Endothelin-1 and D-Dimer as early predictors of multiple organ dysfunction in critically ill patients with sepsis

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ABSTRACT

Severe sepsis is a serious worldwide health problem and is a leading cause of death in intensive care units. Severe sepsis and septic shock are associated with vast cardiovascular changes and multiple organ dysfunction. The study was designed to assess the level of endothelial and vascular dysfunction in patients with severe sepsis and septic shock. Forty two critically ill patients suffering from sepsis as well as fifteen age and sex matched normal controls constituted the subjects of this prospective study. Severity of illness, sepsis and organ dysfunction were assessed by the Acute Physiology Score and Chronic Health Evaluation (APACHE) II Score and the Sepsis Severity Score and the Multiple Organ Dysfunction Score (MODS) respectively. Endothelin-1(ET-1) and D-dimer (DD) values were compared between patients without, with organ dysfunction and patients who did not survive at the end of the study period (groups I, II and III respectively). ET-1 and D-dimer were determined at time of diagnosis (baseline), 6-, 24- and 48-hours following the diagnosis of severe sepsis or septic shock. A significant increase was present regarding the baseline mean levels of ET-1 and D-dimer in all patient groups (I, II and III) compared to controls. The highest levels were found in group III patients. The baseline mean levels of the APACHE II Score and the Sepsis Score and the Multiple Organ Dysfunction Score (MODS) were significantly higher in group II and III compared to group I. ET-1 and D-dimer levels were also higher in group II compared to group I at 6, 24 and 48 hours. In group I, ET-1 and D-dimer levels increased non-significantly after 6 hours compared to baseline levels, then decreased after 24- and 48- hours reaching near baseline values; in group II patients, ET-1 and D-dimer levels increased significantly after 6- and 24- hours compared to baseline levels, and although decreased but did not reach baseline values after 48 hours. ROC curve analysis revealed a cutoff value and positive predictive value (2.5 and 98% for ET-1) and (400 and 99% for DD) respectively. The sensitivity of ET-1 and DD were 99% and 95% respectively. Endothelial dysfunction and hypercoagulation represented by increased ET-1 and D-dimer levels appear to be early and sensitive predictors of the severity of septic shock and of multiple organ dysfunction development. Thus, a therapeutic strategy to improve the microcirculation in such patients could be studied and accomplished based on these levels.

INTRODUCTION

Severe sepsis is a serious worldwide health problem and is a leading cause of death in intensive care units with about mortality rate of at least 30%. Severe sepsis is defined as a systemic inflammatory response to infection associated with one acute organ dysfunction or more. The systemic host response to infection has been associated with coagulation activation, consumption of anticoagulation factors, inhibited fibrinolysis, endothelial injury, and inflammation[1,2].

For classifying patients admitted into the ICU, many scoring systems have been developed; the two popular ones are the Acute Physiology Score and Chronic Health evaluation (APACHE II and III)[3,4] and Sepsis Severity Score (SSS)[5]. APACHE II score above 30 was cited to predict 70% mortality[3,4].

The endothelium lining the circulatory system serves as an important target and a modulator for the effects of endotoxin because of its close contact with circulating blood and its proximity to the underlying vascular smooth muscle. Endothelial cells, normally are responsible for modulating vascular tone, become dysfunctional in sepsis. Pro-thrombotic, pro-inflammatory and vasoactive mediators are released including nitric oxide (NO), endosthelins (ETs) and products of cyclo-oxygenase metabolism. It is probably the disordered production of these mediators in vascular beds that results in multiple organ dysfunction[6,7].

Endothelin-1 (ET-1) is a member of a family of 21–amino acid peptides (the endothelin family) that are the most potent vasoconstrictor substances yet discovered. ET-1 release is stimulated by angiotensin II, antidiuretic hormone, thrombin, cytokines, reactive oxygen species, and shearing forces acting on the vascular endothelium. ET-1 release is inhibited by nitric oxide as well as by prostacyclin and atrial natriuretic peptide[8]. Owing to its vasoconstricting and mitogenic properties, ET-1 is thought to be involved in the pathogenesis of arterial vessel wall tension dysregulation and the development of atherosclerosis[9,10]. In addition, it has been widely assumed that ET-1 may affect blood coagulation, fibrinolysis, and endothelial cell function, thereby playing a pathophysiological role in various cardiovascular diseases in humans, as hypertension, acute myocardial infarction, cardiogenic shock, and disseminated intravascular

coagulation[11]. It has been proposed that the prohemostatic properties of ET-1 may contribute to the increased activation of coagulation[12].

