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Association between sympathoadrenal activation, fibrinolysis, and endothelial damage in septic patients: A prospective study☆,☆☆

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ABSTRACT

Purpose: The purpose of this study is to investigate potential associations between sympathoadrenal activation and/or vasopressor/inotropic therapy and endothelial activation, damage, and coagulopathy in septic patients.
Materials and methods: Septic patients included in the Scandinavian Starch for Severe Sepsis/Septic Shock trial who were expected not to receive catecholamines at screening preintervention (baseline) and had baseline blood sampled. Clinical, outcome data, and measurements of plasma concentration (p-) biomarkers reflecting sympathoadrenal activation, endothelial activation and damage, natural anticoagulation, fibrinolysis, cell damage, and platelet activation.
Results: Sixty-seven patients were included, of whom 14 turned out to receive noradrenaline infusion at blood sampling. These 14 patients had p-noradrenaline 5-fold higher than patients not receiving catecholamines ($n = 53$), whereas no other baseline preintervention biomarkers differed. In the 53 patients not receiving catecholamines at blood sampling, endogenous p-noradrenaline correlated positively with adrenaline, syndecan 1, soluble vascular endothelial growth factor receptor 1, soluble CD40 ligand, tissue-type plasminogen activator, and plasminogen activator inhibitor 1 (PAI-1) and negatively with PAI-1/tissue-type plasminogen activator ratio (all $P < .05$) and was independently associated with syndecan 1, soluble vascular endothelial growth factor receptor 1, and PAI-1 (all $P < .05$), and 28- and 90-day mortality ($P < .05$).
Conclusions: In septic patients, endogenous noradrenaline was independently associated with biomarkers of endothelial activation, damage, fibrinolysis and mortality, comparable with findings in trauma and myocardial infarction patients. The catecholamine surge in critical illness may contribute to balance endothelial damage and procoagulation with hypocoagulability and hyperfibrinolysis in the circulating blood.

1. Introduction

Sepsis is characterized by widespread endothelial disruption and microvascular dysregulation [1,2], which are central components of disease pathology [2,3], and consequently, several endothelial-derived biomarkers are predictors of outcome in septic patients [4].

Sympathoadrenal activation is a hallmark of acute critical illness, and the accompanying rise in circulating catecholamines induces widespread, dose-dependent effects on the vascular system [5,6], including the endothelium [7]. This "fight-or-flight" response may however become excessive and contribute to organ damage [5,6], and in high concentrations, catecholamines directly damage the vascular endothelium resulting in endothelial cell swelling, necrosis, and progressive de-endothelialization [8,9]. Furthermore, it appears that catecholamines induce opposite-directed effects on the endothelium (progressive activation, damage, and hyperpermeability [6,8,9]) and circulating blood (initial hypercoagulability followed by progressive hypocoagulability and hyperfibrinolysis [6,7,10-14]). We infer that the opposite-directed effects of catecholamines on the vascular system reflect an evolutionary adapted response aiming at promoting rapid recruitment of immune cells to infected or injured tissues (by increasing endothelial cell activation and permeability), whereas at the same time maintaining blood flow through a progressively more activated, injured, and procoagulant microvasculature (by increasing hypocoagulability and fibrinolysis in the circulating blood) in the critically ill patient [6].

We have previously reported strong and independent associations between circulating levels of adrenaline and biomarkers of

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endothelial activation and damage in 2 independent cohorts of trauma patients [15,16], and recently, we found similar associations in patients with ST-segment elevation myocardial infarction (MI) [17]. Furthermore, the circulating levels of adrenaline, syndecan 1, and soluble thrombomodulin (sTM), the latter 2 being biomarkers of endothelial glycocalyx (syndecan 1) and cell (sTM) damage, were independently associated with mortality in both trauma [15,18] and MI patients [17].

Patients with sepsis also display evidence of excessive neurohumoral, including sympathoadrenal activation [1], that may be both exaggerated and insufficient, and patients with septic shock are often treated with high doses of noradrenaline and adrenaline as vasopressor/inotropic therapy [19]. Although shock, tissue injury, infection, and hyperinflammation may all activate and/or damage the endothelium and contribute to coagulopathy in sepsis [1,2,4,20], the potential cocontribution of catecholamines to endothelial activation, damage, hypocoagulability, and/or fibrinolysis in septic patients is not known.

Given that sepsis is associated with excessive sympathoadrenal activation in a context with concurrent coagulopathy and endothelial disruption and injury, the aim of the present study was to investigate associations between endogenously derived catecholamines and biomarkers of endothelial activation and damage, platelet activation, and fibrinolysis in these patients. Because catecholamines exert opposite-directed effects on the circulating blood and vascular endothelium, we hypothesized that high catecholamine levels in septic patients would be associated with evidence of concurrent hyperfibrinolysis and endothelial injury.

