Influence of serum epidermal growth factor on mechanical ventilation and survival in patients with acute respiratory distress syndrome

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Background: The mortality rate of acute respiratory distress syndrome has remained high. Studies have shown that concentrations of some of the inflammatory mediators, as well as some of the growth factors in serum and/or bronchoalveolar lavage, are higher in nonsurvivors. **Objectives:** We hypothesized in a previous study that it is possible that the serum level of epidermal growth factor (EGF) in nonsurvived patients would be higher than that of survived patients. **Patients & methods:** Data was evaluated for 30 patients diagnosed with acute respiratory distress syndrome on mechanical ventilation. Blood samples were taken before initiating mechanical ventilation as well as 2, 4 and 8 h after. **Results:** Serum EGF concentration was reduced ($p < 0.05$) in survivors 2 h after initiating mechanical ventilation. In addition, the differences between PaO_2/FiO_2 and Acute Physiology and Chronic Health Evaluation II score at the start and the end of the study was significant ($p < 0.05$). The serum EGF concentration increased after 8 h in nonsurvivors ($p < 0.05$). Significant changes in serum EGF concentrations in nonsurvivors at different time periods in the low positive end expiratory pressure group of patients ($p < 0.05$) were observed. **Conclusion:** Serum levels of EGF on admission may provide valuable information for predicting the outcome of acute respiratory distress syndrome patients.

Keywords: acute respiratory distress syndrome, epidermal growth factor, mortality, outcome

Acute respiratory distress syndrome (ARDS) is characterized by severe acute hypoxemia, increased pulmonary capillary permeability, decreased lung compliance and increased pulmonary vascular resistance [1]. It is associated with a high mortality rate (50–90%) and contributes significantly to the mortality rate in intensive care units [2]. It is generally believed that ARDS occurs as a result of tissue injury secondary to sequestration of inflammatory cells, tissue invasion and secretion of cytotoxic products [3].

It is obvious that ARDS is frequently associated with the fibroproliferative response that is characterized by mesenchymal cell proliferation and extracellular matrix accumulation within the alveolar and interstitial compartments of the injured lung. In the autopsy of patients, pulmonary fibrosis has been identified as a common feature [4,5] and a correlation has been found between pulmonary fibrosis and fatality in established cases of ARDS [6,7]. It has been shown in ARDS patients that in those dying later than 10 days after the onset of the syndrome, pulmonary collagen content is increased [5].

For appropriate clinical interventions, it is crucial to know, not only the mediators involved in the disease, but also the changes of these mediators with time to identify which are useful markers of the mortality rate, as has been suggested in several studies [8–11]. There are cut-off values for some of the inflammatory mediators in nonsurvivors, such as interleukin (IL)-1, -2, -4, -6, -8 and -10 [11–14].

Growth factors have been implicated in abnormal lung remodelling that result in fibrosis and changes in the architecture of the air spaces [15]. Tissue injury results from mesenchymal cell injury, at least in part from the increased expression of growth factors within the tissue microenvironment. Growth factor imbalances have been reported in various lung pathologic conditions, although it cannot be known from these studies whether the imbalance is the cause or the consequence of the disease. Previously it was reported that epidermal growth factor (EGF) and transforming growth factor (TGF)-α increased alveolar epithelial repair in the *in vitro* wound-healing system [16]. These growth factors contribute to IL-1β-induced alveolar epithelial repair [17]. For cytokines that regulate mesenchymal cell proliferation and fibrosis, such as TGF-α and -β, a prominent role has been suggested in view of the association between fatality and pulmonary fibrosis in established ARDS [6]. TGF is a cell surface-associated as well as -secreted mitogen that shares 42% homology with human EGF and binds to the same surface receptor as EGF, referred to as the EGF receptor [18,19]. Activation of the EGF receptor

induces collagen and glycosaminoglycan synthesis by mesenchymal cells, and stimulates the expression of matrix metalloproteinase and tissue inhibitors of metalloproteinases *in vitro* [20–24]. However, a systematic study of the role of EGF in the mortality rate of ARDS has not yet been undertaken.

