Journal of Critical Care (2013) **28**, 577–585

ELSEVIER

Journal of Critical Care

Procollagen type III aminoterminal propeptide as biomarker of host response in severe sepsis☆

Spyros Zakynthinos MD, PhD[a,*], Spyros Papanikolaou MD[c], Spyros Mentzelopoulos MD, PhD[a], Evangellia Konstandelou MD[d], Christina Psachoulia MD[b], Antonis Mavrommatis MD, PhD[c]

[a]*First Department of Critical Care Medicine and Pulmonary Services, Medical School of Athens University, Evaggelismos Hospital, GR-10675, Athens, Greece*
[b]*Biochemistry Laboratory, Evaggelismos Hospital, GR-10675, Athens, Greece*
[c]*Department of Critical Care, General Hospital of Nikea, GR-10356, Piraeus, Greece*
[d]*Hormone Laboratory, General Hospital of Nikea, GR-10356, Piraeus, Greece*

Keywords:
Sepsis;
Severe sepsis;
Septic shock;
Host response;
Biomarkers

Abstract

Purpose: The purpose of this study is to test the hypothesis that procollagen type III aminoterminal propeptide (PIIINP) is early elevated in septic episodes and can indicate the acute organ dysfunction/failure characterizing severe sepsis.

Materials and Methods: This prospective study included 107 consecutive septic patients (44 with sepsis, 13 with severe sepsis, and 50 with septic shock) and 45 controls. After blood sampling (within 48 hours after onset of septic episodes), serum was assayed. Patients were followed up, and their disease severity was daily evaluated.

Results: Procollagen type III aminoterminal propeptide (median [range]) increased in patients with sepsis (9.4 [2.2-42.4] ng/mL) compared with controls (3.6 [1.9-4.9] ng/mL; $P < .001$), exhibiting further significant increase in patients with severe sepsis and septic shock (19.5 [6.0-52.4] and 20.2 [1.8-89.2] ng/mL, respectively; $P < .01$-$.001$ vs sepsis). Among biomarkers of host response severity, PIIINP was the sole that was independently associated with severe sepsis/septic shock ($P = .01$). The area under the receiver operating characteristic curve for PIIINP to predict which patients with sepsis would eventually develop severe sepsis/septic shock was 0.87; the cutoff of 12 ng/mL had sensitivity 82% and specificity 89%.

Conclusions: Increased serum PIIINP can signify severe sepsis/septic shock and predict which patients with sepsis will eventually develop severe sepsis/septic shock, thus representing a biomarker of risk stratification of patients with sepsis.

1. Introduction

Severe sepsis, defined as sepsis associated with acute organ dysfunction, results from a generalized inflammatory response to infection and is now considered to be the most

☆ The authors declare that they have no competing interests.

* Corresponding author.
E-mail address: szakynthinos@yahoo.com (S. Zakynthinos).

0883-9441/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jcrc.2013.04.004

common cause of death in noncoronary critical care units [1]. The rate of death from severe sepsis ranges from 30% to 50% despite advances in critical care [2]. One of the main problems arises from the fact that current knowledge does not allow for precise characterization and staging of patients with sepsis [1]. A clinically useful staging system would stratify septic patients by both their baseline risk of an adverse outcome and their potential to respond to therapy [1]. The Sequential Organ Failure Assessment (SOFA) score that is a simple and effective method to describe organ dysfunction/failure in critically ill patients [3] as well as the Predisposition, Insult/Infection, Response, and Organ dysfunction (PIRO) system that seems to be an effective model for sepsis staging and predictive of mortality [4] represents important advances in the context of characterization and staging of patients with sepsis. However, the host response (R in the PIRO system) has proven to be difficult to characterize because the specific criteria used to define the systemic inflammatory response are widely considered to be too nonspecific [1]. Particularly, the clinical manifestations of systemic inflammatory response are protean, whereas biological markers (biomarkers) may be more consistent [1]. Putative biomarkers of host response severity include circulating levels of procalcitonin [5,6], interleukin (IL) 6 [7-11], and many others.

