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Evaluation of endothelial biomarkers as predictors of organ failures in septic shock patients

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ABSTRACT

Background: Endothelial injury is recognized to trigger organ failures during the first 48 h of septic shock. We evaluate endothelial biomarkers at ICU admission in their ability to predict severity, outcome, and organ failures in septic shock patients.

Methods: This prospective observational pilot study was conducted in a medical intensive care unit of a university hospital. Plasma levels of endothelial biomarkers as angiopoietin-2, sE-selectin or endocan were measured at ICU admission of 20 patients presenting with septic shock. Clinical and biological data were recorded at inclusion and each day during the first week.

Results: Significant correlations were found between angiopoietin-2 and severity scores at Day 1: SAPS2 ($r^2 = 0.620$; $p = 0.004$) and LOD score ($r^2 = 0.681$; $p = 0.001$). The angiopoietin-2 level was significantly higher in patients presenting with organ failure such as hemodynamic, renal or hepatic failure. It correlated with catecholamine infusion dose and was higher in non survivors compared with survivors (33.5 [28.9–51.4] vs. 12.4 [6.4–14.7] ng/ml; $p = 0.001$). In contrast, in that population presenting with septic shock, endocan level at inclusion was not related to any organ failure at inclusion or Day 1 but appeared lower in patients presenting with respiratory failure at Day 3 compared to those who do not (1.9 [0.99–3.1] vs 5.2 [3.1–17.2] ng/ml; $p = 0.032$). The endocan level at inclusion was correlated with the decrease in PaO_2/FiO_2 ratio at Day 2 ($r^2 = 0.628$; $p = 0.0004$) and Day 3 ($r^2 = 0.645$; $p = 0.005$). Endocan level <2.54 ng/ml at admission is predictive of a respiratory failure presence at Day 3.

Conclusion: In septic shock patients, angiopoietine-2 is related with clinical severity during the first 24 h but only endocan is able to predict the presence of respiratory failure at Day 3.

1. Introduction

Despite improvement of care and therapies, the morbidity and mortality of sepsis remain high [1,2]. Numerous efforts have been made for developing pathophysiologic markers sought to be related to the diagnosis, severity and/or outcome of sepsis [3]. As they generally reflect single facets of a complex process, there is actually a lack of clinical acceptance, and none is widely used to guide therapies, in particular specifically oriented organ therapies. Endothelium plays a fundamental role in the pathogenesis of sepsis [4]. Endothelium controls many key functions at the intersection of several systems: inflammation, coagulation, hemodynamic, fluid and electrolyte balance. Endothelial dysfunction appears early and is widely implicated in multiple organ dysfunction syndrome (MODS) and in defavorable evolution of septic patients [5,6]. As the early management of sepsis determines patient outcome [7], the use of endothelial dysfunction biomarkers as early biomarkers

Abbreviations: MODS, multiple organ dysfunction syndrome; Ang-2, Angiopoietin-2; sE-selectin, soluble E-selectin; LFA-1, Leukocyte Function-associated Antigen-1 inhibits; ICAM-1, InterCellular Adhesion Molecule-1; ICU, intensive care unit; ELISA, Enzyme Linked Immuno Sorbent Assays; LOD, Logistic Organ Dysfunction; SAPS2, Simplified Acute Physiology Score 2; MAP, mean arterial pressure.

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could allow faster treatment introduction. Angiopoietin-2 (Ang-2), soluble E-selectin [sE-selectin] and endocan are specific markers of endothelial activation recently related to severity and poor prognosis during sepsis; but none has been evaluated for a correlation with the development of organ dysfunction [3].

Ang-2 is a glycoprotein released by activated endothelial cells. Ang-2 antagonizes the Tie 2 ligand angiopoietin 1, resulting in an increase in vascular permeability and in leukocyte diapedesis across the endothelial barrier [8–10]. Convergent studies suggest that high circulating Ang-2 levels are correlated with the number of organ dysfunctions, clinical sepsis severity scores, and mortality [11–15].

E-selectin is a transmembrane leukocyte adhesion molecule synthesized de novo by endothelial cells upon stimulation by TNFα, IL-1β or LPS. E-selectin is rapidly shed from the endothelial cell surface as its soluble form. Both cell surface expression and circulating level of E-selectin are increased in sepsis. The levels of sE-selectin have been reported to correlate with severity scores during ICU stay, severity of sepsis and hemodynamic failure [16–18].

