Hyperprocalcitonemia in Patients with Noninfectious SIRS and Pulmonary Dysfunction Associated with Cardiopulmonary Bypass

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Background: The incidence of noninfectious systemic inflammatory response syndrome (SIRS) associated with coronary artery bypass surgery and the potential role of several inflammatory parameters as early markers of pulmonary dysfunction induced by cardiopulmonary bypass (CPB) were investigated.

Methods: Forty patients undergoing elective coronary artery bypass surgery were studied prospectively. Perioperative lung function was monitored using the lung injury score introduced by Murray and colleagues, by measuring venous admixture (Qs/Qt), and, in some cases, by measuring extravascular lung water. Serum concentrations of the inflammatory parameters (procalcitonin, interleukin-6, sL-selectin, leukocyte elastase, neopterin, leukocyte counts, and C-reactive protein) were determined sequentially. The American College of Chest Physicians—Society of Critical Care Medicine classification system was used to diagnose SIRS.

Results: According to the entry criteria, SIRS developed in 17 (42%) patients after operation. Nine patients of this group showed signs of acute pulmonary impairment, whereas patients without SIRS had no lung injury. In all patients with acute lung injury, distinct increases in procalcitonin concentrations ranging from 5.1 to 14.3 ng/ml were measured. In patients with SIRS but without acute lung injury and in patients without SIRS, none or only negligible increases in serum concentrations of procalcitonin were seen. Compared with procalcitonin, other inflammatory parameters investigated were less sensitive and less specific to indicate pulmonary dysfunction secondary to CPB.

Conclusions: Procalcitonin seems to be an appropriate parameter indicating the early development of severe noninfectious SIRS and for predicting pulmonary dysfunction secondary to CPB. (Key words: Cardiac surgery; inflammation; lung injury.)

FOR several years it has been known that cardiopulmonary bypass (CPB) is associated with a generalized inflammatory response. The exposure of blood cells and plasma to artificial membranes and the activation of several cell types in the setting of ischemia and reperfusion are believed to play an important role in the development of this generalized inflammatory reaction. Endotoxin and various mediators have been reported to be involved in CPB-induced reactions, which can lead to postoperative organ dysfunction.

In a broader sense, patients’ response to various severe clinical insults, either infectious or noninfectious, has been defined by the Society of Critical Care Medicine and the American College of Chest Physicians as the systemic inflammatory response syndrome (SIRS). This definition was accepted to provide a conceptual framework to distinguish SIRS from sepsis. The former has a low threshold for entering patients into this diagnosis, and the clinical features are rather nonspecific. Whether the specific clinical insult of CPB and patients’ response should be defined separately from the nonspecific SIRS is still a matter of debate. Provided that SIRS is induced in all patients undergoing open heart surgery, the clinical value of this classification would be rather questionable because it does not account for the development of organ dysfunction. Because the severity of SIRS varies, severe complications such as acute lung injury (ALI), myocardial insufficiency, and renal failure develop in only a few patients. As an analogy to organ

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dysfunction associated with sepsis—defined as severe sepsis—that organ dysfunctions occurring during noninfectious SIRS might be defined as severe SIRS. Regarding this aspect, several authors have tried to find clinical features such as hemodynamic and respiratory changes or appropriate biochemical and immunologic parameters that would indicate the onset of organ dysfunction secondary to CPB.

It is generally accepted that many pro- and anti-inflammatory mediators may become predominant and lead to a deficiency of immunologic function during and after CPB. The release of soluble adhesion molecules in the circulating blood are believed to be markers of cellular activation, the extent of inflammation, and endothelial damage. Endotoxemia has also been reported to be associated with cardiac surgery. Leukocyte elastase and neopterin were used to monitor the activation of polymorphonuclear leukocytes or monocytes and macrophages, respectively. The value of commonly used inflammation parameters such as C-reactive protein (CRP), leukocyte count, and body temperature to distinguish between infection and SIRS after CPB is unknown. Procalcitonin (PCT), first described as an infection parameter in 1993, is considered to be a prognostic indicator and marker of the extent and course of severe bacterial infections.

Because the lung is the only organ that receives the entire cardiac output and is therefore exposed to the full load of all circulating mediators, its impairment plays a prominent role in the hierarchy of organ dysfunction associated with SIRS. Thus we set out to investigate the role of proinflammatory mediators as predictors of pulmonary dysfunction caused by CPB.

