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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

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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).
Design: 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 concentration 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.

Key words 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 procalcitonin (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 nitrite and nitrate, 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.

Septic 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 Compactflo, Sorin Monolyth, Jostra Quadrox) 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.

Table 1 Characteristics of septic patients (*WBC* white blood cell count, *CRP* C-reactive protein, *MODS* multiple organ dysfunction syndrome, *SAPS II* Simplified Acute Physiology Score II, *SOFA* Sepsis-Related Organ Failure Assessment)

	Survivors ($n = 16$)	Nonsurvivors ($n = 25$)
Age (years)	47 ± 16	51 ± 15
Gender (male/female)	9/6	15/11
WBC ($\times 10^9$/l)		
At the entry	12.4 ± 7.1	14.6 ± 9.5
On day 5	11.2 ± 3.5	14.3 ± 8.9
CRP (mg/l)		
At the entry	120 ± 67	178 ± 107
On day 5	73 ± 51	146 ± 72*
Diagnosis at admission		
Pneumonia	2	4
Acute abdomen/peritonitis	5	13
Acute pancreatitis	2	3
Multiple trauma/pneumonia	4	3
Wound infection	2	1
Ostitis	1	1
ICU course		
Sepsis	6	3
Severe sepsis	7	5
Septic shock	3	17
MODS during ICU stay	5	25
Positive blood culture		
$Gram^+/Gram^-$/Fungi	5/2/0	9/6/3
SAPS II at the entry	34.5 ± 16.1	52.1 ± 18.3*
SOFA		
Day 1	7.3 ± 2.5	11.0 ± 2.7*
Day 2	7.8 ± 1.9	11.8 ± 2.7*
Day 3	7.5 ± 2.2	12.0 ± 2.9*
Day 5	7.5 ± 2.3	12.1 ± 2.9*
ICU stay (days)	28 ± 14	23 ± 18

*$p < 0.05$ group A vs. B

Table 2 Characteristics of patients subjected to cardiac surgery (*CPB* cardiopulmonary bypass, *AC* aorta clamping, *SAPS II* Simplified Acute Physiology Score II, *SOFA* Sepsis-Related Organ Failure Assessment, *LODS* Logistic Organ Dysfunction Score)

	Patients without complications ($n = 34$)	Patients with complications ($n = 8$)
Age (years)	58 ± 11	59 ± 8
Sex: M/F	24/10	4/4
CPB time (min)	128 ± 30	156 ± 44
AC time (min)	67 ± 23	86 ± 44
Postoperative mechanical ventilation (h)	10.2 ± 5.3	84.7 ± 47.5*
White blood cell count ($\times 10^9$/l)		
Before operation	8.9 ± 3.1	9.2 ± 2.8
2nd day after operation	11.6 ± 2.4	12.8 ± 5.2
SAPS II		
Day of operation	34.3 ± 8.0	41.9 ± 3.2*
SOFA		
Day of operation	5.2 ± 1.2	8.5 ± 2.2*
1st day after operation	3.2 ± 2.2	8.0 ± 2.7*
2nd day after operation	4.3 ± 1.9	8.3 ± 2.3*
LODS		
Day of operation	2.2 ± 1.1	4.0 ± 1.6*
1st day after operation	1.0 ± 1.1	3.8 ± 1.7*
2nd day after operation	1.3 ± 1.0	4.0 ± 2.5*
ICU stay (days)	1.2 ± 0.4	7.2 ± 5.5*

*$p < 0.05$ group C vs. D

Two patients died. No clinical or microbiological signs of infection were observed. Postoperative complications were defined as follows: (a) circulatory failure: requirement for catecholamines infusion and/or intra-aortic contrapulsation to maintain mean arterial pressure higher than 80 mmHg; (b) respiratory failure: postoperative mechanical ventilation longer than 24 h and/or a fraction of inspired oxygen (FIO_2) greater than 0.4; (c) renal dysfunction: serum creatinine level above 3.0 mg/dl and/or renal replacement therapy; (d) hepatic dysfunction: serum bilirubin level above 2.0 mg/dl and aspartate aminotransferase and/or alanine aminotransferase level elevated more then twofold; (e) coagulation dysfunction: thrombocyte count less than 50×10^6/l and international normalized ratio greater than 1.5.

