. Persistent decreased levels after eight days are consistent with the lack of endothelial repair or with continuing injury. Fibronectin might be more an index of prognosis and evolution of sepsis. The decrease in the fibronectin level during the first days of clinical evolution is valuable for prediction of vital prognosis.

REFERENCES

4 Bedrossian CW, Wood J, Miller WC. Decreased ACE levels in

![Figure 4. Evolution of FN levels.](image)

![Figure 5. Evolution of ACE and FN in ten patients with lethal ARDS.](image)

![Figure 6. Evolution of ACE and FN levels in eight patients with sepsis without ARDS.](image)