Materials and Methods

Patient Selection

The study was approved by the local ethics committee and informed consent was obtained from each patient. Forty patients (16 women, 24 men) undergoing elective coronary artery bypass surgery were studied prospectively. Entry criteria for investigation included stable angina pectoris; left ventricular ejection fraction >0.4; left ventricular end-diastolic pressure <17 mmHg; absence of preexisting pulmonary diseases as determined by clinical examination, chest radiography, lung function tests, and blood gas analysis; and absence of clinically relevant renal, hepatic, or cerebrovascular disease.

Patients with preoperative signs of infection (leukocyte count >12,000/µl, body temperature >38°C, CRP >5) and patients who had taken cyclooxygenase inhibitors or steroids within the last 7 days before the operation were excluded. Thirty-nine patients survived and left the hospital. One patient (in group 5) with gastric perforation and multiple-organ failure died of the complications.

Anesthesia and Cardiopulmonary Bypass

Patients were premedicated with flunitrazepam (0.03 mg/kg given orally) on the night before surgery, and on the day of surgery they received 0.1 mg/kg midazolam orally. After preoxygenation, anesthesia (duration, 172 ± 21 min) was induced with etomidate (0.3 mg/kg) and maintained with sufentanil (2 µg·kg⁻¹·h⁻¹), isoflurane (0.25 to 1%), pancuronium (0.1 mg/kg), and midazolam (0.05 to 0.1 mg/kg). Ventilation was performed with an air and oxygen mixture using intermittent positive-pressure ventilation. Arterial carbon dioxide tension (Paco₂) was maintained at 35–45 mmHg during mechanical respiratory support and CPB. Right heart catheterization was performed using a thermobilution catheter (Opticath-catheter, P7110-E, Abbott, Wiesbaden, Germany). The distal lumen was used for mixed venous blood sampling. Radial artery catheterization was performed and used for arterial blood sampling. Cardiac output was measured in triplicate by thermodilution using 10 ml normal saline at room temperature, and the mean values were used for calculations (Oximetrix; Abbott, Wiesbaden, Germany). Blood-hemoglobin saturation and hemoglobin concentration were measured using a cooximeter (OSM-3; Radiometer, Copenhagen, Denmark). Blood gas analyses were performed using a blood gas analyzer (ABL-505; Radiometer). Urinary bladder temperature was used to assess core temperature. Normothermic nonpulsatile CPB was performed with a membrane oxygenator (D 703; Dideco, Milano, Italy) and a centrifugal pump (Lifestream, St. Jude Medical, Chelmsford, MN). A flow of 2.4 l·min⁻¹·m⁻² was maintained during the entire CPB. The circuit was primed with a colloid-crystallloid solution. Breckneidger's cardioplegic solution was infused for myocardial preservation. Volume therapy, blood transfusions, catecholamine support, and vasodilator therapy were administered as clinically indicated by anesthesiologists who were not involved in the study. When the CPB was complete, patients had a net positive fluid balance of 1,850 ± 750 ml.

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Blood Samples
Blood samples were collected 20 min after induction of general anesthesia but before CPB (data point 1), 30 min after the initiation of CPB (data point 2), 5 min after removal of aortic cross-clamping (data point 3), and 4 h after operation (data point 4). All samples were obtained from the cannulated radial artery except the blood samples necessary to assess the venous admixture taken from the distal lumen of the thermodilution catheter. Serum of these samples were immediately stored at −80°C for later analysis of inflammatory parameters.

Inflammatory Parameters Measured in Patient Blood
**Procalcitonin.** The PCT concentrations in serum were measured with a highly sensitive and specific immunoluminometric assay (LUMitest PCT; B.R.A.H.M.S. Diagnostica, Berlin, Germany; reference value, <0.5 ng/ml).

**Interleukin-6.** Interleukin-6 (IL-6) concentrations in serum were determined using a specific enzyme-linked immunoassay obtained from DPC Biemann GmbH (Milenia IL-6; DPC, Bad Nauheim, Germany; reference value, <28 pg/ml).

**Neopterin.** Neopterin concentrations in serum were measured by a specific enzyme-linked immunoassay kit obtained from IBL-Immunoochemistry and Immunobiology mbH (Hamburg, Germany; reference value, <12.5 nm).

**Leukocyte Elastase.** A heterogenous enzyme immunoassay for the specific determination of elastase from polymorphonuclear leukocytes in complex with α1-proteinase inhibitor in plasma was used (Merck Diagnostica, Darmstadt, Germany; reference value, <32 μg/l).