Samples

Arterial blood from all patients and venous blood from volunteers was sampled on heparin. Plasma was obtained immediately and frozen until the assay was performed. Plasma levels of nitrite/nitrate were measured using the procedure based on the Griess reaction after the enzymatic reduction of nitrate to nitrite [15]. Briefly, plasma was ultrafiltrated by centrifuging using 10,000-MW filters (Ultrafree-MC, Millipore). Nitrate was reduced to nitrite by adding nitrate reductase derived from *Aspergillus* spp., NADPH, and FAD. Samples were incubated in 37 °C for 1 h and then mixed with lactate dehydrogenase and sodium pyruvate and further incubated to oxidize excess of NADPH. The nitrite was measured by the addition of Griess reagents and the absorbance was read at a wavelength of 540 nm. The results reflected total plasma nitrite plus nitrate concentrations. Plasma neopterin level was determined with radioimmunoassay (ImmuChem Neopterin-DA RIA, Biomedicals, USA). Procalcitonine concentration was measured by an immunoluminometric assay (Lumitest PCT, BRAHMS Diagnostica, Germany).

Statistical analysis

Statistical analysis was performed with Statistica for Windows (StatSoft, 1997). Quantitative variables for nitrite/nitrate, neopterin, and PCT were expressed as median and quartiles. Mean ± SEM were employed to present other data. The Mann-Whitney *U* test was used to evaluate the statistical significance of differences between groups. Paired data (before and after CPB) were compared by the Wilcoxon test. Values of $p < 0.05$ were regarded as statistically significant. The discriminative power of selected markers was defined by the area under the receiver operating characteristic (ROC) curves, computed by the modification of the Wilcoxon statistics proposed by Hanley and McNeil [16]. A test with perfect predictive power has an area under the ROC curve (AUC) of 1.0. A test that predicts an outcome no better than chance has AUC

Table 3 Postoperative complications in cardiac surgical patients (*CABG* coronary artery bypass grafting, *VR* valvular replacement, *IABP* intra-aortic balloon pump, *DIC* disseminated intravascular coagulation)

Patient no.	Age (years)	Sex	Operation	CPB time (min)	AC time (min)	Specification of postoperative complications	ICU stay (days)
1	60	M	CABG	130	35	Prolonged mechanical ventilation (5 days), circulatory failure (catecholamines, IABP), renal dysfunction, hepatic dysfunction, DIC; death	5
2	62	F	CABG	130	47	Prolonged mechanical ventilation (2 day), circulatory failure (catecholamines), renal dysfunction	6
3	63	F	VR	90	41	Prolonged mechanical ventilation (2 days), circulatory failure (catecholamines)	3
4	61	M	CABG+VR	199	129	Prolonged mechanical ventilation (3 days), circulatory failure (catecholamines), renal dysfunction, hepatic dysfunction	6
5	66	F	CABG+VR	177	127	Prolonged mechanical ventilation (6 days), circulatory failure (catecholamines), renal dysfunction, hepatic dysfunction; death	9
6	67	M	VR	140	41	Prolonged mechanical ventilation (2 days), circulatory failure (catecholamines, IABP), renal dysfunction	6
7	41	M	CABG+R	135	93	Prolonged mechanical ventilation (2 days), circulatory failure (catecholamines)	3
8	70	M	CABG+VR	246	146	Prolonged mechanical ventilation (6 days), circulatory failure (catecholamines, IABP), renal dysfunction, hepatic dysfunction	20

of 0.5. AUC above 0.8 indicates good prediction. Optimal cutoff points for each marker were chosen for the calculation of positive and the negative predictive values. The positive predictive value (PPV) reflects how certain we may be about the presence of the outcome in question with the positive test results (above the chosen cutoff point). The negative predictive value (NPV) indicates the percentage of patients with a negative test (below the chosen cutoff point) who do not develop the outcome.

