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Sympathoadrenal activation and endothelial damage in patients with varying degrees of acute infectious disease: An observational study

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ABSTRACT

Purpose: To investigate levels, associations between, and predictive value of plasma catecholamines and biomarkers of endothelial damage in patients with acute infectious illness stratified according to infection type and sepsis severity.
Material and Methods: This is a post hoc study of plasma samples collected in prospective studies conducted at a department of internal medicine. Plasma catecholamines, syndecan-1, and thrombomodulin were measured. Registration of biochemistry, physiology, and 28- and 90-day mortality was performed.
Results: Patients (n = 321) were stratified into 5 groups: no infection (n = 50), local infection (n = 63), sepsis (n = 95), severe sepsis (n = 100), or septic shock (n = 13). Median Sequential Organ Failure Assessment (SOFA) score in all patients was 2, and 28- and 90-day mortality was 6% and 10%. Syndecan-1 and thrombomodulin increased progressively across groups with increasing disease severity (both $P < .001$), correlating with SOFA score in all groups ($\rho = 0.24$-0.87, all $P < .05$). Plasma noradrenaline, syndecan-1, and thrombomodulin were higher in nonsurvivors ($P < .05$) and by log-rank test, levels above median predicted increased 28-day (noradrenaline and syndecan-1, $P < .05$) and 90-day (thrombomodulin, $P < .05$) mortality.
Conclusions: Biomarkers of endothelial glycocalyx and cell damage increased with increasing acute infectious disease severity, correlated with SOFA score, and predicted mortality together with plasma noradrenaline. Sympathoadrenal activation and endothelial damage are linked to disease pathology also in less sick patients.

1. Introduction

Vascular endothelial dysfunction is a critical driver of organ failure in severe sepsis [1]. A key component of the endothelial dysfunction is down-regulation and/or disruption of the natural anticoagulant systems normally residing at the endothelium [2,3]. Consequently, changes in the circulating levels of biomarkers reflecting endothelial damage and/or breakdown of these natural anticoagulant systems are strong predictors of organ failure and poor outcome in patients with sepsis, severe sepsis, and septic shock [4–8].

Sympathoadrenal activation is also a hallmark of acute critical illness, and the accompanying rise in circulating catecholamines induces widespread, dose-dependent effects on the vascular system [9–11], including the endothelium [12,13]. Patients with sepsis display evidence of excessive neurohumoral, including sympathoadrenal, activation that may be both exaggerated and insufficient [14,15], and septic shock patients are often treated with high doses of catecholamines as vasopressor/inotropic therapy [16]. There is emerging evidence that catecholamines induce opposite directed dose-dependent effects on the endothelium and circulating blood (progressive endothelial activation, damage, and hyperpermeability) [11,17,18] and concurrent initial whole blood hypercoagulability followed by hypocoagulability and hyperfibrinolysis [11,12,19–22]). We infer that this represents an evolutionary adapted response aiming at promoting rapid recruitment of immune cells to infected and/or injured tissues while, at the same time, maintaining blood flow through a damaged and progressively more procoagulant microvasculature in the acute critically ill patient [11].

Shock, tissue injury, infection, and hyperinflammation all contribute to endothelial damage in acute critical illness, including sepsis [1,23,24]. Also, we have previously reported that high plasma (p)-catecholamines are associated with increased circulating levels of biomarkers reflecting endothelial damage in trauma [25,26], severe sepsis and septic shock [27,28] and ST-segment elevation myocardial infarction (STEMI) [29] patients, and furthermore that high p-catecholamines are strong predictors of mortality [25,28,29]. Although this association is evident in the critically ill patient with acute life-threatening disease, it is not known whether this exists in patients with less severe disease as there appears to be a dose-response relationship between the p-catecholamine level

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and organ-, including endothelial, damage [10,11]. Furthermore, it is not known if endothelial damage is evident and/or has predictive value in patients with less severe disease.

Given this, the primary aim of the present study was to investigate the circulating level, associations between, and predictive value of plasma (p)-catecholamines and biomarkers of different types of endothelial damage, namely, endothelial glycocalyx (by measuring syndecan-1 [30]) and endothelial cell damage (by measuring soluble thrombomodulin [31–33]), in patients with acute infectious illness stratified according to infection type and degree of sepsis severity.

2. Materials and methods

2.1. Patients

The present study is a post hoc study of plasma samples and patient data from 3 previously conducted prospective studies [34–36] investigating patients with varying degrees of infection ranging from suspected infection to diagnosed bacteremia, sepsis, severe sepsis, or septic shock. The studies [34–36] were conducted from January 2003 to July 2005 at the Department of Internal Medicine, Odense University Hospital, where patients were referred by a general practitioner or admitted from the emergency department. The Department of Internal Medicine covered the specialties of infectious diseases, rheumatology, pulmonary medicine, and general internal medicine.

Inclusion criteria were as follows: suspected diagnosis of infection as judged by the referring physician and blood cultures drawn at the time of admission or suspicion of sepsis by the doctor in charge and initiation of empirical treatment with antibiotics (research blood sampling done within 24 hours from admission in both cases) or culture-positive bacteremia verified by the Department of Clinical Microbiology (only patients with research blood sampling done within 48 hours from admission were included in the post hoc study).