**sL-Selectin.** sL-Selectin concentrations in serum were measured using a specific enzyme-linked immunoassay kit obtained from R & D Systems (Abingdon, UK; reference value, <1250 ng/ml).

**C-reactive Protein.** C-reactive protein concentrations were determined using an immunoturbidimetric method (Hitachi 717; Boehringer, Mannheim, Germany; reference value, <5 mg/l).

**sCD14.** sCD14 concentrations in serum were measured by a specific enzyme-linked immunoassay kit obtained from IBL-Immunoochemistry and Immunobiology mbH; reference value, <4.5 μg/ml).

**Leukocyte Counts.** Leukocyte counts were determined using a Coulter counter (Celldyn; Abbott, Wiesbaden, Germany). Automated counts were verified by manual counting (reference values, 4,000–12,000 Gpt/l).

The sensitivity, within-run precision (intra-assay coefficients of variation), and run-to-run precision (interassay coefficients of variation) of the assays were as follows: 0.1 ng/ml, ≤8% and ≤10% for PCT; 4 pg/ml, ≤10% and ≤13% for IL-6; 4 nm, ≤7% and ≤9% for neopterin; 2 μg/l, ≤7% and ≤8% for neutrophil elastase; 0.3 nm/ml, ≤6% and ≤8% for sL-selectin; 0.2 mg/l, ≤7% and ≤7% for CRP; and 1 mg/ml, ≤6% and ≤8% for sCD14.

Systemic Inflammatory Response Syndrome
According to the American College of Chest Physicians–Society of Critical Care Medicine classification, SIRS was diagnosed if two or more of the following were found: body temperature abnormalities (>38°C or <36°C), tachycardia (heart rate >90/min), tachypnea or hyperventilation (breathing frequency >20/min or PaCO₂ <32 mmHg), and leukocytosis or leukopenia (leukocyte count >12,000 Gpt/l < 4,000 Gpt/l).

The SIRS classification was performed in all patients on the first postoperative day at 8:00 A.M., taking into account the entire postoperative course (from the end of the operation to the time of evaluation). In patients who remained longer in the intensive care unit, the classification was repeated once daily. Tachycardia was the only accepted criterion for inclusion if it persisted for at least 2 h and under the condition that central venous pressure, cardiac index, pulmonary capillary wedge pressure, and mean systemic arterial pressure were within the normal range. The type and amount of postoperative inotropic support are shown in Results. Transient increases in heart rate, breathing frequency, and signs of hyperventilation resulting from tracheal suctioning and nursing interventions or caused by inadequate analgesia or sedation were excluded.

Pulmonary Function
To assess the extent of acute pulmonary damage, the lung injury score introduced by Murray and colleagues was determined and the venous admixture Qs/Qt was calculated after induction of general anesthesia (data point 1) and 4 h after operation (data point 4). In patients who underwent mechanical ventilation for >24 h after operation, the determination of both, lung injury score, and venous admixture was performed once daily. The Murray score is based on the interpretation of chest
radiography, the calculation of gas exchange parameters (oxygenation index, $\text{PaO}_2/\text{FiO}_2$), the use of positive end-expiratory pressure, and the measurement of respiratory compliance. The venous admixture ($Q_s/Q_t$) was calculated using standard formulas. In patients with impaired oxygenation and a Murray score $\geq 2$, the extravascular lung water index (normal range, 5–10 ml/kg) was measured twice daily by a technique using simultaneous dye and thermal indicator dilution measurements (COLD Z-021, Pulsion, München, Germany) via a fiberoptic thermistor catheter inserted into the radial or femoral artery. Thoracic computed tomography was performed in three patients with ALI.

The tracheal extubation criteria were full consciousness, hemodynamic stability, adequate muscle strength, and adequate respiration (required positive end-expiratory pressure, $\leq 5$ cmH$_2$O; breathing rate, $<30$ /min) as well as adequate gas exchange values ($\text{PaO}_2 \geq 80$ mmHg/\text{FiO}_2 = 0.4; $\text{PaCO}_2$, 35–50 mmHg).

**Infectious Status**

To determine whether pulmonary dysfunction was caused by an infection, plasma concentrations of soluble endotoxin receptor (sCD14) (normal range, $<4.5$ µg/ml) were measured in all patients who had ALI. In addition, sputum samples obtained bronchoscopically were cultured in each patient who had ALI as soon as it was diagnosed.