Results

NO metabolites

In all the septic patients in the study plasma nitrite/nitrate levels exceeded those in healthy volunteers, as summarized in Table 4. The concentrations were higher in nonsurvivors than in survivors throughout the observation period, but the differences reached statistical significance only on day 5 (Fig. 1). The AUC for nitrite/nitrate as a predictor of mortality measured on days 1, 2, 3, and 5 were: 0.58, 0.61, 0.72, and 0.73, respectively. For the cutoff level of 60 μmol/l PPV/NPV values were: 67/47 %, 80/57 %, 74/50 %, and 92/54 %, respectively. Among the cardiac surgical patients there was no significant difference in initial plasma nitrite/nitrate level in patients with and without postoperative complications. A greater discrepancy was found between the two groups during the CPB and on the 1st day after surgery. The AUC for nitrite/nitrate as a predictor of postoperative complications measured before operation, during operation, and on the 1st and 2nd days after operation was: 0.63, 0.79, 0.77, and 0.50, respectively. For the cutoff level of 41 μmol/l PPV/NPV values were: 40/82 %, 67/83 %, 57/89 %, and 38/77 %, respectively.

Neopterin

Neopterin concentration was higher in septic nonsurvivors than in survivors even at the entry into the study (Table 4), and differences increased thereafter ($p < 0.001$; Fig. 1). The AUC for neopterin as a predictor of mortality measured on days 1, 2, 3, and 5 were: 0.77, 0.87, 0.89, and 0.96, respectively. For the cutoff value of 41 nmol/l PPV/NPV values were: 67/64 %, 72/87 %, 83/93 %, and 90/100 %, respectively. In all cardiac surgical patients neopterin levels were elevated in the those who developed postoperative complications and within the reference range in the group of patients with uneventful recovery at the entry to the study. Postoperatively, neopterin concentrations increased significantly in both groups; however, the values were markedly higher in the group D. The differences between the two groups were statistically significant throughout the

