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# Association between early glycemic control and improvements in markers of coagulation and fibrinolysis in patients with septic shock–induced stress hyperglycemia ☆

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ABSTRACT

*Purpose:* The purpose of this study is to evaluate the coagulation and inflammatory profiles in septic shock patients with baseline hyperglycemia under glycemic control.
*Methods:* Prospective, observational study conducted in an intensive care unit of a university hospital, including 41 septic shock nondiabetic patients with hyperglycemia (n = 21) or normoglycemia (n = 20) profiles at baseline. Hyperglycemic patients received a glucose control protocol (target glycemia, <150 mg/dL). Metabolic, inflammatory, and coagulation markers were measured at baseline and after 24 hours.
*Results:* Median glycemic values between groups were different at baseline but not after 24 hours. Baseline coagulation profile was similar in both groups with elevated levels of coagulation markers, reduced factor VII, protein C, and antithrombin activities and fibrinolysis impairment. Normoglycemic patients had unchanged coagulation markers after 24 hours. After treatment, previously hyperglycemic patients exhibited increased plasminogen concentrations ($P = .03$) and reduced levels of plasminogen activator inhibitor 1 ($P = .01$) and tissue plasminogen activator ($P = .03$) as compared with baseline. They also had higher factor VII ($P = .03$), protein C ($P = .04$), and antithrombin ($P = .04$) activities than normoglycemic patients. Inflammatory markers were elevated in both groups and improved after 24 hours, independently of the glycemic profile.
*Conclusions:* Glycemic control during septic shock is associated with improvements in coagulation and fibrinolysis parameters compared with baseline and normoglycemic patients.


## 1. Introduction

Hyperglycemia is a common occurrence during critical illness. Several studies demonstrated that up to 90% of patients develop blood glucose concentrations higher than 110 mg/dL during their intensive care unit (ICU) stay [1]. The occurrence of hyperglycemia is associated with adverse outcomes [2], although a causality relationship is not well established. Hyperglycemic patients might be more severely ill than those with normoglycemia, and the high glucose levels could only be a marker of disease severity. Previous studies from the Leuven group demonstrated that intensive glycemic control (maintaining glycemia at a range of 80-110 mg/dL) was associated with reduced mortality [3,4], although these results were not replicated in subsequent studies [5,6]. Recent glycemic control guidelines in critically ill patients suggested maintaining an intermediate range of glycemic control [7,8].

One beneficial effect of glycemic control may be related to the modulation of inflammation. Patients who were submitted to intensive glycemic control had reduced inflammation and decreased incidence of bacteremia [9]. Experimental studies demonstrated that hyperglycemia is related to increased inflammatory response, oxidative stress, and down-regulation of innate immunity [10]. In clinical scenarios, patients with sepsis and stress-induced hyperglycemia had increased concentrations of inflammatory cytokines [11]. However, the impact of glycemic control on inflammatory response during sepsis is not established.

Another pathophysiological mechanism of sepsis possibly affected by glycemic disturbances is the coagulation activation. Hyperglycemia is associated with an increase in the expression of tissue factor in healthy volunteers after glucose ingestion [12]. Moreover, in healthy volunteers and normal individuals who were submitted to endotoxemia, hyperglycemia was associated with amplification of coagulation, whereas hyperinsulinemia significantly inhibited fibrinolysis

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[13,14]. Studies on glycemic control and its influence on coagulation in critical illness showed discordant results [15,16]. Thus, we designed this study to evaluate the short-term consequences of glycemic control in coagulation and inflammatory parameters in hyperglycemic patients with septic shock.

## 2. Materials and methods

From February 2007 to August 2009, we screened all patients older than 18 years who were diagnosed with septic shock within 48 hours of organ dysfunction onset. Septic shock was diagnosed based on the definition given by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference [17]. The following subjects were excluded: patients who used full-dose heparin in the preceding 7 days, oral anticoagulants, fibrinolytics, or activated protein C; patients who received platelet or plasma transfusions in the preceding 7 days; and patients using insulin. We also excluded patients with previously known diabetes or glycated hemoglobin level greater than 7 mg/dL at the time of enrollment in the study, patients with a previous episode of sepsis during the last 30 days, patients with coagulopathy unrelated to sepsis, and patients with intermediate concentrations of glucose (150-200 mg/dL) at the time of enrollment in the study. The study was approved by the Research Ethics Committee of Hospital São Paulo (no. 0915-06). All patients or their legal representatives provided written informed consent before participation in this study.

