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Original Article

Plasma levels of soluble receptor for advanced glycation end products in patients with acute respiratory distress syndrome

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Abstract: The acute respiratory distress syndrome (ARDS) is a syndrome of acute respiratory failure associated with severe inflammation and diffuse alveolar damage. Recent studies have demonstrated that the soluble receptor for advanced glycation end products (sRAGE) plays an important role in the pathogenesis of ARDS. The aim of this study was to ascertain whether plasma levels of sRAGE were elevated in ARDS patients compared with appropriate controls. Furthermore, we explored whether plasma levels of sRAGE were related to disease severity, ventilatory parameters and clinical outcome. We prospectively enrolled twenty-two ARDS patients, fourteen ventilated controls and twelve healthy subjects. The Sequential Organ Failure Assessment (SOFA) score was applied to assess illness severity. In addition, ventilator parameters (arterial oxygen tension (PaO_2): inspiratory oxygen fraction (FiO_2) ratio, arterial carbon dioxide tension ($PaCO_2$), tidal volume and positive end-expiratory pressure (PEEP)) of ARDS patients and ventilated controls were also recorded. Plasma samples were collected within 24 hours and levels of sRAGE were determined using a commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kit. Possible correlation between plasma sRAGE levels and clinical parameters were explored using a simple linear model. Plasma sRAGE levels were significantly elevated in the plasma samples taken from patients with ARDS (1797 ± 383 pg/ml) when compared with both ventilated (650 ± 192 pg/ml, $P < 0.01$) and healthy (415 ± 178 pg/ml, $P < 0.01$) controls. Significant correlations were found between plasma sRAGE levels and PaO_2:FiO_2 ratio ($P < 0.05$, $r=0.36$). There was no significant difference in plasma sRAGE levels between survivors and non-survivors ($P=0.34$). Our results demonstrate that elevated levels of plasma sRAGE may provide a useful marker for ventilated ARDS patients. Furthermore, the relationship between plasma sRAGE levels and PaO_2:FiO_2 ratio in the ARDS population provides the hypothesis that ventilatory strategy may influence alveolar epithelial damage in ARDS.

Keywords: Acute respiratory distress syndrome, soluble receptor for advanced glycation end products, clinical outcome

Introduction

The acute respiratory distress syndrome (ARDS) is a syndrome of acute respiratory failure associated with severe inflammation and diffuse alveolar damage caused by a variety of injurious insults [1]. ARDS has a high incidence and overall mortality remains high, which brings a substantial impact on public health [1-3]. Disruption of the alveolar epithelial lining is a key feature in the pathophysiology of ARDS, and leads to the development of pulmonary edema and respiratory failure [4].

Recent studies have demonstrated that the receptor for advanced glycation end products (RAGE) plays an important role in the pathogenesis of ARDS, due to the fact that it is abundant in the lung and its expression is primarily located on the basal membranes of alveolar type I epithelial cells [1, 5, 6]. Soluble RAGE (sRAGE), consisting of the extracellular domain but lacking the transmembrane and cytoplasmic domains of RAGE, has been described in human plasma [7]. Circulating levels of sRAGE have been reported to be associated with many diseases, including type 2 diabetes [8], coronary artery disease [9], and Alzheimer disease [10]. In 2006, Uchida T et al. showed in their study that plasma sRAGE levels in patients with acute lung injury were significantly higher compared

Table 1. Characteristics of the studying population

Parameters	ARDS patients	Ventilated controls	Healthy controls	*P*-value (ARDS versus ventilated controls)
Number of subjects	22	14	12	
Age (years, mean ± SD)	61 ± 13	59 ± 15	59 ± 16	*p*=0.67
Female sex (n, %)	9 (41%)	6 (43%)	6 (50%)	*p*=0.91
Cause of ARDS (n, %)				
Pneumonia	16			
Aspiration	3			
Lung contusion	1			
Extra pulmonary sepsis	2			
SOFA score	6 ± 3	7 ± 3		*p*=0.34
PaO_2:FiO_2 ratio (kPa)	16.2 ± 3.3	32.8 ± 3.5		*p* < 0.01
$PaCO_2$ (kPa)	8.1 ± 1.0	5.9 ± 1.1		*p* < 0.01
Tidal volume (mL/kg predicted weight)	9.1 ± 2.2	9.5 ± 2		*p*=0.58
PEEP (cmH_2O)	9.4 ± 2.0	6.2 ± 1.4		*p* < 0.01
sRAGE levels (pg/ml, mean ± SEM)	1797 ± 383	650 ± 192	415 ± 178	*p* < 0.01

ARDS, acute respiratory distress syndrome; SOFA, Sequential Organ Failure Assessment; PaO_2, arterial oxygen tension; FiO_2, inspiratory oxygen fraction; $PaCO_2$, arterial carbon dioxide tension; PEEP, positive end-expiratory pressure; sRAGE, soluble receptor for advanced glycation end products; SD, standard deviation; SEM, standard error of the mean.