The fact that mechanical ventilation can cause an increase in inflammatory mediators has been proven and the effect of this response on multiorgan dysfunction syndrome (MODS) as well as the patient's outcome, has been demonstrated. Although there still remains some debate, large randomized studies have shown improved outcome with lower tidal volumes. However, small tidal volumes alone may not be protective due to the progressive loss of end expiratory lung volume and hypercapnia. The use of positive-end expiratory pressure (PEEP) to prevent this is an essential part of protective ventilation [25].

In our previous study [26], we demonstrated an association between blood EGF decrement 2 h after mechanical ventilation and improvement of oxygenation and Acute Physiologic And Chronic Health Evaluation (APACHE)-II score in ARDS patients. According to the importance of the relationship between mortality and inflammatory mediators, we hypothesized that a relationship could also exist between mortality and EGF serum concentration and we conducted a retrospective study to examine this possible relationship and potential prognostic indicators for outcomes of patients with ARDS.

Methods

Following approval of the study protocol by the ethics committee of Tehran University of Medical Science (TUMS) for human research, files of 30 ARDS patients were retrospectively analyzed. Patient-election criteria were based on the American–European Consensus Conference definition of acute lung injury including acute onset of illness, PaO_2/FiO_2 less than 300, bilateral infiltrates on chest radiograph, pulmonary capillary wedge pressure (PCWP) of 18 mmHg or less, or absence of any clinical evidence of left atrial hypertension [27,28].

All of the ARDS patients with respiratory failure had been supported mechanically for their condition. Exclusion criteria were congestive heart failure (CHF) or any cardiac condition that causes pulmonary hypertension. The APACHE-II scoring system was used for grading the disease severity [29].

A blood sample had been obtained after admission and before initiating mechanical ventilation. The second to fourth blood samples had been taken 2 h after initiating mechanical ventilation with a definite PEEP (ranging between 5 and15 cm H_2O) and tidal volume (6–8 ml/kg), 4 and 8 h after admission, respectively, though the real time of production of inflammatory mediators is not clear. In addition, the process of fibrosing alveolitis apparently begins early in the course of the disorder and may be promoted by early proinflammatory mediators even at the time of intubation and the initiation of mechanical ventilation [30]. At the time of each blood sampling, vital signs and other physiologic parameters had been recorded exactly. Paraclinical parameters such as arterial blood gas, serum electrolytes, creatinin, blood urea nitrogen, albumin, hemoglobin, glucose and cell blood count had been measured before starting PEEP as well as at the end of study. Serum EGF concentrations were measured using Quantikine® (human EGF immunoassay) [27].

Data analysis was carried out using SPSS 10.0 statistical software. Results are expressed as mean ± standard deviation. Since the distribution of EGF values was abnormal (confirmed by one sample Kolmogorov–Smirnov test, $p < 0.05$), EGF values were transformed to log EGF (logarithm of EGF concentration) and then analyzed. The general linear model repeated measures test was used to evaluate the significance of changes in EGF levels at different times. The paired sample t-test was used to compare the mean values of data. A p-value of less than 0.05 was considered significant.

Results

Patient's demographic and clinical data are shown in Table 1. EGF serum concentrations are included in Table 2. The mortality rate in studied patients was 43.3%. Analysis of serum EGF concentrations at different times indicated that in survivors 2 h after PEEP, EGF levels reduced significantly ($p < 0.05$) but not in nonsurvivors. In general, according to the different time points, the serum EGF concentration was elevated significantly after 8 h in nonsurvivors ($p < 0.05$).

Patients were stratified based on PEEP and considered two groups as low (range: 5–10 cm H_2O) versus high PEEP (range: 10–15 cm H_2O) group. In the low PEEP group, the difference between EGF serum levels at different time periods was statistically significant ($p < 0.05$) in nonsurvivors (Figure 1).

Table 1. Clinical features of the studied population on admission.

