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sRAGE is Elevated in Septic Patients and Associated With Patients Outcome[1]

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Background. **(1) To evaluate in septic patients the plasma levels of soluble receptor for advanced glycation end products (sRAGE), a soluble splice variant of the full length receptor RAGE, which is involved in acute inflammation (2) to determine whether sRAGE could be used as a potential diagnostic and prognostic marker in sepsis in the surgical intensive care unit.**

Materials and methods. **An observational clinical noninterventional pilot study in a surgical intensive care unit with patients admitted to the intensive care unit over a 6-mo period with clinical evidence of severe sepsis or septic shock.**

Results. **Twenty-nine intensive care patients were enrolled in the study within the first 24 h after onset of severe sepsis or septic shock. Eight healthy volunteers served as controls. Plasma sRAGE concentrations were elevated in septic patients compared with healthy volunteers (1764 ± 138 *versus* 1026 ± 177 pg/mL, $P < 0.05$). Additionally, nonsurvivors after 28 days have had higher plasma sRAGE concentrations than survivors (2302 ± 189 *versus* 1326 ± 112 pg/mL, $P < 0.001$). Receiver operating characteristic curve analysis of plasma sRAGE concentrations of septic patients showed a specificity of 75% and a sensitivity of 84.6% with 1596 pg/mL as cutoff.**

Conclusions. **This is the first study showing elevated plasma sRAGE concentrations in septic patients. It is noteworthy that nonsurvivors had higher plasma sRAGE concentrations than survivors, suggesting that sRAGE is related to severity and outcome of septic patients. Further clinical studies are required to investigate the usefulness of sRAGE as a new sepsis marker.**

Key Words: **sepsis; severe sepsis; septic shock; clinical trail; sepsis markers; sRAGE.**

INTRODUCTION

Sepsis remains an important clinical and economic challenge for intensive care units throughout the world. Severe complications such as multi-organ failure with high mortality and the lack of specific diagnostic tools characterize the clinical situation in sepsis [1].

The receptor for advanced glycation end products (RAGE) is a member of the Ig superfamily and a multiligand receptor interacting with a diverse class of ligands [2]. RAGE has been shown to be involved in the pathogenesis of several chronic diseases [2].

Recently, we clarified the role of RAGE in experimental sepsis, showing that RAGE-dependent activation of nuclear factor-kappa B (NF-κB) plays a central role in modulating mortality after cecal ligation and puncture (CLP) [3].

RAGE has secretory isoforms referred to as soluble RAGE (sRAGE), which comprise the extracellular ligand-binding domain but are lacking the cytosolic and transmembrane domains. It is noteworthy that sRAGE has the same ligand binding specificity and therefore competes with cell-bound RAGE and serves as a decoy abrogating cellular activation. In a sepsis model of CLP-induced sepsis the administration of exogenous sRAGE did slightly improve survival [3].

In humans, endogenous sRAGE (esRAGE) is produced by alternative splicing of RAGE mRNA. esRAGE, however, does not represent the entire pool of sRAGE present in the bloodstream and it is speculated that sRAGE can also be cleaved proteolytically from

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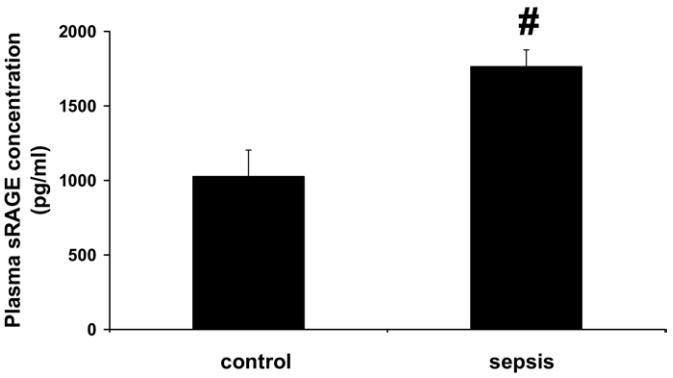

FIG. 1. Circulating sRAGE in patients with severe sepsis or septic shock and healthy controls. Controls ($n = 8$) and septic patients ($n = 29$). Values are means ± SEM; #$P < 0.05$ for controls *versus* septic patients.

the membranous RAGE. However, little is known about the functional role of endogenous levels of sRAGE/esRAGE in healthy patients. In nondiabetic patients sRAGE was elevated in parallel with serum advanced glycation endproduct (AGE) levels [4]. In contrast, Koyama *et al.* found that esRAGE was inversely associated with carotid or femoral atherosclerosis and seems to be a protective factor for the metabolic syndrome and atherosclerosis [5].