Endocan (Endothelial Specific Molecule 1, ESM-1) is a proteoglycan specifically secreted by endothelial cells, mainly in lung and kidney [19–21]. Endocan binds to the Leukocyte Function-associated Antigen-1 (LFA-1), inhibits LFA-1 interactions with endothelial InterCellular Adhesion Molecule-1 (ICAM-1) and thus is able to modulate leukocyte migration from blood flow into tissues [22,23]. The synthesis and secretion of endocan are up-regulated by pro-inflammatory cytokines like TNFα or IL-1β, and LPS [19]. The endocan blood level correlates with sepsis severity and patient survival [16,24].

To date, studies have examined the relationship between these biomarkers levels and the severity of sepsis and patient outcome. But, to our knowledge, none has taken account to their potential relations with organ failure prediction.

The purpose of this study was to determine if at admission in intensive care unit (ICU) these biomarkers can be related with the occurrence of organ dysfunction during sepsis shock in ICU patients.

2. Materials and methods

2.1. Inclusion criteria

Patients presenting a septic shock according to the 2001 Sepsis Consensus Conference [25] were included within 24 h of ICU admission. Non-inclusion criteria were an age below 18 years and pregnancy. Exclusion criteria were (as our preliminary study in 2006 [16]) an immunosuppressive state (cancer or malignant hemopathy or immunosuppressors or chronic corticotherapy), and chronic hemodialysis. The study protocol was approved by the local ethical committee.

2.2. Measurement of endothelial cell markers

From blood sampled for routine patient management, 2 mL were collected once at the time of inclusion. Within 1 h, the blood samples were centrifuged at 1500 g for 15 min at 4 °C, and the plasmas were aliquoted and kept at −20 °C until used. Control plasmas were provided from 9 healthy volunteers, regularly collected in the laboratory for different studies. Blood sample of these healthy volunteers were collected apart from any infectious period.

Commercial Sandwich-type Enzyme Linked Immuno Sorbent Assays (ELISA) were used for marker determination. Ang-2 was measured with the RayBio® Human Angiopoietin-2 ELISA (RayBiotech, Norcross, GA, USA), sE-selectin was measured with the HK305 Human sE-selectin ELISA (Hycult Biotech, Plymouth, PA, USA), and endocan was measured with the DIYEK™ H1 ELISA (Lunginnov, Lille, France).

2.3. Other recorded data

Age, sex, diagnosis and mortality at 28 days after inclusion were registered. Logistic Organ Dysfunction (LOD) score and Simplified Acute Physiology Score 2 (SAPS2) were calculated in the first 24 h after inclusion, and Sequential Organ Failure Assessment (SOFA) score was calculated at Day 1, Day 2, Day 3 and Day 7 after inclusion. Clinical data, treatment modalities and usual biological data sampled for patient management were collected at inclusion, each day during the first week and at Day 28.

2.4. Criteria used for the definition of organ dysfunction

Septic shock were defined according to the 2001 Sepsis Consensus Conference [25]. Septic shock was treated as recommended by the Surviving Sepsis Campaign [7]. We considered the organ dysfunction from a SOFA score for each organ equal to or greater than 2 [26]. Hemodynamic failure was defined as the need of catecholamine infusion to maintain mean arterial pressure (MAP) over 70 mmHg. Respiratory failure was defined by a PaO_2/FiO_2 ratio <300. Neurologic failure was defined by a Glasgow Coma score <13. Renal failure was defined by a serum creatinin >20 mg/dl, or by a urine output <0.5 ml/kg/h or by introduction of renal replacement therapy. Hepatic failure was defined by a serum bilirubin >1.9 mg/dl. Hematologic failure was defined by a platelet count <100,000/mm^3.

2.5. Statistical analysis

This study is conceived as a pilot study aiming to determine which endothelial biomarker performs the best to predict sepsis severity and organ dysfunction occurrence. According to Siner's study [11] concerning Ang-2 and sepsis severity, a 50% difference between the levels of Ang-2 between death and survivor groups could be anticipated. From our previous study [16], a 3–4 fold difference in endocan levels could be expected between these 2 groups. So, with these hypothesizes, a 20 patient sample should be sufficient for a pilot study to show if a biomarker such endocan do better than Ang-2. Qualitative data are expressed in number and percentage is supplied in brackets. Quantitative data are expressed in median [25th–75th percentile] and explored by non-parametric tests (Mann Whitney test) and tested for association by bivariate correlation for non parametric variables (Rho Spearman). Receiver Operating Characteristics (ROC) curves were computed, their area under the curve (AUC) calculated and the best cut-off point evaluated according to the Youden Index. All statistical tests have bilateral significance and the difference was considered statistically significant if $p < 0.05$. Statistical analysis was performed using the SPSS statistical package (version 15.0, SPSS, Chicago).

3. Results

Twenty patients were recruited. Demographic data are summarized in Table 1. Median SAPS2 was 55 [44–69], and there was 25% of mortality at Day 28.