Fibrin split product D-dimer (DD) results from the destruction of cross-linked fibrin and therefore is a measure of clot formation and lysis. D-dimer is often measured in the evaluation of patients with suspected disseminated intravascular coagulation, and is emerging as a screening test for venous thromboembolism[13]. D-dimer is thought to be involved in the development of vascular disorders, and its level increases gradually with increasing severity of peripheral vascular sclerosis[14]. The mechanism of a possible D-dimer effect remains unclear, although this soluble fibrin-derived molecule is known to exert distinct biological effects in various cell types, including the endothelium. It alters cell adhesion and spreading, modifies the cytoskeleton and influences the system of plasminogen activation[15].

Aim of work: The study was designed to assess the degree of endothelial and coagulation dysfunction in critically-ill patients with sepsis. This was accomplished by measuring plasma levels of ET-1 and D-dimer (DD) at the time of diagnosis of sepsis and for the following 48 hours. In addition the prognostic value of the previous markers and their relationship to the severity of sepsis was assessed.

SUBJECTS AND METHODS

This prospective study included 42 patients who were admitted to the intensive care unit from February 2004 till November 2004 with the diagnosis of sepsis. Human sepsis was defined according to the criteria proposed by the American College of Chest Physician/ Society of Critical Care Medicine consensus statement by an identifiable site of infection and evidence of a systemic inflammatory response manifested by at least three of the following criteria:

1- Temperature > 38°C or < 36°C
2- Heart rate > 90 beats/min
3- Respiratory rate > 20 breaths per minute
4- White blood cell count > 12000/mm^3 or < 4000/mm^3 (16).

Causes of sepsis included: pneumonia, bronchopneumonia, severe trauma, device-related, and urinary tract infections.

After approval of the Research Ethical Committee, informed written consent for participation was obtained from conscious patients when feasible otherwise consent was obtained from relatives. Patients were monitored for 48 hours after the diagnosis of sepsis for the development of multiple organ dysfunction and/or death. Patients were divided into 3 groups, group I comprised 19 patients without multiple organ dysfunction, group II comprised 11 patients with multiple organ dysfunction, and group III patients who did not survive at the end of the study period (48 hours). All patients were managed according to standard intensive care protocols for sepsis and septic shock including the use of antibiotics, vasoactive agents, nutritional support and hemodynamic management.

Exclusion criteria included: Children, neoplasia, autoimmune disorders, hypertension, end-stage renal or hepatic disease, recent acute cardiovascular event, recent attack of deep venous thrombosis, and use of steroids, and immunosuppressive agents.

- Severity of illness was measured via the APACHE II Score [3,4].
- The severity of sepsis was scored using sepsis score (5).The range of this score is 0 – 55. The score depends on 4 attributes of sepsis:
  (1) Local effects of tissue infection (range of score: 0 – 22);
  (2) Pyrexia (range of score: 0 – 6);
  (3) Secondary effects of sepsis (range of score: 0 – 13)
  (4) Laboratory findings e.g. blood culture, leukocyte count, hemoglobin level, and platelet count (range of score: 0 – 14).
- The incidence of multiple organ dysfunction and failure was assessed according to The Multiple Organ Dysfunction Score (MODS)[17,18].
- Hemodynamic monitoring: as soon as sepsis or septic shock was diagnosed, baseline mean arterial pressure (MAP), pulmonary artery occlusion pressure (PAOP), heart rate (HR), and oxygen consumption index (VO_2I) were measured.

Fifteen age and sex matched healthy volunteers were included in the study as a control group. They had no history nor clinical signs of hypertension, cardiovascular, renal or other diseases and were not receiving any medication.