In the screening phase, we used an arterial catheter to collect the first blood sample to measure metabolic, coagulation, and inflammatory parameters (T0). According to the initial arterial glycemia (Cobas; Roche, Burlington, NC), we allocated patients into 1 of 2 screening groups: the normoglycemia group (blood glucose $\leq$150 mg/dL) and the hyperglycemia group (blood glucose $\geq$200 mg/dL). Patients in the hyperglycemia group immediately received a continuous intravenous infusion of insulin according to the ICU protocol, which is adapted from Yale's protocol [18] that targeted a glycemia less than 150 mg/dL. We measured arterial glycemia at least every 4 hours in normoglycemic patients and hourly in hyperglycemic patients (Medsense Optium glucose strip; Abbott, Abbott Park, IL).

After the 24 hours screening phase (T1), we collected the second blood sample, but only if the patient had successfully completed the screening phase. To be included in the normoglycemia group, patients must have maintained a blood glucose level less than or equal to 150 mg/dL without the use of insulin. A maximum of 2 isolated glycemic measurements higher than 150 mg/dL was allowed if they did not occur in the last 6 hours before blood sampling. We repeated any measurement greater than 150 mg/dL for confirmation. In the hyperglycemia group, we allowed a 6-hour period for insulin dose adjustment. We only included patients that did not have any glycemia greater than 200 mg/dL. A maximum of 3 single or 2 double measurements greater than 150 mg/dL was allowed, if none of them occurred in the 6-hour period before blood sampling. Fig. 1 illustrates the study design.

Coagulation tests were performed on frozen samples in duplicate, according to the manufacturer's instructions. Immunoenzyme assays (enzyme-linked immunosorbent assay [ELISA]) for measurement of thrombin-antithrombin (TAT), prothrombin fragment 1 + 2, and D-dimer were made using kits from Dade Behring (Deerfield, IL). The measurement of tissue plasminogen activator (tPA), tissue factor, plasminogen activator inhibitor 1 (PAI-1), and tissue factor pathway inhibitor (TFPI) was also performed by ELISA method with kits from America Diagnostica (Stamford, CT). The measurement of plasminogen, antithrombin, and protein C was done by the chromogenic method using kits from Dade Behring (Deerfield, IL). Measurement of factor VII was performed by a coagulometric method using plasma deficient in factor VII from America Diagnostica (Stamford, CT). Fibrinogen was measured by the coagulometric method of Clauss using kit form America Diagnostica (Stamford, CT). Inflammatory profile was evaluated by measuring interleukin (IL) 6, IL-8, and IL-10 levels by capture

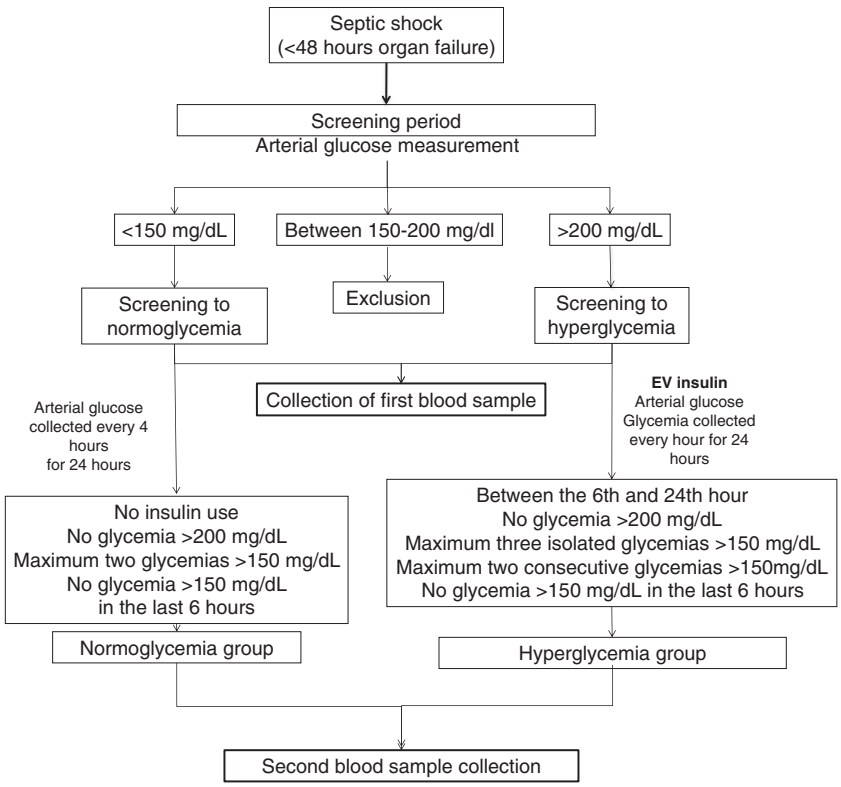


**Fig. 1.** Study algorithm.