Group	n	Sex	Age	PaO_2/FiO_2	APACHE II
Survivor	17	M = 11 F = 6	59 ± 16	191 ± 75	26.2 ± 5.8
Nonsurvivor	13	M = 9 F = 4	54 ± 19	213 ± 80	24.2 ± 5.3

APACHE: Acute Physiology and Chronic Health Evaluation; ARDS: Acute respiratory distress syndrome; F: Female; M: Male

In survivors, the differences between $PaO2/FiO_2$ and APACHE II score at the start and the end of the study was significant ($p < 0.05$).

Expert opinion

The last decade has seen the appearance of several large studies directed at identifying factors that affect the persistent high mortality rate in ARDS [31–33]. It has been reported that in ARDS nonsurvivors, blood concentrations of proinflammatory cytokines at the onset of disease is elevated and persist during the time course of ARDS [11,34,35]. Many studies proved the potential for pulmonary fibroproliferation at the early stages of ARDS. There is however, a high probability of significant crosstalk between immune and fibrotic pathways, with inflammatory cells playing an important role in stimulating the repair process [36]. In addition, it was suggested by some of the investigators that pulmonary fibroproliferation is an important determinant of outcome [37]. Alveolar macrophages, for example, are a potent source of fibroblast growth factors [38]. In patients with ARDS, a protein of similar molecular weight to platelet-derived growth factor (PDGF) [39] and TGF-α have both been determined in bronchoalveolar fluid (BALF), but the functional role of these and other profiberotic mediators in ARDS is not known [40].

In the present study, it is demonstrated that the increment of serum EGF concentration in nonsurvivors and in the low PEEP group was significant ($p < 0.05$). The increased EGF serum concentration after 8 h in nonsurvivors indicates that the persistence of fibroproliferative responses may be of importance in determining outcome. The rationale for the analysis of EGF concentrations in serum is that during ARDS, the alveolar epithelial–endothelial barrier is disrupted and cytokines produced in the lung are released into circulation, which is the potential mechanism for the development of the systemic inflammatory response syndrome [41,42]. The relationship between circulatory and pulmonary cytokine levels and outcomes provides support for the hypothesis that poor outcome in ARDS is related to a persistent inflammatory process [14]. In agreement with the present findings, it has been demonstrated that TGF-α levels in BALF are significantly elevated in most patients with established ARDS [39]. In patients with persistent ARDS, there was a trend toward increased fatality when lavage TGF-α levels are elevated at days 7 and 14 [39]. The results of another study implied that elevated lavage concentrations of TGF-α might be associated with an increased fatality rate in patients with delayed resolution of ARDS [39], as did our study group.

In contrast, the other study could not document any correlation between TGF-β from a time point of view and on the mortality rate [43]. It has been shown that plasma concentrations of IL-8 or leukotriene B4 alone were not good markers of mortality rates in ARDS patients [44]. The elevation of EGF in nonsurvivors at day 1 is in agreement with many of the previous reports which demonstrated elevated inflammatory concentrations in BALF [37,45–47] as well as in serum [11]. Prior studies have shown that IL-8 concentrations were found to predict the onset and the outcome of ARDS [9–11,48].

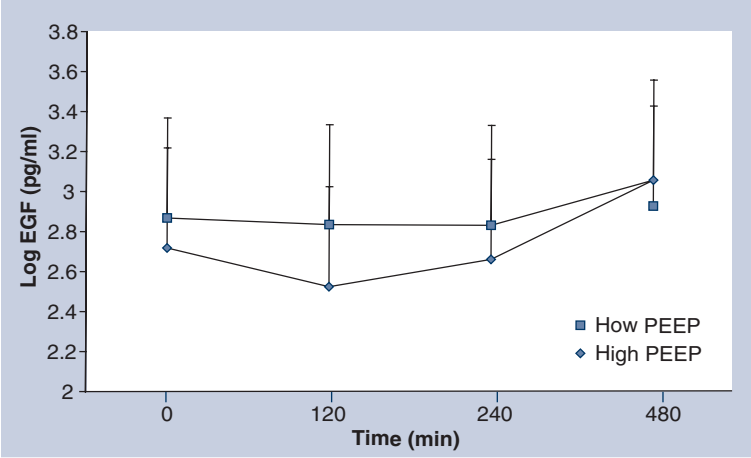
Determining the key profibrotic factors present in ARDS is an important future goal and we are currently working on a number of approaches to identify growth factors present in the BALF or serum of these patients. The ability to time the onset of injury in many ARDS patients opens the door to study the temporal association between pathophysiologic

Table 2. Serum EGF concentrations in two groups of patients.

