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Endothelial Cell Activation in Emergency Department Patients with Sepsis and Non-sepsis related Hypotension

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Abstract

Introduction—Previous studies found increased circulating levels of biomarkers related to endothelial cell activation in patients with sepsis, particularly in the most severe sepsis stages of sepsis shock. It remains unclear, however, whether this activation is mainly driven by sepsis-specific mechanisms or occurs as a generalized inflammatory response. The objective of this analysis was to compare patterns of biomarkers of endothelial cell activation in patients with hypotension due to sepsis and non-sepsis etiologies.

Methods—This is a secondary analysis of a prospective, observational cohort study including emergency department patients aged >17 years with an episode of hypotension defined as any systolic blood pressure measurement <100mmHg. Etiology of hypotension episodes was classified as sepsis or non-sepsis (e.g. cardiac or hemorrhagic). Endothelial activation biomarkers of cell adhesion (E-selectin, VCAM-1 and ICAM-1), coagulation (PAI-1) and VEGF signaling (VEGF, sFLT-1) were assayed.

Results—A total of 161 patients were analyzed. Hypotension was classified as sepsis (n=69), non-sepsis (cardiac [n=35], hemorrhagic [n=12]) or indeterminate (n=45). With the exception of PAI-1, median plasma levels of all endothelial markers were significantly higher in patients with sepsis compared to non-sepsis etiology (p<0.05 for all comparisons). Logistic regression analysis adjusted for age, gender, mean blood pressure level and mortality, confirmed a significant association of E-selectin (OR 3.7, 95% confidence interval: 1.7–7.8, p<0.001) and sFLT-1 (2.0, 1.1–3.8, p<0.03) with sepsis etiology. Biomarkers VCAM-1 (2.0, 0.88–4.4, p=0.1), VEGF (1.5, 0.98–2.2, p=0.06), ICAM-1 (1.5, 0.9–2.6, p=0.2) and PAI-1 (1.4, 0.8–2.3, p=0.2) did not reach statistical significance.

Conclusions—This study found a sepsis-specific activation of endothelium activation markers, particularly E-selectin, and sFLT-1 in emergency department patients with hypotension.

Keywords

Hypotension; sepsis; cardiac; hemorrhagic; endothelium; coagulation; inflammation

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INTRODUCTION

Emerging evidence suggests that the endothelium plays an essential role in the progression of sepsis to severe sepsis and septic shock (1–5). The endothelium participates in the inflammatory response during sepsis through signaling molecules such as E-selectin, which adheres to circulating white blood cells to facilitate cell rolling, or soluble vascular cell adhesion molecule (VCAM)-1 and soluble intercellular adhesion molecule (ICAM)-1, which solidify cellular bonds for transmigration (6–8). In addition, vascular endothelial growth factor (VEGF) contributes to vascular leak and propagation of host response, while its soluble receptor (sFLT-1) is an anti-inflammatory peptide that inhibits VEGF activity (4,8,9). Additionally, molecules such as plasminogen activator inhibitor (PAI)-1 act at the level of the endothelium to help regulate coagulant and anti-coagulant properties (2,8).

During sepsis, the endothelium becomes activated and dysfunctional (3,8). Endothelial cells are highly responsive to changes in their extracellular milieu. They are capable of sensing a myriad of biomechanical and biochemical forces. They integrate these signals and respond in ways that are usually beneficial, but at times harmful to the host (8). The term endothelial activation describes the phenotypic response of the endothelium to an inflammatory stimulus. The activation phenotype varies between different sites of the vascular tree and in response to different agonists. However, it usually consists of some combination of a procoagulant surface, increased leukocyte trafficking, altered vasomotor tone, and loss of barrier function. EC activation may be adaptive or non-adaptive. The non-adaptive phenotype is termed endothelial dysfunction. There is compelling evidence – based on in vitro and preclinical studies – that sepsis is associated with widespread EC activation and dysfunction (3,8). Once activated, ECs acquire a procoagulant, proadhesive phenotype. Moreover, activated ECs may propagate the inflammatory response by releasing its own complement of cytokines (e.g., interleukin [IL]-6, PAF, IL-1, and IL-8). If uncorrected, the process is thought to lead to cellular hypoxia, organ dysfunction and death (10,11).