**Statistical Analysis**

Patients were divided post hoc for analysis into three groups according to the absence of SIRS (group 1), existence of SIRS without ALI (group 2), and existence of SIRS with ALI (group 3). All results are expressed as mean $\pm$ SD unless otherwise stated. Data separated in groups 1, 2, and 3 were assessed using analysis of variance to compare groups at a given data point. For multiple comparison of data in groups with not normally distributed data, the Kruskal-Wallis test was then applied. Dunn's all-pairwise multiple comparison procedure was used to isolate differing groups. To describe the relation between the change in venous admixture (from data point 1 to data point 4) and PCT concentration (at 4 h after CPB), a linear regression analysis was performed. Probability values $<0.05$ were considered significant. The sensitivity of inflammatory parameters to indicate ALI was defined as the number of ALI patients with the respective parameter above a given threshold divided by the sum of these patients plus the number of patients with ALI beneath this threshold. The specificity of inflammatory parameters to indicate ALI was defined as the number of patients without ALI and the respective parameter beneath a given threshold divided by the sum of these patients plus the number of patients without ALI but the respective parameter above the given threshold.

**Results**

Table 1 shows demographic and clinical data of all patients divided into subgroups. The duration of stay in the intensive care unit and time of endotracheal intubation were significantly longer in patients with lung dysfunction compared with those without lung dysfunction or without SIRS (table 1). No significant differences were seen in other characteristics.

The incidence of SIRS was independent of the duration of CPB. Postoperative inotropic support was given to patients from all groups, and table 2 summarizes dose ranges. Similarly, perioperative hemodynamic monitoring and measurements of body temperature and hematocrit did not show statistically significant differences between patients with or without SIRS (table 3). Table 4 shows the relative increase from preoperative to postoperative markers to indicate an inflammatory process.

Nine patients (22%; group 3) showed signs of acute pulmonary impairment as reflected by an increased venous admixture (6.1 $\pm$ 2.4% at data point 1 compared with 25.7 $\pm$ 8.4% at data point 4) and an increased Murray score (ranging from 1–3 points). All patients in groups 1 and 2 were classified with a Murray score of 0. In patients without ALI (groups 1 and 2), no significant increase in venous admixture was found (5.8 $\pm$ 1.8% at data point 1 compared with 7.1 $\pm$ 2.2% at data point 4). Extravascular lung water index measured in seven patients in group 3 was within the normal range in all cases (7.8 $\pm$ 1.6 ml/kg). Using thoracic computed tomography (three patients in group 3) and chest radiography (all patients in group 3), no macroatelectasis or pleural effusions were found. In two patients in group 3, a mild increase in extravascular lung water was diagnosed by means of chest radiography. Pneumonia was excluded in all cases by radiography and in three patients by thoracic computed tomography. In all patients of group 3, no pathogenic organisms were found in tracheal or bronchial secretions.
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Table 1. Demographic and Clinical Data of Patients Entering the Study

<table>
<thead>
<tr>
<th></th>
<th>No SIRS</th>
<th>SIRS without ALI</th>
<th>SIRS with ALI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>23</td>
<td>8</td>
<td>9</td>
<td>0.606</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>61 ± 9</td>
<td>62 ± 12</td>
<td>64 ± 7</td>
<td></td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>13/10</td>
<td>5/3</td>
<td>6/3</td>
<td></td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>77 ± 11</td>
<td>79 ± 9</td>
<td>81 ± 9</td>
<td>0.576</td>
</tr>
<tr>
<td>NYHA (median)*</td>
<td>2 (2–3)</td>
<td>2 (2–2)</td>
<td>2 (2–3)</td>
<td></td>
</tr>
<tr>
<td>Preoperative EF (%)</td>
<td>52 ± 11</td>
<td>57 ± 10</td>
<td>48 ± 4</td>
<td>0.141</td>
</tr>
<tr>
<td>Days in ICU</td>
<td>1 ± 0</td>
<td>1.4 ± 0.5</td>
<td>3.9 ± 2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intubation time (h)</td>
<td>5.8 ± 1.3</td>
<td>6.6 ± 1.9</td>
<td>58.3 ± 31.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cross clamp time (Aortic) (min)</td>
<td>42.2 ± 7.8</td>
<td>45.6 ± 8.6</td>
<td>40.6 ± 7.3</td>
<td>0.404</td>
</tr>
<tr>
<td>Total bypass time (min)</td>
<td>64.8 ± 12.8</td>
<td>64.4 ± 10.2</td>
<td>60 ± 7.9</td>
<td>0.495</td>
</tr>
<tr>
<td>No. of grafts (median)*</td>
<td>3 (2–3)</td>
<td>3 (2–3)</td>
<td>3 (2–3)</td>
<td>0.924</td>
</tr>
</tbody>
</table>

