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## **The influence of extracorporeal circulation and inflammatory responses such as SIRS and sepsis on secretion of procalcitonin (PCT)**

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# The influence of extracorporeal circulation and inflammatory responses such as SIRS and sepsis on secretion of procalcitonin (PCT)

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The reasons for a systemic inflammatory response syndrom (SIRS) following extracorporeal circulation (ECC) are not yet fully understood. PCT shall be a parameter to distinguish between bacterial infections and a non-bacterial systemic inflammation. We investigated the influence of cardiopulmonary bypass (CPB), systemic inflammation and septic conditions on the PCT-values.

We analyzed 30 patients undergoing coronary artery bypass grafting (CABG). Blood samples for PCT-measurement were taken 6 times perioperatively. 21 of these patients did not develop postoperative complications (group A), while 9 patients suffered from a "post-perfusion-syndrome" (PPS) for at most 36 hours (group B). Furthermore blood samples were taken from 30 preoperatively comparable patients who suffered from bacterial infection ( $n = 15$ ) (group C) or a SIRS ( $n = 15$ ) (group D) after ECC; in this group PCT was determined daily after the onset of inflammation.

There was no significant PCT-elevation in groups A and B at all 6 times of measurement. In sepsis patients a significant elevation of PCT with the peak level of  $19.7 \pm 6.2$  ng/ml on the second day after diagnosis was seen, compared to  $0.7 \pm 0.4$  ng/ml in SIRS patients.

In this study it was demonstrated that ECC and a temporarily limited PPS did not have any influence on the secretion of PCT. A systemic bacterial infection caused a significant increase of PCT, whereas PCT-values remained normal in case of a SIRS. So it seems to be possible to distinguish between a SIRS and a bacterial proven sepsis by means of PCT. *J Clin Basic Cardiol* 1999; 2: 225–7.

**Key words:** procalcitonin, C-reactive protein, systemic inflammatory response syndrome, sepsis, cardiopulmonary bypass, post-perfusion-syndrome

Procalcitonin (PCT) is a 116-amino-acid peptide that undergoes posttranslational proteolysis into the mature hormone calcitonin and is produced in the thyroid gland [1]. Normally, in healthy individuals, PCT plasma concentrations are very low and often even below the detection limit of the presently used assay (normal range of PCT  $< 0.1$  ng/ml). *In vivo* half-life time of PCT is approximately 24–30 hours [2]. Blood levels of the prehormone have been found to be elevated in medullary thyroid carcinoma [3] as well as ectopically in a large number of other tumours [4]. PCT levels are closely related to serum tumour necrosis factor  $\alpha$  and interleukin-6 levels (IL-6) [5]; these parameters and other cytokines are elevated in severe infections. Especially interleukin-6 and interleukin-8 levels are also elevated during and after cardiopulmonary bypass (CPB).

"Post-perfusion-syndrome" (PPS) in patients after extracorporeal circulation means a temporarily limited need for catecholamines despite sufficient substitution of volume accompanied by a low systemic vascular resistance (SVR). This PPS can be found in almost 10 % of the patients after cardiac surgery [6]. It is yet unclear whether a PPS is immunologically caused and so associated with changes of, ie, interleukin- or even PCT-levels. Furthermore, it is necessary to investigate whether a PPS may be a precursor of a systemic inflammatory response syndrome (SIRS) that some of these patients develop after CPB operation.

Compared to CRP, PCT is a very specific parameter for bacterial, fungal, and parasitic infections and is induced only in the more severe states of the disease, but neither in minor bacterial infections, viral infections and autoimmune disorders nor in chronic or non-bacterial inflammation [7]. Accordingly, no increased PCT concentrations were reported in SIRS patients without proven microbial infection [8].

There is still no parameter to predict a systemic inflammation. Furthermore we are not able to reduce the incidence of a SIRS by perioperative administration of special drugs like corticosteroids, the use of a leucocyte depletion filter and heparin-coated circuits [9].

It was the aim of the present study to find out the levels of PCT in case of sepsis or SIRS and to assess the influence of extracorporeal circulation – possibly followed by a post-perfusion-syndrome – on the PCT-secretion.