- Blood samples were withdrawn from each patient and control for estimation of plasma Endothelin-1 (ET-1) and D-dimer (DD). ET-1 and D-dimer were estimated at time of diagnosis of sepsis or septic shock (0 hour or base line) and at 6-, 24-, and 48-hours after the diagnosis.

For plasma ET-1 estimation, blood samples were collected into chilled syringes and transferred to polypropylene tubes containing EDTA (1mg/mL) and aprotonin (500KIU/mL), and then centrifuged at 1600 g for 15 minutes at 4°C within 30 minutes of collection. The separated plasma was then applied to a C18 microcolumn (Sep-Pak waters Inc. Rochester, MN) that was activated by 60% acetonitrile. The column was then washed by 0.1% trifluoroacetic acid and ET-like materials eluted with 60% acetonitrile into polypropylene tubes. The eluent was evaporated to dryness under a nitrogen stream. The residue was reconstituted in 0.05M phosphate buffer, pH 7.0 and stored at ≤- 20° C avoiding repeated freeze-thaw cycles until assayed for ET-1 by the radioimmunoassay kit provided by Peninsula Laboratories, Belmount CA[19]. The sensitivity of this kit is 0.14 pg/ml, and the slope for linearity is 0.846. Intra-assay precision was assessed using a known positive and a negative control assayed three times each on one plate.

Quantitative determination of D-dimer (DD) using an enzyme immunoassay supplied by Diagnostic Systems

Laboratories (DSL), Texas, USA. The test is performed in two steps; in the first, the diluted tested plasma (diluted 1: 50 with sample diluent) is introduced into a microwell coated with a highly purified monoclonal antibody specific to D-dimer. When present, this analyte is captured onto the solid phase. Following a washing step, the immunoconjugate which is a monoclonal antibody coupled to horse radish peroxidase is introduced and bonds to another epitope of the immobilized D-dimer. Following a new washing step, the peroxidase substrate, Tetramethylbenzidine in presence of hydrogen peroxide is introduced and a blue colour develops. The blue colour turns yellow when the reaction is stopped with sulphuric acid. The amount of colour developed is directly proportional to the concentration of D-dimer in the tested sample[20].

Results were presented as means ± SD, and percentage. For comparison of means one way analysis of variance (ANOVA) was performed. To assess the relationship between the studied variables, Pearson's and Spearman's correlation coefficient was used. P value < 0.05 was considered significant. ROC curve analysis was done to estimate the cut-off point and predictive value of ET-1 and D-dimer.

RESULTS

Forty two patients constituted the study population. At the end of the study (48 hours) 19 patients did not develop multiple organ dysfunction (group I) (45.2%), 15 patients developed multiple organ dysfunction (group II) (35.7%) and 8 did not survive (group III) (19%). As regards group III three died less than 6 hours after diagnosis of sepsis (i.e. after baseline),and the rest within 20 hours. Thus, only baseline parameters were presented in the study for those patients who did not survive as the remaining size of population was too small for statistical analysis.

Table (1) shows no significant differences between the groups concerning age, sex and weight, or height.

Group III patients showed significantly higher values of HR and VO_2I and significantly lower values of MAP compared to group I. MAP was significantly lower and HR was significantly higher in group III compared to group II patients. No significant differences in the mean levels of PAOP was detected among the different groups (Table 2).

A significant increase was present regarding APACHE II score, sepsis score, MODS, in group III patients (compared to both groups I and II). The levels of the previous parameters were also significantly higher in group II compared to group I patients [Table (3)].

A significant increase was present regarding ET-1 and D-dimer in all patient groups (I, II and III) compared to controls. The highest levels were found in group III patients (compared to both groups I and II). The levels of the previous parameters were also significantly higher in group II compared to group I patients (Table 4).

ET-1 levels were significantly higher in group II from the corresponding levels in group I in all time intervals (base line, 6, 24, 48 hours). In group I, levels of ET-1 increased non-significantly after 6 hours (5.4 ± 1.2) compared to baseline (4.7 ± 1.2), then decreased after 24 hours (5.2 ± 1.7) and reached near base line values at 48 hours (4.7 ± 1.1). While in group II, levels of ET-1 increased significantly after 6 hours (9.9 ± 2.4) compared to baseline (7.3 ± 1.2), then decreased after 24 (8.8 ± 1.9) but remained statistically significantly higher than baseline values. There was further decrease of ET-1 values at 48 hours (8.0 ± 1.6) without reaching base line values (Fig. 1).