No SIRS = patients without systemic inflammatory response syndrome; SIRS without ALI = patients with systemic inflammatory response syndrome but without acute lung injury; SIRS with ALI = patients with systemic inflammatory response syndrome and with acute lung injury; NYHA = New York Heart Association classification for cardiac insufficiency; ICU = intensive care unit; EF = left ventricular ejection fraction.

* Data are median values and 25–75th percentile in parentheses.

which has been considered an indicator of bacterial infection, was measured in patients in group 3, and plasma concentrations were within the normal range (2.4 ± 0.6 μg/ml) in all cases.

Figures 1 to 3 summarize individual courses of biochemical markers of inflammation. Plasma concentrations of IL-6 and leukocyte count tended to increase 4 h after operation with only mildly elevated intraoperative values, and no significant differences were found compared with patients without impaired lung function (fig. 1). In contrast, CRP concentrations of all patients increased only marginally even 4 h after operation compared with preoperative values.

Plasma concentrations of elastase generally peaked during operation. Again, although one patient in group 3 had clearly increased concentrations even before operation, no statistically significant differences were found among the groups. Similarly, increases in sL-selectin and neopterin did not show any statistically significant differences among the groups (fig. 2).

All patients with ALI (group 3) showed increased serum concentrations of PCT > 5 ng/ml, whereas patients without lung injury had plasma concentrations <5 ng/ml at all time points (fig. 3). Three of the patients with ALI and two patients without ALI had high serum concentrations of PCT before operation. Table 5 shows the sensitivity and specificity of plasma concentrations of all inflammatory parameters to indicate ALI. The PCT was the only parameter that was highly sensitive and specific.

There was a significant relation between serum concentrations of PCT and venous admixture 4 h after the end of surgery. Figure 4 shows a linear regression analysis between serum concentrations of PCT at data point 4 and change in venous admixture (between data points 1 and 4).

Discussion

It is widely accepted that extensive surgical interventions such as cardiac surgery with CPB are associated
with generalized inflammation. One particular form of generalized inflammation has been defined by the American College of Chest Physicians - Society of Critical Care Medicine as SIRS. However, only few data are available about the incidence of SIRS in patients having cardiac surgery. Cremer et al. found that SIRS occurred in about 10% of their patients. In our study, SIRS developed in 40% of our patients, obeying strictly the American College of Chest Physicians - Society of Critical Care Medicine criteria. The clinical features of this classification are rather nonspecific. For example, the presence of pyrexia >38°C and a moderate tachycardia or tachypnea are sufficient to include a patient. Nevertheless, in the acute postoperative period, vital sign abnormalities may be caused by perioperative factors not attributable to an inflammatory response. After CPB, many patients have transient elevations in heart rate, which can be the result of physiologic reactions such as pain, change in inotropic status, alterations in preload or afterload (or both), or as patients become more awake. Transient tachypnea may be caused by postoperative medical or nursing interventions such as suctioning. Other factors, such as body temperature during the extracorporeal circulation, the use of pulsatile or nonpulsatile flow, and the duration of CPB, that may influence the incidence of SIRS have not been investigated. In the current study, normothermic nonpulsatile CPB was performed in all patients. The frequency and severity of SIRS were inde-