## Patients and methods

We took blood samples from 30 patients who underwent an aortocoronary bypass operation (CABG). The blood samples were taken at the following time points as shown in table 1. 21 of these patients did not develop postoperative complications (group A), while 9 patients suffered from a "post-perfusion-syndrome" (PPS) for at most 36 hours (group B). PPS means the need for catecholamines (epinephrine or norepinephrine, and/or doses of dopamine or dobutamine of more than  $3 \mu\text{g/kg}$  per min.) despite sufficient volume substitution, accompanied by a low systemic vascular resistance (SVR). In all these 9 patients the PPS was self-limiting, and no patient

**Table 1.** Time points at which blood samples for PCT-measurement in group A and B were taken

| Sample time point                                               |
|-----------------------------------------------------------------|
| 1. Control values before induction of anaesthesia               |
| 2. 10 minutes after beginning of the extracorporeal circulation |
| 3. At the end of extracorporeal circulation                     |
| 4. 30 minutes after the administration of protamine             |
| 5. After arrival of the patient in the intensive-care unit      |
| 6. On the morning of the second postoperative day               |

developed a SIRS due to PPS. Both groups (A and B) did not show significant differences in the patterns of age, left ventricular function and clinical data (table 2). Reoperations, emergency interventions, severe accompanying diseases and an ejection fraction of less than 40 % were regarded as exclusion criteria.

PCT levels were determined using antibody-coated-tubes provided by Brahms Diagnostica, Berlin, Germany, as a complete diagnostic kit (LUMitest ProCalcitonin) in a Lumino-meter (Behring Diagnostica, Marburg, Germany). All samples were processed by the same person as double measurements directly following the calibration of the standard curve by provided standards.

Furthermore we took blood samples for PCT measurement of 30 preoperatively comparable CABG-patients (table 3) who suffered postoperatively from a sepsis (group C, n = 15) (positive blood cultures) or a SIRS without microbial infection (group D, n = 15) as defined by the Consensus

Conference 1992 [10]. Patients of group C and D were selected after onset of the inflammation, but the samples in these groups were taken daily starting with the operation until 7 days after beginning of sepsis or SIRS.

All 60 patients did not have clinical signs of an infection preoperatively; there were also no significant differences in preoperative leucocyte counts, erythrocyte sedimentation rate (ESR) and C-reactive protein. All data were compared by t-test and  $p < 0.05$  was regarded as significant.

## Results

In all patients of group A (no postoperative complication) and group B (PPS) the preoperative PCT-values did not exceed the baseline level ( $< 0.1$  ng/ml). Three intraoperative measurements and one at the time of arrival in intensive-care unit resulted in not significantly different values of less than  $0.2$  ng/ml in both groups. On the second postoperative day the PCT-value was  $0.21 \pm 0.11$  ng/ml in group A, compared to  $0.45 \pm 0.17$  ng/ml in group B (no significant difference). There was no intraoperative complication in all patients of group A and B. Table 4 shows the mean of the PCT-concentrations in both groups.

In group C (septic patients with positive blood cultures) the PCT-value on the second day after diagnosis was  $19.7 \pm 6.2$  ng/ml, whereas it was only  $0.7 \pm 0.4$  ng/ml in SIRS patients (group D) ( $p < 0.05$ ). The follow-up of the PCT-levels of both groups (C+D) for one week after the onset of inflammation is shown in figure 1.

During the first 36 hours after diagnosis of SIRS/sepsis, the pre-hormone is found in a near tenfold higher concentration (up to  $9$  ng/ml) in the sepsis group compared to the patients with SIRS only. The peak level is reached on the second day with a PCT-value of  $19.7 \pm 6.2$  ng/ml. It then decreases to normal levels, showing to a clinical resolution of sepsis. An antibiotic treatment was started in both groups immediately after appearance of the first clinical symptoms of inflammation, mostly even before knowing the specific infective cause. In case of a SIRS, PCT remains constantly low ( $< 0.9$  ng/ml).