Similar to ET-1 changes, D-dimer levels were significantly higher in group II from the corresponding levels in group I in all time intervals. In group I, levels of D-dimer

Table 1
Patients' Characteristics and Causes of Sepsis

	Controls (15 cases)	Group I (19 cases)	Group II (15 cases)	Group III (8 cases)
Age (years)	48.9 ± 6.8	50.5 ± 6.2	48.3 ± 5.5	49.4 ± 8.3
Sex (M/F)	8/7	10/9	8/7	4/4
Weight (kg)	77±11	79±10	82±15	79±14
Height (cm)	168±9	165±11	170±6	166±8
Causes:		number	number	number
- Pneumonia		6	5	5
- Bronchopneumonia		4	3	0
- Severe Trauma		4	4	0
- Device-related		3	2	3
- Urinary tract infection		2	1	0

Values are presented as means ± S.D.
Group I: patients without multiple organ dysfunction; Group II: patients with multiple organ dysfunction; Group III: patients who did not survive at the end of the study period (48 hours).
M/F: male: female.

Table 2
Baseline Hemodynamic Parameters in patients' groups (I, II and III)

	Group I (19 cases)	Group II (15 cases)	Group III (8 cases)
MAP (mm Hg)	76.1 ± 6.9	68.8 ± 10.2	60.5 ± 6.4 [b]
PAOP (mm Hg)	16.2 ± 3.8	16.0 ± 3.4	15.1 ± 2.6
HR (bpm)	105.6 ± 11.2	111.3 ± 13.8	127.6 ± 7.4 [ab]
VO_2 I (mL/min/m^2)	129.2 ± 20.3	147.9 ± 30.2	174.7 ± 18.4 [a]

Values are presented as means ± S.D.
Baseline: at the time of diagnosis of sepsis; Group I: patients without multiple organ dysfunction; Group II: patients with multiple organ dysfunction; Group III: patients who did not survive at the end of the study period (48 hours).
MAP; mean arterial pressure; PAOP: pulmonary artery occlusion pressure; HR: heart rate; bpm: beat per minute; VO_2I: oxygen consumption index
[a]denotes that the difference between the corresponding means of the present group and group I is statistically significant, i.e. P < 0.05.
[b]denotes that the difference between the corresponding means of the present group and group II is statistically significant, i.e. P < 0.05.

Table 3
Baseline Values of APACHE II score, Sepsis score, MODS in groups I, II and III

	Group I (19 cases)	Group II (15 cases)	Group III (8 cases)
APACHE II score	16.4 ± 4.4	24.5 ± 3.3 [a]	30.3 ± 2.5 [ab]
Sepsis score	25.8 ± 5.0	30.0 ± 4.4 [a]	36.7 ± 2.8 [ab]
MODS	3.8 ± 1.9	8.3 ± 2.4 [a]	12.6 ± 5.1 [ab]

Values are presented as means ± S.D.
Baseline: at the time of diagnosis of sepsis; Group I: patients without multiple organ dysfunction; Group II: patients with multiple organ dysfunction ; Group III: patients who did not survive at the end of the study period (48 hours); MODS: Multiple organ dysfunction score.
[a] denotes that the difference between the corresponding means of the present group and group I is statistically significant, i.e. P < 0.05
[b]denotes that the difference between the corresponding means of the present group and group II is statistically significant, i.e. P < 0.05

Table 4
Baseline Values of ET-1 (pg/mL), and D-dimer (ng/mL) in controls and patients' groups (I, II and III)

	Controls (15 cases)	Group I (19 cases)	Group II (15 cases)	Group III (8 cases)
ET-1(pg/mL)	1.4 ± 0.48	4.7 ± 1.26 *	7.3 ± 1.25 *[a]	14.1 ± 1.66 *[ab]
D-dimer(ng/mL)	212.3 ± 78.4	653.0± 194.9 *	842.6 ± 185.6 *[a]	1507.5± 223.8 *[ab]