In previous work, we and others found that sepsis was associated with increased circulating plasma levels of E-selectin, ICAM-1, VCAM-1, PAI-1 and sFLT-1 (3,5,12–14). These endothelial biomarkers were associated with sepsis severity, organ dysfunction and patient outcomes. This finding is consistent with the hypothesis that the endothelium is activated in sepsis and dysfunction of the endothelium is implicated in adverse sepsis outcomes (3). Yet, increased levels of endothelial markers have also been reported in non-sepsis patients, particularly in patients with cardiovascular disease, hemorrhagic shock or trauma (13, 5–21); thus, the specificity of the markers to sepsis is unclear. The objective of this analysis was to compare patterns of endothelial cell activation markers in emergency department patients with hypotension due to sepsis and other non-sepsis etiologies.

METHODS

Study design and setting

This is a secondary analysis of a prospective, observational cohort study of patients who presented to the emergency department (ED) of the Carolinas Medical Center, an 800-bed teaching and tertiary referral hospital with >100,000 patient visits per year from July 2004 to June 2005. A more detailed description of the assembly of the original cohort is reported elsewhere (19).

The aim of the present analysis is to investigate different markers of endothelial activation in ED patients with hypotension due to sepsis or non sepsis etiologies. The study was approved by the Institutional Review Board and Privacy Board at Carolinas Healthcare System prior to conduct of the study.

Selection of participants and outcome assessment

For this analysis, we included adult patients (>17 years of age) with at least one systolic blood pressure (SBP) measurement of <100 mm Hg during their visit in the ED. Patients were classified by one of the investigators (AEJ) using the results from laboratory testing, culture results, and clinical discharge summaries. The etiology of shock was categorized as: sepsis, hemorrhagic, cardiac or indeterminate. The reviewer was blinded to biomarker results.

Method of endothelial marker measurement

In all patients, blood was drawn on admission to the ED (typically within 3 hours of initial presentation) in EDTA tubes, centrifuged at $2500 \times g$ at 4°C , and frozen at -80 within 1 hour of collection. Biomarkers of different endothelium-related pathways (E-selectin, ICAM-1, VCAM-1 and PAI-1) were assayed with a multiplex panel using the human cardiovascular-1 panel (Millipore, Billerica, MA, USA). The sFLT-1 levels were assayed using Quantikine ELISA kits (R&D systems, Minneapolis, MN). All assays were performed in duplicate and the average levels were used for analysis.

Statistical analysis

The marker levels were compared between groups with the Wilcoxon-Mann-Whitney U (MWU) test. Area under the receiver operating characteristics curves (AUC) were calculated to investigate the markers potential to discriminate between sepsis and non-sepsis etiology. To obtain the independent association of marker level and etiology of hypotension, we performed multivariate logistic analysis adjusted for age, gender, severity (defined as in-hospital mortality) and mean blood pressure levels during the ED visit. We log transformed biomarker levels to achieve a normal distribution. All reported confidence intervals are two-sided 95% intervals and tests were performed at the two-sided 5% significance level. All analyses were performed with SAS 9.2.

RESULTS

Study cohort characteristics

From a total of 161 patients, etiology of hypotension was determined as sepsis in 69 (43%) patients and as non-sepsis in 47 (29%) patients, including cardiac in 35 and hemorrhagic in 12 patients; the remaining 45 patients had hypotension of indeterminate etiology. The study population had a mean age of $60 (\pm 16.7)$ years, 42% were females, and the mean SBP was $107 (\pm 14.4)$ mmHg. Patients had a broad range of co-morbid conditions including diabetes in 26%, congestive heart failure in 18%, hypertension in 39%, and chronic renal disease in 6%. The all-cause in-hospital mortality was 8.6% (95% CI 3.4–13.8%) and most deaths occurred in patients with hypotension due to sepsis (8 out of 10). Table 1 shows additional patient characteristics of the overall cohort.

Association of Endothelial Biomarkers and type of hypotension

Figure 1 shows box-plots of the circulating plasma levels of endothelial activation biomarkers in patients with hypotension due to sepsis or non-sepsis etiology, which includes cardiac and hemorrhagic hypotension. The third group represents the 45 patients with unclassified etiology of hypotension, which were excluded from further analyses. With the exception of PAI-1 ($p=0.08$), median plasma levels of all endothelial markers were significantly higher in patients with sepsis compared to non-sepsis etiology ($p<0.05$ for all comparisons, see detailed results in Table 2). Similarly, all patients with sepsis induced hypotension had higher values compared to patients with unclassified hypotension; there was no significant difference in levels between non-sepsis and unclassified hypotension.