Furthermore there was no significant difference in the CRP-values on the second day of inflammation: In both groups (C, D) the C-reactive protein was clearly elevated, with  $18.6 \pm 11.7$  mg/l in group C, compared to  $15.0 \pm 10.5$  mg/l in SIRS patients ( $p > 0.05$ ).

**Table 2.** Patients' characteristics (group A and B)

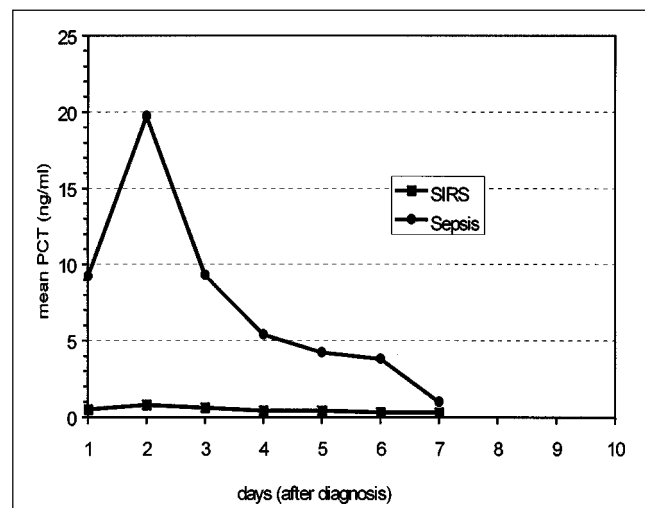
|                                                                                | Group A<br>(no complication) | Group B<br>(PPS) |
|--------------------------------------------------------------------------------|------------------------------|------------------|
| n                                                                              | 21                           | 9                |
| Age (years)                                                                    | $65.2 \pm 2.2$               | $63.3 \pm 1.3$   |
| Gender (m/f)                                                                   | 12/9                         | 5/4              |
| EF (%)                                                                         | $64.1 \pm 6.2$               | $62.9 \pm 5.4$   |
| Arterial hypertension pre-OP (%)                                               | 66.7                         | 55.6             |
| Diabetes mellitus pre-OP (%)                                                   | 57.1                         | 44.4             |
| CRP pre-OP (mg/l)                                                              | $14.8 \pm 9.3$               | $12.3 \pm 8.7$   |
| Mean arterial blood pressure<br>(2 min. after finishing ECC) (mm Hg)           | $90 \pm 12.4$                | $83 \pm 9.7$     |
| Heart rate (beats $\times$ min <sup>-1</sup> )<br>(2 min. after finishing ECC) | $77 \pm 6$                   | $82 \pm 7$       |
| Duration of surgery (min)                                                      | $212 \pm 7.8$                | $215 \pm 7.2$    |
| Number of bypasses                                                             | $2.9 \pm 0.5$                | $3.2 \pm 0.3$    |
| Bypass time (min)                                                              | $77.4 \pm 8.3$               | $79.0 \pm 7.6$   |

**Table 3.** Patients' characteristics (group C and D)

|                                          | Group C<br>(sepsis) | Group D<br>(SIRS) |
|------------------------------------------|---------------------|-------------------|
| n                                        | 15                  | 15                |
| Age (years)                              | $63.8 \pm 2.6$      | $64.9 \pm 2.7$    |
| Gender (m/f)                             | 9/6                 | 7/8               |
| EF (%)                                   | $60.2 \pm 5.9$      | $59.7 \pm 5.3$    |
| Arterial hypertension pre-OP (%)         | 66.7                | 66.7              |
| Diabetes mellitus pre-OP (%)             | 53.3                | 40.0              |
| Number of bypasses                       | $3.0 \pm 0.5$       | $2.8 \pm 0.4$     |
| CRP (mg/l)                               |                     |                   |
| Pre-OP                                   | $12.2 \pm 9.6$      | $11.7 \pm 7.3$    |
| 2 <sup>nd</sup> day of inflammation      | $18.6 \pm 11.7$     | $15.0 \pm 10.5$   |
| Leucocytes ( $\times$ nl <sup>-1</sup> ) |                     |                   |
| Pre-OP                                   | $6.3 \pm 3.2$       | $5.9 \pm 2.9$     |
| 2 <sup>nd</sup> day of inflammation      | $12.2 \pm 3.7$      | $10.7 \pm 4.4$    |
| Fibrinogen (mg/dl)                       |                     |                   |
| Pre-OP                                   | $380 \pm 130$       | $340 \pm 111$     |
| 2 <sup>nd</sup> day of inflammation      | $712 \pm 245$       | $680 \pm 263$     |
| Presence of fever post-OP (%)            | 93.3                | 93.3              |