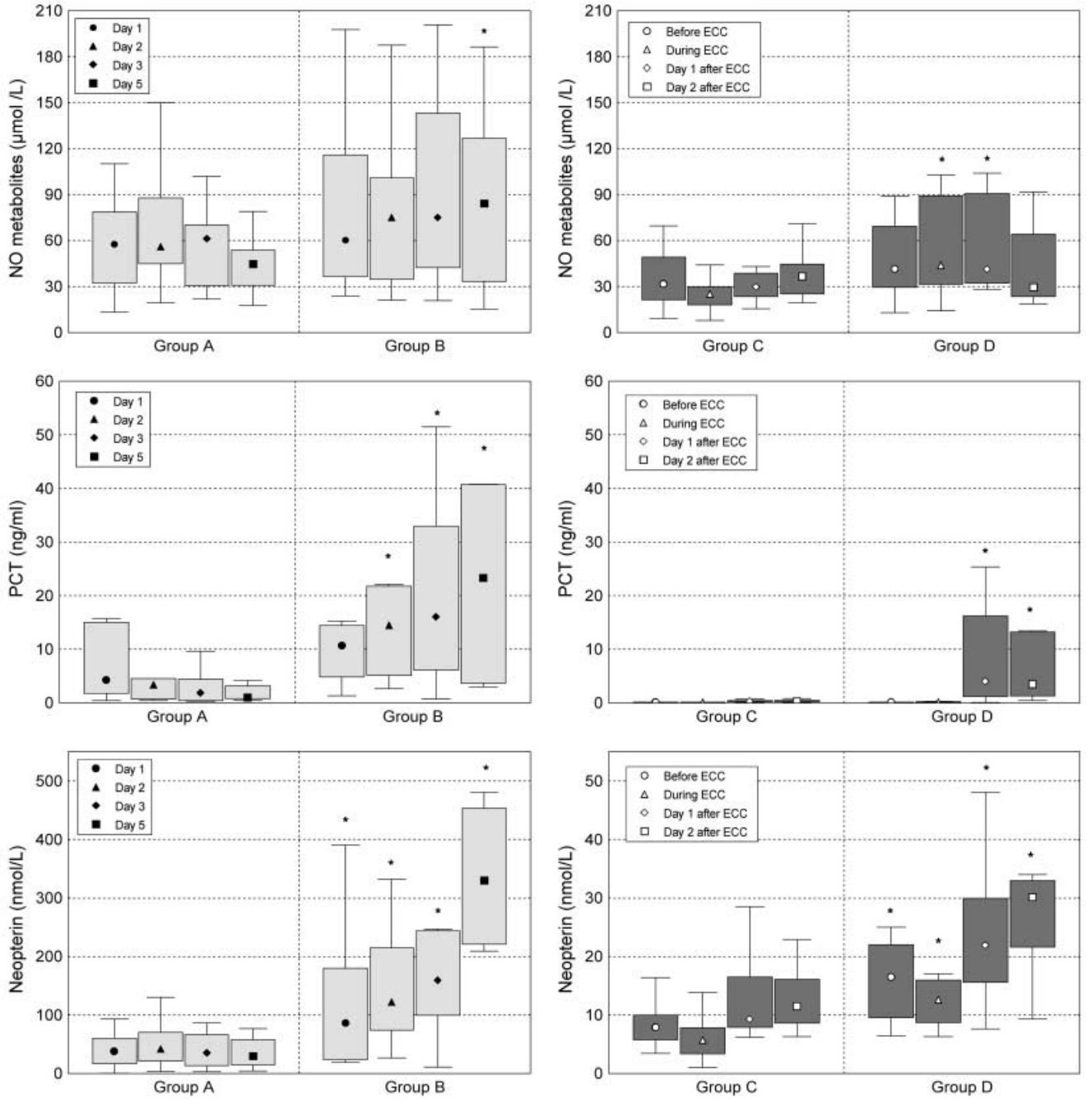

Fig. 1 NO metabolites, neopterin, and procalcitonin *(PCT)* levels in septic survivors *(group A)* and nonsurvivors *(group B)* on the 1st, 2nd, 3rd, and 5th days of treatment and in patients undergoing cardiac operation, who recovered uneventfully *(group C)*, or who developed postoperative complications *(group D)* before and during operation and on the 1st and 2nd days after the surgery. Median and quartile values. $*p < 0.05$

study. The AUC for neopterin as a predictor of postoperative complications measured at four times: 0.83, 0.87, 0.81, and 0.81, respectively. For the cutoff value of 14.5 nmol/l PPV/NPV values measured before operation was 71/91 %, and those for the cutoff value of 20 nmol/l measured during operation and on the 1st and 2nd days after operation were: 100/80 %, 71/90 %, and 67/93 %, respectively.

Table 4 NO metabolites, neopterin, and procalcitonin in groups A and B on the 1st, 2nd, 3rd, and 5th days of treatment, and in groups C and D before and during operation *(OP)* and on the 1st and 2nd days thereafter: medians (quartiles). Reference ranges: neopterin < 10 nmol/l, procalcitonin < 0.5 ng/ml, nitrite/nitrate 34.0 (19.3–78.1), as calculated from the control group

	Group A	Group B	Group C	Group D
Nitrite/nitrate (μmol/l)				
1st day of treatment	57.5 (32.3–78.5)	60.3 (36.3–115.7)	–	–
Before OP	–	–	31.6 (21.1–49.3)	41.4 (29.4–69.3)
2nd day of treatment	55.9 (44.8–87.8)	75.0 (34.7–101.0)	–	–
During OP	–	–	25.0 (18.0–29.6)	43.7 (31.5–89.1)**
3rd day of treatment	61.1 (30.3–70.1)	75.0 (42.4–143.2)	–	–
After OP, 1st day	–	–	29.6 (23.4–38.6)	41.1 (32.2–90.7)**
5th day of treatment	44.5 (30.8–53.7)	84.2 (33.3–126.8)*	–	–
After OP, 2nd day	–	–	36.6 (25.0–44.6)	29.4 (23.4–64.2)
Neopterin (nmol/l)				
1st day of treatment	25.5 (9.1–47.3)	64.4 (28.6–179.8)*	–	–
Before OP	–	–	7.8 (5.7–10.0)	16.4 (9.5–22.0)**
2nd day of treatment	28.7 (14.1–57.7)	93.6 (58.7–181.7)*	–	–
During OP	–	–	5.6 (3.3–7.7)	12.6 (8.7–15.8)**
3rd day of treatment	25.7 (11.8–38.4)	122.6 (67.5–233.2)*	–	–
After OP, 1st day	–	–	9.3 (7.9–16.5)	21.9 (15.6–30.0)**
5th day of treatment	21.0 (14.6–35.9)	227.5 (196.7–481.0)*	–	–
After OP, 2nd day	–	–	11.5 (8.6–16.1)	30.1 (21.6–33.0)**
Procalcitonin (ng/ml)				
1st day of treatment	4.19 (1.8–15.0)	10.6 (4.8–14.5)	–	–
Before OP	–	–	0.1 (0.1–0.1)	0.1 (0.1–0.1)
2nd day of treatment	3.36 (0.7–4.5)	14.4 (5.1–21.8)*	–	–
During OP	–	–	0.1 (0.1–0.1)	0.1 (0.1–0.2)
3rd day of treatment	1.82 (0.42–4.4)	16.0 (6.1–32.9)*	–	–
After OP, 1st day	–	–	0.2 (0.2–0.4)	4.0 (1.2–16.2)**
5th day of treatment	0.98 (0.8–3.1)	23.3 (3.7–40.8)*	–	–
After OP, 2nd day	–	–	0.3 (0.2–0.5)	3.5 (1.35–13.2)**