| Table 3. Perioperative Values of Hemodynamic Parameters, Body Temperature, and Hematocrit |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                | No SIRS         | SIRS without ALI| SIRS with ALI   |
|                                | Preop | After CPB | Postop | Preop | After CPB | Postop | Preop | After CPB | Postop |
| CI                              | 2.3 ± 0.6 | 3.0 ± 0.7 | 3.0 ± 0.6 | 2.4 ± 0.6 | 2.7 ± 0.9 | 2.9 ± 1 | 2.0 ± 0.4 | 3.0 ± 1 | 2.7 ± 0.8 |
| PCWP                            | 10 ± 3  | 10 ± 3   | 10 ± 3   | 11 ± 4  | 11 ± 4   | 11 ± 4  | 10 ± 2   | 11 ± 2  | 11 ± 2   |
| CVP                             | 8 ± 3   | 7 ± 2    | 8 ± 3    | 7 ± 4   | 7 ± 2    | 8 ± 3   | 7 ± 3    | 7 ± 2    | 7 ± 2    |
| MAP                             | 77 ± 13 | 72 ± 11  | 79 ± 10  | 74 ± 12 | 72 ± 10  | 76 ± 6  | 77 ± 14 | 72 ± 12 | 79 ± 16  |
| MPAP                            | 16 ± 4  | 17 ± 4   | 17 ± 5   | 16 ± 4  | 18 ± 6   | 19 ± 7  | 18 ± 3  | 17 ± 2  | 18 ± 3   |
| Temp                            | 36.5 ± 0.6| 35.9 ± 0.4| 36.7 ± 0.4| 36.7 ± 0.5| 36.0 ± 0.7| 36.8 ± 0.5| 36.7 ± 0.5| 36.5 ± 0.4| 36.9 ± 0.5|
| HR                              | 73 ± 9  | 73 ± 9   | 78 ± 13  | 68 ± 5  | 74 ± 10  | 80 ± 14 | 77 ± 8  | 72 ± 8  | 87 ± 12  |
| Hct                             | 37 ± 3  | 32 ± 3   | 33 ± 3   | 36 ± 4  | 32 ± 4   | 32 ± 3  | 39 ± 3  | 33 ± 4  | 33 ± 3   |

CI = cardiac index (L·min⁻¹·m⁻²); PCWP = pulmonary capillary wedge pressure (mmHg); CVP = central venous pressure (mmHg); MAP = mean systemic arterial pressure (mmHg); MPAP = mean pulmonary arterial pressure (mmHg); Temp = temperature (°C); HR = heart rate (beats/min); Hct = hematocrit (%); No SIRS = patients without systemic inflammatory response syndrome (N = 23); SIRS without ALI = patients with SIRS but without acute lung injury (N = 8); SIRS with ALI = patients with SIRS and with acute lung injury (N = 9); Preop = after induction of anesthesia; After CPB = after aortic declamping; Postop = 4 h postoperatively.

| Table 4. Increase in Plasma Concentrations of Inflammatory Mediators from Preoperative Data Point 1 to Postoperative Data Point 5 |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                | No SIRS         | SIRS            | SIRS + ALI      | P Value         |
| IL-6 (pg/ml)                   | 242 ± 130       | 182 ± 74        | 515 ± 572       | 0.47            |
| CRP (mg/L)                     | 1.8 ± 4.3       | 2.6 ± 3.3       | 1.8 ± 1.3       | 0.84            |
| WBC (Gpt/L)                    | 4.6 ± 2.7       | 7.5 ± 3.6       | 11.8 ± 4.3      | <0.001*         |
| Elastase (μg/ml)               | 86 ± 56         | 61 ± 30         | 81 ± 64         | 0.59            |
| sL-selectin (ng/ml)            | 185 ± 302       | 262 ± 266       | 479 ± 509       | 0.23            |
| Neopterin (nmol/l)             | 2.8 ± 3.0       | 4.4 ± 4.6       | 4.2 ± 3.3       | 0.37            |
| PCT (ng/ml)                    | 0.9 ± 1.0       | 0.9 ± 0.7       | 8.0 ± 2.7       | <0.001†         |

No SIRS = patients without systemic inflammatory response syndrome (N = 23); SIRS without ALI = patients with SIRS but without acute lung injury (N = 8); SIRS with ALI = patients with SIRS and with acute lung injury (N = 9); IL-6 = interleukin-6; CRP = C-reactive protein; WBC = white blood cell count; Elastase = leucocyte elastase; sL-selectin = soluble L-selectin; PCT = procalcitonin.

* Significant difference between SIRS + ALI and No SIRS.
† Significant difference between SIRS + ALI and SIRS as well as between SIRS + ALI and No SIRS.
Fig. 1. Plasma concentrations of interleukin-6, C-reactive protein, and leukocyte counts in patients without systemic inflammatory response syndrome (no SIRS; n = 23), in patients with SIRS but without acute lung injury (SIRS without ALI; n = 8), and in patients with SIRS and acute lung injury (SIRS with ALI; n = 9). Data point 1: after induction of general anesthesia but before CPB. Data point 2: 30 min after the initiation of cardiopulmonary bypass. Data point 3: 5 min after removal of aortic cross-clamping. Data point 4: 4 h after operation.