Values are presented as means ± S.D.
Baseline: at the time of diagnosis of sepsis; Group I: patients without multiple organ dysfunction; Group II: patients with multiple organ dysfunction; Group III: patients who did not survive at the end of the study period (48 hours); MODS: Multiple organ dysfunction score; ET-I: endothelin-1.
(*) denotes that the difference between the corresponding means of the present group and the control group is statistically significant, i.e. P < 0.05
([a]) denotes that the difference between the corresponding means of the present group and group I is statistically significant, i.e. P < 0.05
([b]) denotes that the difference between the corresponding means of the present group and group II is statistically significant, i.e. P < 0.05

increased non-significantly after 6 hours (713.1 ± 225.8) compared to baseline (653.1 ± 167.3), then decreased after 24- and 48- hours (623.6 ± 193.3) and (528.4 ± 185.4) respectively reaching near base line values. While in group II, levels of D-dimer increased significantly after 6- (1184.0 ± 275.7) and then decreased after 24- hours (1072.6 ± 254.7) but values remained statistically significantly higher than baseline (842.6 ± 185.6). At 48- hours, D-dimer levels showed further decrease (939.3 ± 215.2) but did not reach base line values (Fig. 2).

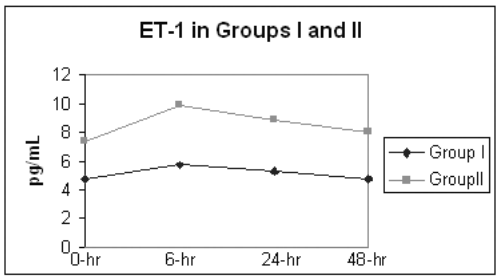

Figure 1
Endothelin – 1 (ET-1) in groups I and II
(Endothelin – (ET-1) (pg/mL) in Group I (patients without multiple organ dysfunction) and Group II (patients with multiple organ dysfunction) at baseline or 0, 6, 24, and 48 hours).

Incidence of death showed significant positive correlation with each of APACHE II (r = 0.62, P < 0.001), sepsis score (r = 0.53, P < 0.001), ET-1 (r = 0.87, P < 0.001) and D-dimer (r = 0.82, P < 0.001).

APACHE II values showed significant positive correlation with each of sepsis score (r = 0.53, P < 0.001), MODS (r = 0.53, P < 0.001), ET-1 (r = 0.72, P < 0.001) and D-dimer (r = 0.66, P < 0.001) .

Sepsis score values showed significant positive correlation with each of MODS(r = 0.59, P < 0.001), ET-1 (r = 0.52, P < 0.001, Fig. 3), and D-dimer (r = 0.63, P < 0.001, Fig. 4).

MODS showed significant positive correlation with each of ET-1 (r = 0.68, P < 0.001) and D-dimer (r = 0.57, P < 0.001).

ET-1 values showed significant positive correlation with D-dimer (r = 0.83, P < 0.001) (Fig. 5).

ROC curve analysis revealed a cutoff value and and positive predictive value (2.5 and 98% for ET-1) and (400 and 99% for DD) respectively.: The sensitivity of ET-1 and DD were 99% and 95% respectively.

DISCUSSION

Timely identification of outcome predictors in sepsis and septic shock remains challenging as it may support early therapeutic approaches and bring insights into possible implications[21].

In the present study the baseline hemodynamic parameters in group III showed significantly higher values of HR and VO_2I and significantly lower values of MAP compared to group I patients. The heart rate was also significantly higher and the mean arterial blood pressure was significantly lower in group III compared to group II patients. PAOP showed non-significant difference. Thus, hemodynamic assessment seems to be only a predictor of mortality in patients with severe sepsis or septic shock, but it could not differentiate between patients who developed multiple organ dysfunction syndrome from those who did not (groupsII and I). However, due to the very small size of the population of group III (8 patients), further assessment of the previous result is mandatory. Tuchschidt et al.[22] reported that hemodynamic monito-