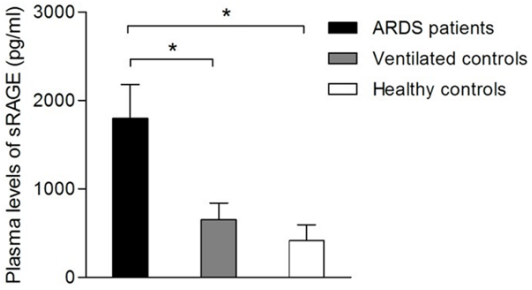

Figure 1. Plasma soluble receptor for advanced glycation end products (sRAGE) levels in patients with acute respiratory distress syndrome (ARDS), ventilated controls and healthy controls. Data are presented as means ± SEM (*P < 0.05).

with patients with hydrostatic pulmonary edema or healthy volunteers [6].

The aim of this study was to ascertain whether plasma levels of sRAGE were elevated in ARDS compared to appropriate controls in our intensive care unit. Furthermore, we also explored whether plasma levels of sRAGE were related to disease severity, ventilatory strategy and clinical outcome.

Materials and methods

Study patients

We prospectively enrolled twenty-two ARDS patients from our hospital between January 2012 and August 2013. Patients with ARDS participated in this study met the American-European Consensus Conference (AECC) criteria [11] and were included within the first 24 hours of disease onset. The exclusion criteria were age < 18 years, pregnancy, and left ventricular failure [12]. Fourteen mechanically ventilated patients of non-pulmonary disorders and twelve healthy subjects matched for age and sex served as controls.

Clinical data and plasma samples collection

The following clinical data were collected at enrollment: age, gender, aetiology of ARDS. The Sequential Organ Failure Assessment (SOFA) score was also applied to assess illness severity. In addition, ventilator parameters (arterial oxygen tension (PaO_2): inspiratory oxygen fraction (FiO_2) ratio, arterial carbon dioxide tension ($PaCO_2$), tidal volume and positive end-expiratory pressure (PEEP)) of ARDS patients and ventilated controls were also recorded. Blood were sampled and processed within 24 hours at enrollment. Plasma samples then were stored at -80°C until analysis.

Measurement of plasma sRAGE levels

Plasma levels of sRAGE were determined using a commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kit which

Table 2. Correlation of plasma sRAGE levels and clinical parameters

Parameters	Correlation with plasma sRAGE (pg/ml)
SOFA score	P=0.38, r=0.21
PaO_2:FiO_2 ratio (kPa)	P < 0.05, r=0.36
$PaCO_2$ (kPa)	P=0.78, r=0.06
Tidal volume (mL/kg predicted weight)	P=0.08, r=0.39
PEEP (cmH_2O)	P=0.18, r=0.33

sRAGE, soluble receptor for advanced glycation end products; SOFA, Sequential Organ Failure Assessment; PaO_2, arterial oxygen tension; FiO_2, inspiratory oxygen fraction; $PaCO_2$, arterial carbon dioxide tension; PEEP, positive end-expiratory pressure.

Table 3. Characteristics, ventilatory parameters and sRAGE levels for survivors and non-survivors of ARDS patients

Parameter	ARDS survivors	ARDS non-survivors	*P*-value
Number of subjects	12	10	
Age (years, mean ± SD)	60 ± 12	62 ± 14	*P*=0.73
Female sex (n, %)	9 (41%)	6 (43%)	*P*=0.91
SOFA score	4 ± 2	9 ± 3	*P* < 0.01
PaO_2:FiO_2 ratio (kPa)	19.6 ± 3.5	12.2 ± 3.1	*P* < 0.01
$PaCO_2$ (kPa)	8.5 ± 1.2	7.6 ± 0.8	*P*=0.05
Tidal volume (mL/kg predicted weight)	8.1 ± 2.0	10.9 ± 2.4	*P* < 0.01
PEEP (cmH_2O)	8.7 ± 2.1	10.2 ± 1.9	*P*=0.09
sRAGE levels (pg/ml, mean ± SEM)	1548 ± 431	2096 ± 317	*P*=0.34

sRAGE, soluble receptor for advanced glycation end products; ARDS, acute respiratory distress syndrome; SOFA, Sequential Organ Failure Assessment; PaO_2, arterial oxygen tension; FiO_2, inspiratory oxygen fraction; $PaCO_2$, arterial carbon dioxide tension; PEEP, positive end-expiratory pressure; SD, standard deviation; SEM, standard error of the mean.

was purchased from R&D Systems (Minneapolis, MN, USA).

Statistical analysis

All Statistical analyses were performed using SPSS version 17.0 (SPSS Inc.) and GraphPad Prism version 5.01 (GraphPad Software Inc.). Qualitative data were expressed as numbers or proportions. Proportions between groups were compared using Chi-square test. Variables with numbers were expressed as means ± standard deviation or means ± standard error of the mean (for sRAGE levels) and comparisons between different groups were subjected to Students' *t* test or one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test, previously checking the homogeneity of variables. Regressions were computed by using a simple linear model. Differences were considered significant when P < 0.05.