Pendent of the duration of CPB. Taking all these factors into account, it still has been presumed that SIRS occurs in all patients after cardiac surgery.

The widespread inflammatory response to CPB almost certainly affects all organ systems. However, the lung appears to be particularly susceptible and this has been documented by many early reports since the introduction of CPB for cardiac surgery. In the past, terms such as “bypass lung” or “postperfusion lung syndrome” characterized by an increased venous admix-
ture secondary to ventilation-perfusion mismatch and accompanying hypercapnia and hypoxemia have been used. Messent et al. reported a 1.3% incidence of adult respiratory distress syndrome that was associated with a mortality rate of 53% in patients undergoing cardiac surgery with CPB. However, because of the retrospective design of this study, only very severe courses of ALI were included. We suppose that the incidence of milder courses with transient impairment of lung function is much higher, as has been shown by our
Fig. 3. Plasma concentrations of procalcitonin (PCT) in patients without systemic inflammatory response syndrome (No SIRS; n = 23), in patients with SIRS but without acute lung injury (SIRS without ALI; n = 8), and in patients with SIRS and acute lung injury (SIRS with ALI; n = 9). Data point 1: after induction of general anesthesia, but before cardiopulmonary bypass. Data point 2: 30 min after the initiation of cardiopulmonary bypass. Data point 3: 5 min after removal of aortic cross-clamping. Data point 4: 4 h after operation.

investigation (approximately 20%). We used clinically relevant parameters such as venous admixture, oxygenation index, positive end-expiratory pressure, respiratory compliance, chest radiography, computed tomography, and measurement of extravascular lung water to assess postoperative lung function. Oxygenation index, venous admixture, and positive end-expiratory pressure were increased in most patients with ALI. Increased lung water may have contributed to the impairment of lung function. However, radiologic signs of extravascular lung water were found only in two patients with ALI. In none of these patients was an extravascular lung water index, as measured by the COLD system, found to be above normal. In addition, surgical factors can potentially influence postoperative lung function that

Table 5. Sensitivity and Specificity of All Mediators to Indicate ALI in Patients with SIRS

<table>
<thead>
<tr>
<th>Marker</th>
<th>ALI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT &gt; 5 ng/ml</td>
<td>100</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>100</td>
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<tr>
<td>Specificity</td>
<td>33</td>
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<tr>
<td>IL-6 &gt; 400 pg/ml</td>
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<td>Sensitivity</td>
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<td>Specificity</td>
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<td>Neopterin &gt; 10 nmol/L</td>
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<td>Specificity</td>
<td>67</td>
</tr>
<tr>
<td>WBC &gt; 12,000/µl</td>
<td>50</td>
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<td>Sensitivity</td>
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</tr>
<tr>
<td>Specificity</td>
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</tr>
<tr>
<td>Elastase &gt; 150 µg/l</td>
<td>13</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>22</td>
</tr>
<tr>
<td>Specificity</td>
<td>100</td>
</tr>
</tbody>
</table>

IL-6 = interleukin-6; CRP = C-reactive protein; WBC = white blood cell count; Elastase = leukocyte elastase; sL-selectin = soluble L-selectin; PCT = procalcitonin.

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are not related primarily to the inflammatory response, such as internal mammary artery harvesting, violation of pleura, pleural effusions, and transient phrenic nerve palsy. From our results, we conclude that these factors were of minor importance. Because we did not find signs of mechanical alteration in lung function such as macroatelectasis, increased lung water, or pleural effusions, and because pulmonary impairment was accompanied in all cases by a distinct increase in venous admixture, we believe that microvascular and microcirculatory changes are predominant factors responsible for the development of transient forms of ALI. The presence of macroatelectasis caused by swelling of endothelial cells, interstitial edema, interstitial hemorrhage, and obstruction of the pulmonary microvasculature by microaggregates may be an explanation for impaired oxygenation. The controversially high incidence of ALI in the patients entered into the current study may also be biased by the relatively small number of patients investigated.