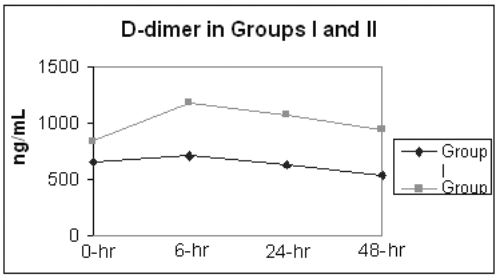

Figure 2
D-dimer in groups I and II
(D-dimer (ng/mL) in in Group I (patients without multiple organ dysfunction) and Group II (patients with multiple organ dysfunction) at baseline or 0, 6, 24, and 48 hours)

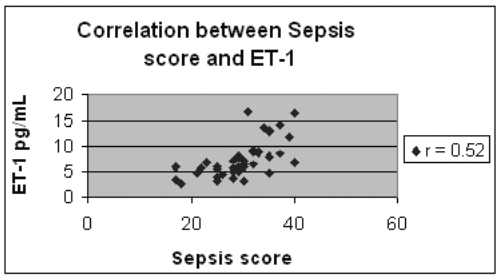

Figure 3
Correlation between baseline Sepsis score and Endothelin – 1 (ET-1) in patients of the study
(Baseline: at the time of diagnosis of sepsis)

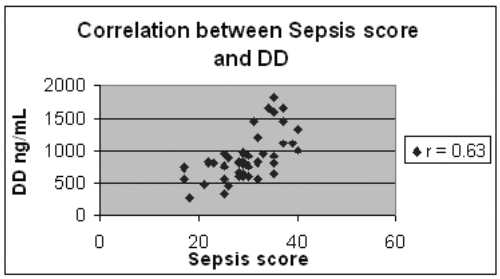

Figure 4
Correlation between baseline Sepsis score and D-dimer (DD) in patients of the study
(Baseline: at the time of diagnosis of sepsis)

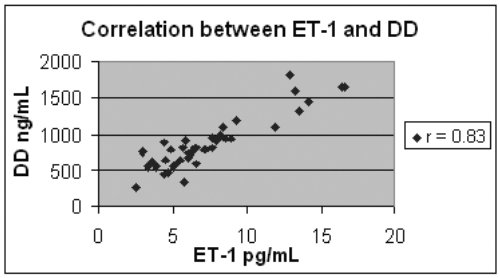

Figure 5
Correlation between baseline Endothelin-1(ET-1) and D-dimer (DD) in patients of the study.
(Baseline: at the time of diagnosis of sepsis)

ring did not reveal significant differences among survivors and non-survivors and reported that hemodynamic variables are poor discriminators of clinical outcome.

The present study showed a general host response of endothelial dysfunction and deranged coagulation in a population of patients with severe sepsis. A significant increase was present regarding ET-1 and D-dimer in all patient groups (I, II and III) compared to controls. The highest levels were found in group III patients (compared to both groups I and II). The levels of ET-1 and D-dimer were also significantly higher in group II compared to group I patients (at baseline and also at 6-, 24-, and 48-hours). A significant positive correlation was present between ET-1 and D-dimer and between each of ET-1 and D-dimer and incidence of death, and indices of severity of disease as APACHE II and sepsis scores and MODS. The highly significant correlation between ET-1 and D-dimer may indicate that the endothelial dysfunction and hypercoagulation present in the course of severe sepsis are closely inter-related and in turn appear to play a major role in the pathogenesis of the condition and its clinical outcome.

While in group I patients, ET-1 and D-dimer levels were increased non-significantly after 6 hours compared to baseline levels, then decreased after 24- and 48-hours reaching near baseline values; in group II patients, ET-1 and D-dimer levels increased significantly after 6- and 24- hours compared to baseline levels, and although decreased but did not reach baseline values after 48 hours. Thus, it seems most probably that the initial significant increases in ET-1 and D-dimer levels and failure to return to baseline levels is indicative to poorer prognosis and MODS development. Thus, ET-1and D-dimer levels appear to be early and sensitive predictors of the severity of septic shock and of multiple organ dysfunction development. ROC curve analysis confirmed this as the cutoff value and positive predictive value were (2.5 and 98% for ET-1) and (400 and 99% for DD) respectively.: The sensitivity of ET-1 and DD were 99% and 95% respectively.