	Survivors	Nonsurvivors
Log_{EGF1}	2.94 ± 0.36	2.82 ± 0.31
Log_{EGF2}	2.81 ± 0.29*	2.72 ± 0.30
Log_{EGF3}	2.87 ± 0.20	2.77 ± 0.30
Log_{EGF4}	2.91 ± 0.31	2.99 ± 0.25‡
Low PEEP	8	5
High PEEP	9	8

Serum EGF concentrations are given at four different time points (0, 120, 240, 480 min).
**Difference with point 0 is significant ($p < 0.05$)*
‡Overall difference after 8 h is significant ($p < 0.05$).
EGF: Epidermal growth factor; PEEP: Positive end expiratory pressure.

Figure 1. Changes in serum EGF levels in nonsurvivors of acute respiratory distress syndrome regarding low and high PEEP.



Data are presented as mean ± standard deviation. The two lines are significant when tested by General Linear Model Repeated Measures Test ($p < 0.05$).
EGF: Epidermal growth factor; PEEP: Positive-end expiratory pressure.

processes following diffuse lung injury. According to this process, it seems that inflammatory and repair mechanisms occur in parallel, rather than in series [37]. It is also possible that the process of mechanical ventilation in these patients is itself injurious to the lung [49–51]. Mechanical ventilation, the therapeutic intervention that is continuously used in the treatment of ARDS, can itself lead to an increase in cytokine levels in the lung, as well as in the systemic circulation. Our data show that if we divide all of the patients into two groups (low vs. high PEEP), the EGF serum concentration is higher in the low PEEP group in nonsurvivors. In this study we showed that PaO_2/FiO_2 in survivors increased significantly and that in one study, oxygenation failure as reflected by increasing FiO_2 requirements was an important predictor of outcome [52]. These data propose that low levels of PEEP should be avoided but does not imply the value of very high (>15 cm H_2O) PEEP levels [52]. Also, there is evidence that mechanical ventilation could cause injury due to overdistention as more of the tidal volume is distributed to the small, relatively normal alveolar regions [53–55] and/or repeated recruitment or derecruitment of alveolar units that may be amplified by ventilation at low PEEP levels [53–57].

Highlights

- It seems that there is a relationship between epidermal growth factor (EGF) and mortality in acute respiratory distress syndrome (ARDS).
- A total of 2 h after mechanical ventilation, serum EGF concentration decreases in survivors of ARDS.
- There is a significant change in serum EGF concentration of nonsurvivors in the low positive-end expiratory pressure.
- Fibroproliferative response may be of importance in determining the outcome of ARDS.

Discussion

The present study shows that blood EGF concentration was higher in nonsurvivors of ARDS. The remaining patients obtained similar results with hepatocye growth factor and keratinocyte growth factor in lung edema fluid [58,59]. This study brings to mind many questions about ARDS and its inflammatory cytokines, such as is EGF beneficial or damaging for ARDS patients? In addition, there also remain some questions regarding other growth factors. Regarding serum levels in nonsurvivors, it is suggested that systemic inflammatory over-response in critically ill patients may be destructive leading to MODS and poor outcome. Serum levels of all patients in this study suggest that elevated EGF might reflect the severity and extension of inflammation but is not the only factor related to ARDS development and outcome.

Outlook

Our results demonstrated the predictive role of one of the other molecules in serum of established ARDS patients that is valuable for outcome. Further studies with greater numbers of patients and various subgroups of ARDS as well as stricter grouping criteria should be designed to investigate the complex network of these molecules and their contributions and predictive values in outcome.

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