Results

Characteristics of patients

Baseline characteristics and ventilatory parameters of the study population are presented in **Table 1**. The primary disorders in the studying ARDS patients were pneumonia (n=16), aspiration (n=3), lung contusion (n=1), extra pulmonary sepsis (n=2). There were no differences in baseline characteristics (neither age nor gender) among three groups. As also illustrated in **Table 1**, $PaCO_2$ levels and PEEP were significantly higher in ARDS compared with the ventilated controls (both P < 0.01). However, PaO_2:FiO_2 ratios were significantly lower in patients with ARDS (P < 0.01).

Correlation between plasma sRAGE levels and clinical parameters

Plasma sRAGE levels were significantly elevated in the plasma samples taken from patients with ARDS (1797 ± 383 pg/ml) when compared with both ventilated (650 ± 192 pg/ml, P < 0.01) and healthy (415 ± 178 pg/ml, P < 0.01) controls (**Figure 1**). We next explored the possible correlation between plasma sRAGE levels and clinical parameters using a simple linear model. As shown in **Table 2**, there was no correlation between plasma sRAGE levels and global illness severity as assessed by SOFA score (P=0.38, r=0.21). However, significant correlations were found between plasma sRAGE levels and PaO_2:FiO_2 ratio (P < 0.05, r=0.36) in patients with ARDS.

Plasma sRAGE levels and clinical outcome

To further determine whether plasma sRAGE levels were associated with the outcome of ARDS, we analyzed the data from survivors and nonsurvivors of ARDS patients. As shown in **Table 3**, survivors and non-survivors displayed significant differences in SOFA score and tidal

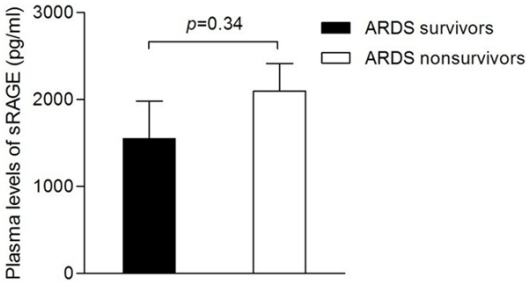

Figure 2. Plasma soluble receptor for advanced glycation end products (sRAGE) levels in survivors and nonsurvivors of ARDS patients. Data are presented as means ± SEM.

volume, which were both higher in the non surviving group, both $P < 0.01$). PaO_2:FiO_2 ratios were significantly lower in the non surviving group ($P < 0.01$). However, there was no significant difference in plasma sRAGE levels between survivors and non survivors (**Figure 2**, P=0.34), as well as $PaCO_2$ and PEEP (P=0.05 and 0.09, respectively).

Discussion

In this study, our results demonstrate that plasma levels of sRAGE from patients with ARDS were elevated when compared with ventilated and healthy controls. Furthermore, significant correlations were detected for the first time between plasma sRAGE levels and PaO_2:FiO_2 ratio in the ARDS population. However, there was no relationship between sRAGE and global illness severity as assessed by SOFA score in our study.

RAGE is abundantly expressed in alveolar type I epithelium in the lung, and its soluble isoform (sRAGE) is released into the plasma when lung tissue is injured [4, 13, 14]. The precise mechanism of its release into plasma has not been clearly elucidated. However, animal studies suggested that sRAGE was shed from alveolar type I epithelial cells by proteases [6]. Previous studies have already shown that plasma sRAGE were higher in ARDS patients compared with controls [4, 6, 15]. Our first results were in conformity with these findings, which suggests that increased plasma levels of sRAGE in patients with ARDS reflect the pathophysiology of lung injury.

We next explored possible correlation between plasma sRAGE levels and clinical parameters such as SOFA score and ventilatory parameters. Significant correlations were found between plasma sRAGE levels and PaO_2:FiO_2 ratio in patients with ARDS. Previous study has reported that patients with high plasma sRAGE were those who benefited most from lung protective ventilation [16]. Our results also indicated that ventilatory strategy may relate to plasma sRAGE levels, which is a marker of alveolar epithelial damage in ARDS.

Finally, we analyzed whether plasma sRAGE levels were associated with clinical outcome of ARDS patients. Although plasma sRAGE levels were elevated in nonsurvivors compared with survivors of ARDS patients, this difference was not significant in our study. Previous studies also presented inconsistent results. Mauri T et al in 2010 found this difference was not statistically significant [15], whereas Nakamura T et al in 2011 demonstrated significant difference [4]. In our limited opinion, some reasons can explain this disparity. First, numbers of patients enrolled in our study and those two studies were relatively small and may not be adequate to provide statistically meaningful data. Second, as previously reported, different isoforms of sRAGE have been described and different ELISA techniques may detect different isoforms [6, 13]. Third, plasma samples used in our study had been stored for several days or months at -80°C, as reported in previous studies [16, 17]; whether this extended storage has any effects on plasma sRAGE levels remains unknown.

In conclusion, our study demonstrates that elevated levels of plasma sRAGE may provide a useful marker for ventilated ARDS patients. Furthermore, the relationship between plasma sRAGE levels and PaO_2:FiO_2 ratio in the ARDS population provides the hypothesis that ventilatory strategy may influence alveolar epithelial damage in ARDS.

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Disclosure of conflict of interest

None.

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