Recently several attempts were made to prevent CPB-related organ failure: Various cellular and humoral factors were examined to describe the generalized inflammatory response secondary to CPB. As shown in our results, leukocytosis occurred nearly always after operation. However, the effect of CPB on leukocyte function is probably more important than the count alone. To assess CPB-dependent functional alterations of these cells, we measured plasma levels of leukocyte- elastase, neopterin, and L-selectin. Cellular interactions between vascular endothelium and leukocytes are mediated by surface adhesion molecules such as L-selectin. Dreyer et al. studied animals to determine if surface expression of L-selectin is appropriate to identify subjects at risk for pulmonary dysfunction secondary to CPB. They found no relation between L-selectin expression and postoperative lung function. Galanines et al. found no effect of CPB on expression of L-selectin. In our study, S-selectin increased 4 h after operation in all patients and did not show significant differences in patients with or without SIRS and also was not suitable to predict pulmonary dysfunction associated with CPB.

The release of proteolytic enzymes such as leukocyte elastase is considered to be involved in the damage of endothelial membranes. Elastase release from neutrophils during CPB has been implicated in neutrophil-mediated endothelial injury in vitro and was shown to initiate the breakdown of vital tissues if released extracellularly. Both leukocyte elastase and neopterin have been used to monitor the neutrophil activity or the activity of monocytes and macrophages, respectively, in patients undergoing cardiac surgery with CPB. In our patients, neither leukocyte elastase nor neopterin concentrations were related to ALI.

Recent interest has focused on the role of proinflammatory cytokines. Increases in plasma levels of IL-1, IL-6, IL-8, and tumor necrosis factor have been reported. We measured IL-6 because this cytokine is involved in modulating the acute-phase response and is produced by various activated cell types. Butler et al. showed that IL-6 increased to its peak level 4 h after termination of CPB and stayed elevated for 48 h. In the study by Cremer et al., the highest IL-6 concentrations were measured immediately after CPB and 3 h after operation, and this increase was associated with hemodynamic instability. Our data also show peak concentrations 4 h after operation in nearly all patients. However, the relation between serum concentration of IL-6 and the occurrence of SIRS and pulmonary impairment was very poor.

Another known marker of inflammatory activity, the plasma concentration of CRP, has been reported to be increased after open heart surgery, with peak concentrations occurring 24 - 48 h after operation. In the current study, 4 h after operation, no significant change in CRP was found compared with preoperative values. Thus CRP seems to be inappropriate to indicate early pulmonary dysfunction after CPB.

In bacterial inflammation, sepsis and multiorgan dysfunction PCT concentrations of up to 1,000-fold the normal value can be found. In patients with chronic infections, localized infections, only negligible increases in serum PCT, ranging from 0.5 to 5 ng/ml, have been reported. Recently, it was shown that both bacterial infectious pneumonia and nonbacterial pneumonitis caused by inhalational lung injury were associated with a rapid increase in plasma PCT. Thus, in case of pulmonary inflammation, hyperprocalcitonemia seems to be more than a specific marker for bacterial infections. However, the cellular sources and mechanisms underlying the release of PCT during infection are not known. Currently several cell types have been implicated as potential sources of PCT in such patients. It was suggested that a hyperprocalcitonemia may reflect the response of the bronchoepithelial pulmonary neuroendocrine cells to ALI. This hypothesis is based on the observation that in humans the total amount of calcitonin per 100 g weight is
greater in the lung than in most other organs. Thus elevated serum concentrations of PCT in pulmonary dysfunction may reflect a hyperactivity of such cells. The results of the current study confirm the relation between hyperprocalkitemia and ALI. Because we hypothesize a noninfectious cause of ALI, we had to exclude an infectious cause, such as pneumonia, by means of chest radiography, thoracic computed tomography, by culturing sputum samples, and by determination of sCD14. Soluble CD14 is believed to indicate bacteremia. Distinct increases in serum PCT >5 ng/ml have been reported very rarely in cases of nonbacterial infections. In the current study, five patients showed PCT values between 5-10 ng/ml, and three patients showed PCT values even above this level without any sign of bacterial infection. Three patients with pulmonary dysfunction and two patients without ALI showed abnormal PCT concentrations (<5 ng/ml) even before operation. Because no signs of bacterial infection were found in these patients, we speculate that they may have been suffering from undetected chronic inflammatory processes. However, further studies are required to investigate the effect of distinct patient-related preoperative and procedural intraoperative factors on PCT release. Furthermore, it remains to be determined whether increased preoperative PCT concentrations may be considered a risk factor for SIRS and postoperative pulmonary dysfunction.

In conclusion, the markedly increased plasma concentrations of PCT were related to ALI. Regarding this relation, PCT was more sensitive and reliable than other investigated inflammatory parameters. Therefore hyperprocalkitemia seems to be specific not only for bacterial infections but also for pulmonary inflammation resulting from CPB.

References

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