*$p < 0.05$, group A vs. B, **$p < 0.05$, group C vs. D (Mann-Whitney U test)

Procalcitonin

In both groups of septic patients plasma PCT concentration exceeded the reference range (Table 4). In the following days high PCT level decreased in survivors and increased in patients who died due to septic shock/MODS (Fig. 1). The AUC for PCT as a predictor of mortality measured on days 1, 2, 3, and 5 were: 0.66, 0.84, 0.87, and 0.94, respectively. For the cutoff value of 3.0 ng/ml PPV/NPV values were: 70/67 %, 80/83 %, 84/88 %, and 88/100 %, respectively. PCT concentrations before and during operation were almost undetectable in all the patients undergoing CPB. Postoperatively, the low PCT levels remained unchanged in patients with uneventful recovery and increased in patients with complications, especially in those who developed renal and hepatic dysfunction in addition to respiratory and circulatory insufficiency. The AUC for PCT as a predictor of postoperative complications measured at four times were: 0.56, 0.61, 0.85, and 0.94, respectively. For the cutoff value of 0.15 ng/ml measured before and during operation the PPV/NPV values were 23/86 % and 67/82 %. For the cutoff value of 2.0 ng/ml measured on the 1st and 2nd day after operation PPV/NPV values were 100/93 % and 100/87 %.

Additional parameters

SAPS II and SOFA scores were significantly higher in septic nonsurvivors than in survivors. There were no differences in white blood cell count. C-reactive protein levels were significantly higher in the group B on day 5. However, the AUC value of 0.71 indicated poor predictive power of this parameter compared to neopterin and PCT. Among the cardiac surgical patients all scores were significantly higher in patients with postoperative complications as early as in the evening of the operating day. While scores among patients with an uncomplicated course decreased significantly over the following days, they remained high in patients with complications. Extracorporeal circulation time was longer in group D, but the values were not correlated with those of other measured parameters. The differences in white blood cell count and aorta clamping time between groups were negligible and statistically nonsignificant.

Discussion

Changes in NO production in systemic inflammatory response, sepsis, trauma or infection have been reported in many studies [17]. Increased plasma nitrite/nitrate concentration has been detected in patients with sepsis, septic shock, burns, after tumor immunotherapy, and in transplant rejection [18, 19]. However, they have been found to be decreased in postsurgical and posttrauma patients [20]. PCT levels reflect the severity of the inflammatory response and is highly elevated in patients with septic shock [12]. Measurement of neopterin in serum has been used in monitoring sepsis severity in critically ill patients [4]. Surgery involving CPB may also lead to the development of systemic inflammatory response. The release of inflammatory mediators such as interleukin-6, interleukin-8, tumor necrosis factor, PCT, neopterin, and NO during and after the operation has previously been reported [2, 21, 22].