Indeed, there is a lack of knowledge regarding the role of sRAGE/esRAGE in sepsis. In view of these data, the aim of this work was to set up a pilot study to investigate whether total pool of sRAGE is increased in plasma of septic patients. Furthermore, we assessed the ability of sRAGE to predict mortality in patients with severe sepsis or septic shock.

MATERIALS AND METHODS

This observational clinical study was conducted in the surgical intensive care unit of the University Hospital of Heidelberg, Germany, after the study protocol was approved by the local ethical committee in accordance with the Helsinki Declaration of 1975.

Eight healthy volunteers served as controls. Twenty-nine consecutive patients of the surgical intensive care unit were enrolled in the study within the first 24 h after onset of severe sepsis or septic shock. Patients were classified according to the Sepsis Consensus Conference on 1992 [6], and clinical data, diagnosis, treatment modalities, and blood samples were collected. All patients were mechanically ventilated and were cared for by the intensive care unit staff. The severity of a patient's illness was estimated using the APACHE II score. Patients with acute primary central nervous system disorders (e.g., meningitis or cerebrovascular accident), acute metabolic disorders, chronic renal disorders, and acute primary liver disease were excluded from the study.

At enrollment, blood samples were taken and sRAGE antigen was detected in plasma by enzyme-linked immunosorbent assay (R and D Systems, Wiesbaden, Germany). At the same time, APACHE II score, mean arterial pressure, arterial oxygen partial pressure/fraction of inspired oxygen ratio, temperature, pH, lactate, and creatinine was documented. A follow-up at 28 d was performed to distinguish between survivors and nonsurvivors. After enrollment of patients, data were blinded to avoid potential bias.

Data are expressed as mean and SEM. A stepwise multivariate linear regression model was calculated to detect independent associations of age, gender, APACHE II score, mean arterial pressure, arterial oxygen partial pressure/fraction of inspired oxygen ratio, temperature, pH, lactate, and creatinine with sRAGE. Comparison of means was performed using Student's *t*-test after testing normal distribution. Receiver operating characteristic (ROC) curves were computed. SPSS 13.0 software was used for statistical analysis (SPSS Inc., Chicago, IL).

RESULTS

sRAGE Measurement in Plasma of Healthy Volunteers and Patients

To test if sRAGE concentrations of septic patients differ from healthy controls, blood samples of eight controls and 29 septic patients were performed. Plasma sRAGE concentrations were higher in septic patients than in healthy volunteers (1764 ± 138 *versus* 1026 ± 177 pg/mL, $P < 0.05$) (Fig. 1).

sRAGE Measurement in Plasma of Survivors and Nonsurvivors

To determine whether sRAGE may serve as an early marker of septic patients outcome, we divided the septic patients according to 28 d mortality in survivors ($n = 16$) and nonsurvivors ($n = 13$) and compared sRAGE concentrations of both groups. Within 24 h of the onset of sepsis, plasma sRAGE concentrations of nonsurvivors were significantly elevated compared with survivors (2302 ± 189 *versus* 1326 ± 112 pg/mL, $P < 0.001$) (Fig. 2).

Patient Characteristics

In the present study, APACHE II score, mean arterial pressure, arterial oxygen partial pressure/fraction of inspired oxygen ratio, temperature, pH, lactate, and creatinine did not significantly distinguish between survivors and nonsurvivors (Table 1).

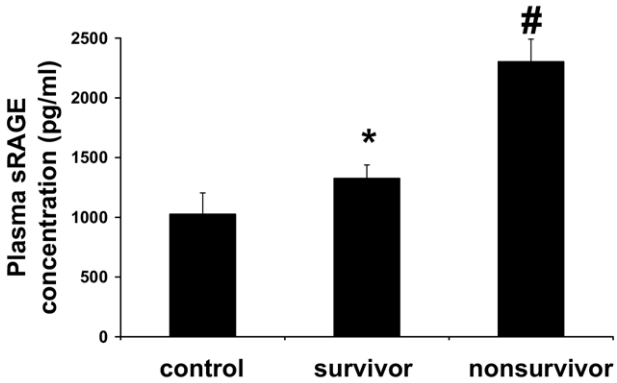

FIG. 2. Circulating sRAGE in controls, survivors, and nonsurvivors. Controls ($n = 8$), survivors ($n = 16$), and nonsurvivors ($n = 13$) of sepsis at day 28. Values are means ± SEM; *$P < 0.05$ for survivors *versus* controls; #$P < 0.001$ for survivors *versus* nonsurvivors.