Exclusion criteria were as follows: age less than 18 years, earlier participation in the study, prior hospitalization within 7 days before admission, or growth of bacteria considered to be nonpathogenic in the blood cultures.

All patients received standard of care treatment according to the department guidelines.

Data on demography, comorbidity including Charlson Index, admission biochemistry, physiology and vital status, systemic inflammatory response syndrome (SIRS) criteria, disease severity (Sequential Organ Failure Assessment [SOFA] score), length of stay (LOS) in hospital (non–intensive care unit [ICU] medical wards, total including ICU), and outcome (28-day and 90-day mortality) were available.

Infection was categorized according to the following definitions [34,36]: culture/microscopy of a pathogen from a clinical focus, positive urine dip test result in the presence of dysuria symptoms, chest x-ray–verified pneumonia with no identified pathogen, infection documented with another imaging technique with no identified pathogen, obvious clinical infection (eg, erysipelas and wound infection), and identification of a pathogen by serology or polymerase chain reaction. The classification of the status of infection was made by only one physician, who was blinded to all biochemical results.

In the present study, patients were stratified into the following groups (based on previous stratifications [34–36]): no infection (no verified infection, with or without SIRS), local infection (verified/suspected infection without SIRS), sepsis (verified/suspected infection with SIRS), severe sepsis (sepsis with organ dysfunction), or septic shock (severe sepsis with persisting hypotension despite fluid resuscitation for at least 1 hour). If a patient had any comorbidity that could more probably explain one or more of the criteria for organ dysfunction, the patient could not be categorized as having severe sepsis.

The protocols were approved by the Ethics Committee of Fyns and Vejle Counties and the Danish Data Protection Agency and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from patients or their legal surrogates before enrollment.

2.2. Blood sampling and routine biochemistry

Blood sampling was performed before any antibiotic treatment was started at the hospital in 2 of the cohorts used in this study [34,36]. In the bacteremia cohort, most patients had received antibiotic treatment for 24 to 48 hours before sampling of plasma for research analyses [35]. Samples were processed and plasma was frozen at −80 °C. Routine biochemistry variables were analyzed in a standardized routine laboratory (hemoglobin, white blood cell and platelet counts, factors II-VII-X, alanine aminotransferase, bilirubin, creatinine, blood urea nitrogen [BUN]) together with arterial blood gasses (ABL; Radiometer, Copenhagen, Denmark), procalcitonin (Kryptor PCT; Brahms, Hennigsdorf, Germany; lower limit of detection [LLD] 0.06 ng/mL), C-reactive protein (CRP; Modular P; Hitachi, Tokyo, Japan), and lipopolysaccharide (LPS) binding protein (Immulite-1000; DPC, Los Angeles, Calif; LLD 0.2 μg/mL).

2.3. Biomarkers reflecting sympathoadrenal activation and endothelial damage

Biomarkers of sympathoadrenal activation (adrenaline, noradrenaline) and endothelial glycocalyx (syndecan-1) [30] and cell (soluble thrombomodulin)[31–33] damage were measured in uniplicate by commercially available immunoassays in EDTA plasma according to the manufactures recommendations: plasma (p)-adrenaline and p-noradrenaline (2-CAT ELISA$^{FAST\ TRACK}$; Labor Diagnostica Nord GmbH & Co KG, Nordhorn, Germany; LLD 10 pg/mL [adrenaline] and 50 pg/mL [noradrenaline], respectively), syndecan-1 (Diaclone; Nordic Biosite, Copenhagen, Denmark; LLD 4.94 ng/mL), and thrombomodulin (Diaclone; Nordic Biosite; LLD 0.31 ng/mL).

2.4. Statistics

Statistical analysis was performed using SAS 9.1.3 (SAS Institute Inc, Cary, NC).

Patients stratified according to infection severity (no infection, local infection, sepsis, severe sepsis, septic shock) were compared by a mixed model with Tukey post hoc tests or χ^2/Fisher exact test, as appropriate. Circulating catecholamines and biomarkers of endothelial damage in patients stratified according to vital status days 28 and 90 were compared by Wilcoxon rank sum test.

Simple correlations were investigated by Spearman correlations with results displayed as ρ and P values.

The predictive value of p-catecholamines and endothelial damage biomarkers was investigated by log-rank tests based on Kaplan-Meier survival curves in patients stratified according to the median level of the respective variables (high vs low). Results are presented with χ^2 and P values.

Descriptive data are presented as medians with interquartile ranges (IQRs) or as n (proportions). P values less than .05 were considered significant.

3. Results

3.1. Patients

A total of 321 patients were included in the study and stratified into the following groups: no infection (n = 50), local infection (n = 63), sepsis (n = 95), severe sepsis (n = 100), or septic shock (n = 13; Tables 1 and 2).

Increasing disease severity (from no to local infection to sepsis, severe sepsis, and septic shock) was associated with increased Charlson