Multivariate logistic regression analysis adjusted for age, gender, mean blood pressure level and in-hospital mortality confirmed a significant association of E-selectin (OR 3.7, 95% confidence interval: 1.7–7.8, $p=0.001$) and sFLT-1 (2.0, 1.1–3.8, $p=0.03$) with sepsis etiology. Biomarkers VCAM-1 (2.0, 0.88–4.4, $p=0.1$), VEGF (1.5, 0.98–2.2, $p=0.06$); ICAM-1 (1.5, 0.9–2.6, $p=0.17$) and PAI-1 (1.4, 0.8–2.3, $p=0.20$) did not reach statistical significance. Calculation of the area under the receiver operating characteristics curve showed that E-selectin (AUC 0.74) and sFLT-1 (AUC 0.70) had the highest discrimination between sepsis and non-sepsis hypotension (Figure 2).

DISCUSSION

We investigated circulating levels of biomarkers related to endothelial activation markers in patients with hypotension of different etiologies during their ED visit. Endothelial markers were similar in hypotension due to cardiac and hemorrhagic etiology, but increased in sepsis. This persisted for E-selectin and sFLT-1 in multivariate analysis adjusted for age, gender, degree of hypotension and mortality. This finding provides evidence in favor of endothelial activation being more pronounced when part of an acute sepsis-specific pathway.

Endothelial dysfunction has been implicated in the pathogenesis and progression of a variety of diseases presenting with a systemic inflammatory response (SIRS) such as sepsis (1–3), cardiovascular disease (17,20) and hemorrhagic shock/ Trauma (15,18,21). In cardiovascular research, dysfunction of the endothelium has been found to be an early marker of atherosclerosis. In patients with acute coronary syndromes dysfunctional endothelium triggers the devastating event of plaque rupture by promoting adhesion of leukocytes, vasoconstriction, activation of platelets and thrombus formation (20,22). Large-scale clinical studies found that endothelial markers correlated well with the risk for cardio-vascular events (23,24). Similarly in trauma research, studies found increased levels of endothelial markers in experimental models of trauma and hemorrhagic shock (16,18,21). Yet, whether endothelial activation is a feature of a generalized systemic response seen in sick patients, or a pathway that is more pronounced during sepsis is still undefined.

Within the presented study, sepsis patients had the most pronounced increase in endothelial cell markers compared to patients with cardiac or hemorrhagic disease, even when adjusted for disease severity and other potential confounders. The most pronounced differences between sepsis and non-sepsis hypotension within this study were found for E-selectin, a soluble leukocyte adhesion molecule, and sFLT-1, a circulating soluble VEGF receptor. Unlike ICAM-1 and VCAM-1, E-selectin is endothelial specific and is only expressed during activated endothelial states. The biomarker sFLT-1 is the antagonist to VEGF and functions in essence as a decoy receptor with anti-inflammatory effects; thus, while its biologic activity may be serve to reduce inflammation, high levels are commonly associated with a highly activated state. In fact, prior studies have shown that sFLT-1 is strongly prognostic in sepsis. Calculation of receiver operating characteristics curves in this study showed a good discrimination of patients with sepsis and non-sepsis hypotension. This observation is in line with our hypothesis that endothelial activation is a sepsis-specific pathway.

While we submit that our study is a novel contribution to the literature in that we assess a broad array of endothelial related biomarkers in an undifferentiated group of patients with Emergency Department hypotension, other investigators have compared sepsis patients to non-sepsis patients previously. In a study of 30 surgical ICU patients, Boldt et al found that trauma patients showed lower plasma levels of endothelial leukocyte adhesion molecules (sELAM-1), ICAM-1 and VCAM-1 than did sepsis patients indicating more pronounced

endothelial activation or damage in sepsis (15). Similarly, sepsis in our study was associated with a more pronounced activation of endothelial cell markers and thus validates and expands these previous results to patients from the emergency department setting and other endothelial activation markers.

Our study has a number of limitations. We assessed endothelial dysfunction solely by means of circulating levels of plasma biomarkers and do not have other measures of direct vascular physiology. A previous study comparing endothelial biomarkers with skin biopsies suggested that caution is required in the interpretation of these markers in plasma, which does not necessarily reflect the in situ activation state of endothelium. Also, we did not assess other endothelium-associated mediators, such as nitric oxide, which has been found up-regulated in sepsis and other disease states (16,25,26). We classified the etiology via a final assessment incorporating lab findings, cultures results, and discharge summary; however we are prone to misclassification bias/error. We also relied upon a single investigator, so we do not have kappa values for reproducibility. Our numbers, while relatively large compared to other studies investigating endothelial biomarkers, are still too small to draw definitive conclusions.