Determination of nitric oxide radical itself is difficult because of its very short half-life. NOS activity can be determined only in tissue and cell homogenates. This assay is time consuming and is not suitable for routine practice. Therefore determination of stable end products, nitrite/nitrate, in plasma is most often used as a measure of NO production [23]. A positive correlation has been reported between NO metabolite levels and mortality of patients with septic complications [17]. In contrast, our data suggest that the NO metabolite level is not a useful predictor of mortality. Statistically significant differences between groups, observed on the 5th day of treatment, we explained as a result of renal dysfunction that developed in the course of MODS. The AUC values remained below 0.8, which confirms the poor sensitivity and specificity of this test.

The correlation between plasma neopterin level and mortality in sepsis had been reported previously [24]. In our study neopterin levels increased progressively in the course of disease in nonsurvivors, and there were statistically significant differences between first and the following days. Likewise, the PCT concentrations in these patients increased constantly. There was no marked drop in neopterin level in septic survivors, probably because of sustained immune activation occurring in sepsis. Referring to PCT, improvement in patients' condition was reflected by an evident decrease in the PCT levels. Our data are consistent with those of other studies showing neopterin and PCT to be of a prognostic value in septic patients [1, 25, 26]. The AUC values of both parameters measured on days 2, 3, and 5 were above 0.8, which indicates good prediction. On day 5, when the AUC exceeded even 0.9, all nonsurvivors had PCT levels higher than 3.0 ng/ml (NPV = 100 %) and neopterin levels higher than 41 nmol/l (NPV = 100 %). Most of survivors had PCT and neopterin levels below these values (PPV = 88 % and 90 %, respectively). It follows that these two cutoff points are the most sensitive and specific in prediction of mortality in sepsis.

In cardiac surgery the early identification of patients at risk of postperfusion syndrome may help in determining therapeutic intervention. We observed that immune response to CPB was more pronounced in patients with postoperative complications than in patients with an uneventful postoperative course. Almost all the patients who postoperatively developed organ dysfunction had had elevated concentration of neopterin even before surgery. A diagnostic value of 14.5 nmol/l derived from the ROC curve analysis might help identify patients at risk. Elevated preoperative neopterin levels have also been observed in another study [27]. A possible explanation of this finding is either undetected bacterial or viral infection or chronic autoimmune disorders or any other conditions that can activate immune response. However, further studies are required to investigate the effect of various preoperative factors on neopterin release.

Statistically significant differences in nitrite/nitrate level between groups were observed during operation and on the first day after the surgery; however, the AUC values remained below 0.8. The release of nitric oxide was probably caused by ischemia/reperfusion of the organs and the translocation of endotoxins from gut to the bloodstream after aorta declamping, as has been reported in the literature [28]. The effect of prolonged CPB time on activation of the immune system cannot be excluded. On the second day NO metabolite concentrations returned to the values similar to those before surgery. Findings reported by other authors are inconsistent. Rouvolo et al. [21] observed an increase in nitrite level in patients who underwent surgery involving CPB, but another study, carried out on the similar group of patients, detected no changes in either systemic or epithelial NO production [29]. We also noted that CPB alone could induce release of neopterin from activated monocytes/macrophages since both groups of patients had significantly higher neopterin levels after operation. We observed no similar increase in PCT.

PCT and neopterin levels after surgery were significantly higher in patients with complications, and the AUC values of both parameters exceeded 0.8. Most patients with PCT levels higher than 2.0 ng/ml and neopterin levels higher than 20 nmol/l developed organ dysfunction. Earlier studies have demonstrated that CPB itself does not have a significant effect on the PCT secretion; however, infection following cardiac surgery is always accompanied by high PCT values [22, 30]. Moreover, in the study by Hensel et al. [31] all patients with postoperative acute lung injury and

without any sign of infection had a PCT level above 5 ng/ml. Our results confirm that increased PCT may be caused by noninfectious factors, such as organ failure following CPB. On the other hand, the endotoxin release from the ischemic gut to the systemic circulation could also affect on PCT and neopterin secretion.

In conclusion, PCT and neopterin have better sensitivity, specificity, and predictive values than either nitrite/nitrate or other routine laboratory parameters in predicting mortality in sepsis and postoperative complications secondary to CPB. The measurement of these parameters may provide useful additional diagnostic tools in monitoring the clinical course of patients in ICUs.

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