Dysfunction of the vascular endothelium is an early event in septic shock. Microvascular injury and endothelial dysfunction not only result in overproduction of nitric oxide and other vasodilators, but also enhance the synthesis/release of vasoconstrictors, including ET-1[23]. In accordance to our results, Hirata and Ishimaru[24] reported that in septic shock, circulating levels of ET-1 have been shown to be markedly elevated. Bacterial lipopolysaccharide and several proinflammatory cytokines, such as interleukin-1 and tumour necrosis factor á (TNF-α), induce ET-1 gene expression in endothelial cells. Weitzberg and colleagues[25] and Sanai et al.[26] showed that ET-1 levels correlated to APACHE II score and were associated with a poor outcome in sepsis syndrome. ET-1 may be directly involved in the pathophysiology of septic shock. ET-1 plays an important role in the regulation of microcirculatory blood flow in splanchnic as well as in peripheral tissues during septic shock[27] and plays a compensatory role in the reversal of systemic vasodilatation, but exerts deleterious effects on renal and pulmonary circulation[28]. Ando et al.[29] reported that ET-1 production correlated to the degree of hypoxemia and suggested that ET-1 could be a mediator of hypoxemic organ damage secondary to actions at the microvasculature level. Filep[30] indicated a role for ET-1 in the regulation of plasma volume and albumin escape. Injection of exogenous ET-1 evoked losses in plasma volume and promoted total-body albumin escape which are characteristic features of endotoxin shock and contribute to the progression of shock to a multiple organ dysfunction syndrome. Rossi e al.[31] reported that the endothelin receptor antagonists may be of value in the treatment of sepsis-related acute injury.

The clinical syndrome of severe sepsis is characterized by systemic inflammation and coagulopathy that may not be unique to a particular class of microbe. The universal coagulopathy observed in patients with severe sepsis is more reflective of activation of coagulation than of impaired fibrinolysis. This increased coagulopathy may result in the formation of microthrombi which occlude the vascular beds of the various organs and may contribute to their eventual failure[32,33]. In accordance to our results, D-dimer levels were significantly increased in patients with severe sepsis and septic shock compared with control subjects[34]. D-dimer levels correlated with activation of the proinflammatory cytokine cascade (TNF-α, Il-6, and IL-8) but not to the anti-inflammatory cytokines (IL-10) which suggests that the presence of D-dimer may reflect the imbalance between proinflammatory and anti-inflammatory cytokines[15]. Kollef et al.[20] reported that the circulating levels of D-dimer are associated with clinical outcomes among patients admitted to a medical intensive care unit. Multiple logistic regression analysis identified the presence of increased concentrations of D-dimer as being independently associated with vascular thrombosis and the development of multiple organ dysfunction[20]. Shilon et al.[35] reported that D-dimer levels were positively correlated with the APACHE II score on admission and the length of hospital stay. Shitrit et al.[36] reported that the 24- and 48-hour D-dimer level correlated with the APACHE II. Angstwurm et al.[37] suggested that elevated d-dimer levels may reflect the extent of microcirculatory failure. El-Nawawy et al.[38] reported that the combination of D-dimer and fibrinogen degradation products assay showed the best correlation for early pre-disseminated intravascular coagulation diagnosis among high-risk patients admitted to a pediatric intensive care unit. Iba et al.[39] reported that D-dimer levels were significantly higher, in the patients with sepsis with organ dysfunction and concluded that the changes in the hemostatic molecular markers were associated with organ dysfunction from an early stage of sepsis. On the contrary to our results, Kinasewitz et al.[33] reported that no biomarker could clearly predict the mortality outcome or correlate with disease severity (APACHE II score).

CONCLUSION

Endothelial dysfunction and hypercoagulation repre-

sented by increased ET-1 and D-dimer levels appear to be early and sensitive predictors of the severity of septic shock and of multiple organ dysfunction development.

A therapeutic strategy to improve the microcirculation in such patients could be studied and accomplished based on these levels.

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