In conclusion, our data suggest that sepsis induces a more pronounced activation of endothelial pathways, as represented by increased endothelial activation markers. Future studies continuing to explore the diagnostic potential of these biomarkers, as well as validating our findings in a broader population are warranted.

List of abbreviations

ED	emergency department
ICAM-1	soluble intercellular adhesion molecule
IL-6	Interleukin-6
PAI-1	plasminogen activator inhibitors -1
sFLT-1	soluble fms-like tyrosine kinase-1
VCAM-1	soluble vascular cell adhesion molecule
VEGF	vascular endothelial growth factor

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Figure 1. Box plots showing levels of endothelial markers in patients with non-sepsis (grey), sepsis (light grey) and unclassified hypotension; in each plot, the horizontal bar represents the median value, the box represents the IQR, and the whiskers represent values up to 1.5 IQRs. Significant differences between groups ($p<0.05$) are marked with an asterisk (*)

Figure 2. Receiver-operating characteristics curve (ROC) for differentiation between sepsis and non-sepsis hypotension
 AUC, area under the curve

Table 1

Patient characteristics

All patients (n=116)	
<u>Demographics</u>	
Age (years), <i>mean (± standard deviation)</i>	60 (±16.7)
Female gender, n (%)	49 (42.2%)
<u>Race</u>, n (%)	
African-American	42 (36.2%)
Caucasian	70 (60.3%)
Other	4 (3.4%)
<u>Initial clinical presentation</u>, <i>mean (± standard deviation)</i>	
Systolic blood-pressure (mmHg)	107 (±14.4)
Heart rate (bpm)	98 (±31.2)
Respiratory rate (bpm)	21 (±7.3)
<u>Comorbid conditions</u>, n (%)	
Diabetes	30 (25.9%)
Chronic heart failure	21 (18.1%)
Hypertension	45 (39.0%)
Chronic obstructive lung disease	20 (17.2%)
Chronic renal disease	7 (6.0%)
Neoplasm	13 (11.2%)
<u>Characteristic of hypotension</u>, n (%)	
Episodic	36 (31.0%)
Transient	46 (39.7%)
Sustained	27 (23.3%)
<u>Cause of hypotension</u>, n (%)	
Sepsis	69 (59.4%)
Cardiac	35 (30.1%)
Hemorrhagic	12 (10.3%)
<u>Hospital Outcomes</u>, n (%)	
Inhospital mortality	10 (8.6%)

Data are presented as mean (± standard deviation) or total number (percentage); bmp, beats per minute

Table 2

Endothelial markers in patients with sepsis and non-sepsis etiologies of hypotension

Parameter	Sepsis Median (IQR)	Non-sepsis Median (IQR)	<i>P</i> *	AUC	Multivariate adjusted result Odds ratio (95%CI)	<i>P</i> **
E-selectin (ng/mL)	53.2 (34.9-79.2)	30.5 (20.0-40.8)	<0.001	0.74	3.67 (1.72-7.84)	0.001
ICAM-1 (ug/mL)	202 (152-267)	149 (115-224)	0.04	0.61	1.49 (0.85-2.61)	0.17
VCAM-1 (ng/mL)	1260 (997-1710)	1090 (968-1430)	0.04	0.61	1.96 (0.88-4.35)	0.10
PAI-1 (x100) (ng/mL)	571 (417-9730)	522 (3391-687)	0.08	0.60	1.39 (0.84-2.31)	0.20
VEGF (pg/mL)	271 (91-496)	118 (43-270)	0.01	0.64	1.48 (0.98-2.22)	0.06
sFLT-1 (pg/mL)	227.4 (142.4-328.2)	136.2 (96.3-211.0)	0.001	0.70	2.01 (1.07-3.79)	0.03

AUC, area under the receiver operating characteristics curve for discrimination of sepsis and non-sepsis hypotension; IQR, interquartile range;

* *p* value refers to Wilcoxon MWU tests;** *p* value refers to results from multivariate logistic regression analysis adjusted for age, gender, mean blood pressure level during the emergency department visit and in-hospital mortality