Effect of sepsis and cardiac surgery with cardiopulmonary bypass on plasma level of nitric oxide metabolites, neopterin, and procalcitonin: correlation with mortality and postoperative complications

Abstract  Objectives: To examine the hypothesis that nitrite/nitrate, neopterin, and procalcitonin (PCT) levels can be useful predictors of sepsis-associated mortality and predictors of the postoperative complications after cardiopulmonary bypass (CPB). 
Setting: Prospective clinical study. Setting: Intensive care unit of the Medical University Hospital. 
Patients: 41 patients with sepsis, 42 patients subjected to open heart surgery with CPB, and 30 healthy volunteers.
Measurements and results: Nitrite/nitrate, neopterin, and PCT levels were measured in septic patients as soon as sepsis was recognized and then on the 2nd, 3rd, and 5th days of treatment. Statistically significant differences between survivors and nonsurvivors were found for neopterin and PCT. The area under receiver operating characteristic curve (AUC) for both parameters as predictors of mortality was above 0.8. The nitrite/nitrate level was also higher in nonsurvivors, but the AUC remained below 0.8, which indicates poor predictive power. The same parameters were measured in patients undergoing cardiac surgery before, during and after CPB establishment. The development of postoperative complications was correlated with increased postoperative neopterin and PCT levels. Additionally, neopterin was found as an early marker for the prognosis of postoperative complications, since patients who developed organ dysfunction had had elevated concentrations of this parameter even before surgery (AUC 0.83). Measurement of NO metabolite levels was less specific and less sensitive. 
Conclusions: Our results confirm the value of PCT and neopterin measurement as diagnostic tools in monitoring the clinical course of patients in intensive care units.

Keywords Sepsis · Cardiopulmonary bypass · Nitrite/nitrate · Neopterin · Procalcitonin · Receiver operating characteristic curve
Introduction

Sepsis and sepsis-associated organ dysfunction have been well documented to induce systemic inflammatory response including the release of inflammatory mediators [1]. After operations with cardiopulmonary bypass (CPB) the activation of inflammatory cascades, due to cytokine release, has also been reported, and this reaction shows strong similarities to those observed in sepsis [2]. Plasma levels of various inflammatory mediators have been used to assess the severity of the inflammatory state and to establish the clinical prognosis. Nitric oxide metabolites, neopterin, and procyclitomin (PCT) have been suggested as clinically useful markers of inflammatory response [3, 4]. Endotoxin and cytokines stimulate the inducible calcium-independent nitric oxide synthase (NOS), which generates up to 1000 times more nitric oxide than constitutive NOS, and cellular production continues for hours [5, 6]. Consequently it has been proposed that excess production of NO by inducible NOS causes the hypotension and myocardial depression in septic shock, and that inhibition of this isoform of NOS might be beneficial in treating this highly lethal syndrome [7]. Plasma levels of nitrate and nitrite, the stable oxidative end-products of NO, are used as an indirect measure of in vivo whole body NO production in sepsis and in surgery involving CPB.

Neopterin, a low molecular weight pteridine compound, is secreted by macrophages in response to stimulation by interferon-γ, interleukin-1β, tumor necrosis factor-α, and lipopolysaccharide [8]. Although its function in the immune response is unknown, neopterin has been used as an indicator of cellular immune activation [9]. Neopterin secretion is increased in patients suffering from viral, bacterial, or parasitic infections and with immune and autoimmune diseases [10]. PCT, a 13-kDa peptide produced under physiological conditions in thyroid glands, is almost undetectable in serum of healthy humans. The PCT level, however, increases substantially during severe bacterial, parasitic, and fungal infections and therefore has been used to differentiate between infectious and noninfectious causes of severe inflammatory state [11, 12]. Recently it was proposed that PCT, in addition to being an important marker of severity of inflammation, is an integral part of the inflammatory process [13].

The aim of this study was: (a) to analyze plasma nitrite/nitrate, neopterin, and PCT concentrations in sepsis and in cardiac surgery, and (b) to examine the hypothesis that nitrite/nitrate, neopterin, and PCT levels are useful predictors of mortality during sepsis as well as predictors of postoperative complications after CPB.

Materials and methods

The study, approved by the local ethics committee, was conducted in the Intensive Care Unit (ICU) of the Medical University Hospital, Wroclaw, Poland. Nitric oxide metabolites, neopterin, and PCT levels were measured in 41 patients with sepsis and 42 patients undergoing open heart surgery with CPB. The reference range of nitric oxide metabolites was calculated from values obtained in the control group consisting of 30 healthy volunteers.

Sepsis patients

Sepsis, severe sepsis, septic shock, and multiple organ dysfunction syndrome (MODS) were diagnosed using the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference guidelines [14]. Forty-one patients were enrolled in the study during first 12 h after they had fulfilled the criteria of sepsis or severe sepsis. All the patients had microbiologically documented infection originating from abdomen (56%), respiratory tract (32%), surgical wounds (7%), or bones (5%).

Patients were retrospectively divided into two groups: group A consisted of 16 survivors (39%) and group B of 25 patients (61%) who died during the course of septic shock and/or MODS. Nitrite/nitrate, neopterin, and PCT levels were measured as soon as sepsis or severe sepsis was recognized (day 1) and then on the 2nd, 3rd, and 5th days of treatment. Patients’ status was assessed with the Simplified Acute Physiology Score II (SAPS II) at the entry to the study and with the Sepsis-Related Organ Failure Assessment (SOFA) score every day. Patient characteristics are presented in the Table 1.

Patients subjected to cardiac surgery

Forty-two patients scheduled for elective cardiac procedures with CPB were studied. Routine preoperative chest roentgenograms, electrocardiograms, and complete chemistry and morphology profiles were normal in all studied patients. They had no clinical signs of infection. Ejection fraction values were within range from 0.35 to normal. Patients with a history of endocrine disorders, anemia, or hepatic or renal diseases were excluded. Thirty-one patients underwent coronary artery bypass grafting, six valvular replacement, and five both. A standard CPB technique was used in all patients. Myocardial preservation strategy used cold crystalloid cardioplegia and moderate hypothermia (28–32°C). A membrane oxygenator (Dideco Compacfito, Sorin Monolyth, Jostra Quadox) and a roller pump were used to provide nonpulsatile bypass. Cephamandole was used for perioperative antibiotic prophylaxis. Blood samples for nitrite/nitrate, neopterin, and PCT levels were obtained after induction of anesthesia but before CPB, during CPB, and on the 1st and 2nd postoperative days. The Logistic Organ Dysfunction Score (LODS), SOFA, and routine laboratory data were daily recorded. SAPS II was determined once after the operation. Patient characteristics are presented in the Table 2.

The 42 patients were divided into two groups. Group C consisted of the 34 patients (76%) who recovered uneventfully and left the ICU within 1 or 2 days, and group D of 8 patients (24%) who developed postoperative complications and required prolonged stay in the ICU (Table 3). Patients in group C had SOFA values less than 8 and LODS values less than 3 throughout the time of observation. Patients in group D had SOFA values of 8 or higher and LODS values of 3 or higher after operation, and all of them experienced respiratory and circulatory insufficiency.