The host defense response to an insult consists of an interactive network of simultaneously activated pathways—inflammation, coagulation, and tissue repair—that work in synergy to increase the host's chance of survival [12]. Tissue repair consists of angiogenesis, epithelial growth, fibroblast migration and proliferation (fibroproliferation), and deposition of extracellular matrix (fibrogenesis). A uniform connective tissue repair response has been demonstrated to occur in various organs following different types of injury [13]. During tissue repair, intact and fragmented matrix components are liberated into the extracellular fluid and circulation [13]. The procollagen type III aminoterminal propeptide (PIIINP), cleaved from the precursor procollagen molecule by specific proteinases in the extracellular space [14], has been used as a biological marker of collagen synthesis, and several studies have substantiated that elevated plasma PIIINP levels reflect collagen synthesis at the site of disease and may be used as marker of a reparative process independent of etiology [13,15-17]. Sepsis (ie, infection and the systemic inflammatory response to it) represents an extensive tissue injury [1] that should potentially initiate connective tissue repair. However, to the best of our knowledge, such host response has been studied only once in a limited number of patients with severe sepsis [18].

In acute respiratory distress syndrome (ARDS), the early (on the first day) elevated blood PIIINP levels were correlated with indices indicating severity of both pulmonary and extrapulmonary organ dysfunction [19]. Moreover, early and persistent elevation of circulating and bronchoalveolar lavage fluid PIIINP levels was associated with increased disease severity and mortality [16,19-23]. Therefore, in ARDS which is frequently due to sepsis and beyond the lung affects many other organs [24] just like sepsis, elevated blood PIIINP levels seem to be related with increased disease severity, and this could also be the case in sepsis.

The purpose of this study was to test the hypothesis that serum PIIINP levels (marker of new collagen synthesis) (*a*) are elevated in septic patients early in the course of their disease and (b) can indicate the acute organ dysfunction characterizing severe sepsis by being higher in patients with severe sepsis/septic shock compared with patients with sepsis and potentially by predicting which patients with sepsis will eventually develop severe sepsis/septic shock. Another purpose was to compare PIIINP with other putative biological markers of host response severity (ie, procalcitonin, IL-6, C-reactive protein).

2. Materials and methods

2.1. Patients and control subjects

This prospective observational study was conducted in the general intensive care units (ICUs) of 2 tertiary university hospitals in Athens, Greece. The patients were treated in the ICU and were enrolled in the study during the first 48 hours after the onset of a septic episode. During a 12-month period, all consecutive septic patients were included, except those (*a*) younger than 16 years; (*b*) who were immunocompromised because of receipt of bone marrow or organ transplants, leucopenia (leukocyte count $<1.0 \times 10^9$ cells/L) or neutropenia (polymorphonuclear granulocyte count $<0.5 \times 10^9$ cells/L), a hematologic malignant condition or other malignancies under chemotherapy, or AIDS; (*c*) with a documented history of condition involving tissue fibrosis (eg, pulmonary fibrosis, sarcoidosis, cirrhosis), except of trauma and surgery associated with the present admission; (*d*) treated with drugs known to influence collagen metabolism (eg, corticosteroids, amiodarone, statins); (*e*) with chronic hepatic or renal failure or a disease affecting leukocyte counts; and (*f*) without a written informed consent.

Soon after patient entry to the study and before blood sample collection, 3 experienced intensivists, blinded to the goals of the study, categorized each patient as having sepsis, severe sepsis, or septic shock [1,25], determined whether the patient had ARDS [24] or multiple organ dysfunction syndrome (MODS) [25,26] and calculated the Acute Physiology and Chronic Health Evaluation (APACHE) II score [27], and SOFA score [3,28]. Patients were followed up prospectively until death or ICU discharge and their disease severity was daily evaluated.

Control subjects were healthy volunteers, receiving no medications. None had shown any evidence of febrile illness during the previous 3 months. Their hematologic indices and liver and kidney functions were within reference ranges. Appropriate institutional ethics committee reviewed and