2. Materials and methods

2.1. Patients

The study was approved by the regional ethical committee (H-A-2009-056) and the Danish Data Protection Agency and was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from patients or their legal surrogates before enrollment.

All patients were participants in the investigator-initiated Scandinavian Starch for Severe Sepsis/Septic Shock (6S) trial [21], comparing fluid resuscitation in the intensive care unit (ICU) with either 6% hydroxyethyl starch (HES), 130/0.42 HES or Ringer's acetate (RA) in adults patients who were in the ICU, needed fluid resuscitation, and fulfilled the criteria for severe sepsis within the previous 24 hours.

Eligible patients for the present study were patients randomized at 2 specific ICUs where blood samples were collected and stored as part of the protocol (Rigshospitalet and Bispebjerg Hospital) and who had baseline (preintervention ie, samples taken before resuscitation with trial fluids) plasma and serum sampled and were expected not to receive vasopressor/inotropic therapy with catecholamines at the time of screening for randomization/baseline blood sampling. Of 229 patients randomized at the 2 ICUs, we identified 67 patients who we initially inferred not to receive vasopressor/inotropic therapy at the time of randomization and baseline blood sampling, and we measured biomarkers at baseline/preintervention in all of these. However, the final trial database revealed that 14 of these 67 patients had started noradrenaline infusion between the time of randomization and that of

Table 1
Baseline characteristics and outcome of septic patients stratified according to treatment with noradrenaline infusion at blood sampling

		Noradrenaline infusion at blood sampling		*P*
		No	Yes	
n		53	14	
Age	Years	65 (55-73)	72 (69-77)	**.024**
Sex	Males	35 (66%)	5 (36%)	**.040**
Hematologic malignancy	n (%)	8 (15%)	1 (7%)	.672
Emergency surgery	n (%)	8 (15%)	4 (29%)	.257
SAPS II at inclusion	Score	45 (37-60)	50 (37-56)	.677
SOFA at inclusion	Score	5 (5-7)	6 (4-8)	.932
Shock at inclusion	n (%)	29 (55%)	10 (71%)	.364
Ventilator at inclusion	n (%)	37 (70%)	8 (57%)	.369
Source of sepsis				.756
Lungs	n (%)	34 (64%)	11 (79%)	
Abdomen	n (%)	12 (23%)	3 (21%)	
Soft tissue	n (%)	7 (13%)	1 (7%)	
Urinary tract	n (%)	2 (4%)	3 (21%)	
Other	n (%)	8 (15%)	2 (14%)	
Baseline physiology and biochemistry				
MAP	mm Hg	62 (56-72)	60 (50-69)	.267
HCO_3^-	mmol/L	21.3 (17.5-24.3)	23.9 (15.8-26.9)	.441
Lactate	mmol/L	1.8 (1.4-3)	3.5 (2.0-4.8)	**.033**
Hemoglobin level	mmol/L	6.5 (5.8-7.6)	6.3 (5.6-7.9)	.896
WBC	$*10^9$/L	14.3 (7.3-19.9)	13.6 (10.1-19.9)	.890
Platelet count	$*10^9$/L	150 (93-278)	246 (173-404)	**.028**
Outcomes				
28-d mortality	n (%)	19 (36%)	7 (50%)	.334
90-d mortality	n (%)	24 (45%)	11 (79%)	**.036**
RRT within 90 d	n (%)	12 (23%)	3 (21%)	1.000
Ventilation within 90 d	n (%)	47 (89%)	12 (86%)	.669
Bleeding in ICU	n (%)	13 (25%)	4 (29%)	.740
Severe bleeding in ICU	n (%)	7 (13%)	0 (0%)	.330

WBC indicates white blood cells; RRT, renal replacement therapy.
Data are presented as medians (IQR) or n (%). Patients with or without noradrenaline infusion at blood sampling were compared by Wilcoxon rank sum tests and χ^2/Fisher exact tests, as appropriate, with *P* values <.05 shown in bold.
Emergency surgery, emergency surgery before ICU admission; shock, MAP <70 mm Hg or plasma lactate >4.0 mmol/L in the hour before randomization; SAPS, calculated from 17 variables with higher scores indicating more severe disease; SOFA, subscores ranging from 0 to 4 for each of 5 components (circulation, lungs, liver, kidneys, and coagulation with aggregated scores ranging from 0 to 20, with higher scores indicating more severe organ failure); source of sepsis, some patients had more than 1 source of infection. The "other" category included sepsis from vascular catheter-related infection, meningitis, or endocarditis as well as sepsis from unknown sources; bleeding in ICU, any bleeding; severe bleeding in ICU, serious adverse reaction bleeding requiring transfusion with 3 red blood cells or more.
* Multiplicate.