**Table 4.** Mean PCT-values in group A and B (ng/ml)

| Sample time point | Group A<br>(no complication) | Group B<br>(PPS) | difference |
|-------------------|------------------------------|------------------|------------|
| 1                 | $< 0.1$                      | $< 0.1$          | n.s.       |
| 2                 | $0.13 \pm 0.20$              | $< 0.1$          | n.s.       |
| 3                 | $0.18 \pm 0.21$              | $0.19 \pm 0.49$  | n.s.       |
| 4                 | $0.14 \pm 0.31$              | $0.18 \pm 0.62$  | n.s.       |
| 5                 | $0.18 \pm 0.60$              | $0.17 \pm 0.37$  | n.s.       |
| 6                 | $0.21 \pm 0.11$              | $0.45 \pm 0.17$  | n.s.       |



**Figure 1.** Follow-up of PCT-values in group C (sepsis) and D (SIRS) during the postoperative course

## Discussion

Cardiopulmonary bypass (CPB) initiates a biochemical and cellular "whole-body inflammatory response", which may be associated with substantial morbidity and mortality [11]. A common mechanism is thought to be responsible, involving the inflammatory mediators of the complement system and cytokines [12]. Cytokines are potent intercellular signalling molecules known to participate in the regulation of cellular growth, function and differentiation. Interleukin-6 and interleukin-8 (IL-6, IL-8) levels have been shown to be elevated during and after CPB and are associated with cardiac and pulmonary dysfunction after bypass [6]. Although there is a close relation of interleukin-levels to the procalcitonin, it is yet not clear whether ECC causes an elevation of PCT.

Low SVR after cardiac surgery often leads to a "post-perfusion-syndrome" (PPS) with increased need for volume and catecholamines. Further investigations showed that 2–10 % of these patients develop a SIRS with all its consequences [13]. Today we do not know exactly the immunologic changes, including PCT-levels, in patients with PPS.

In the present study we were able to show that neither an ECC nor a PPS have any influence on the secretion of PCT. During and after CPB we could not see an elevation of PCT in CABG patients without intraoperative complications. Our results are in contrast to the investigation of Kilger et al. [14] who found increased PCT-levels after cardiopulmonary bypass. In their patients the peak level of PCT was 2.0 ng/ml 15 hours after operation. Different, partly unknown factors could have been responsible for this moderate elevation (ie, bypass circuit, oxygenator, drug administration, duration of surgery/ischaemia), so that these results do not disprove the statement of our investigation.

Procalcitonin has been reported to be a specific marker of bacterial infections [15]. In a clinical investigation, Assicot et al. [16] showed that high serum PCT concentrations appear together with normal concentrations of calcitonin in pediatric patients with sepsis or severe infections. Although its cellular origin and metabolic pathways are not known, PCT has been demonstrated to be released into the blood 3–6 hours after endotoxin injection in rabbits or humans. Dandona et al. [17] showed that after one injection of bacterial endotoxin, high peak levels of serum PCT exceeding the base line levels up to 1700-fold were reached within 24 hours in healthy volunteers. In this context, a PCT rise could precede the increase in serum concentration of CRP, which is the typical marker of acute inflammation and bacterial infection [18]. Furthermore, high serum PCT-levels seem to correlate with the severity of sepsis and may be useful in prognosis, because they rapidly reflect appropriate antibiotic therapy or poor outcome in sepsis [19]. Gramm [20] and Oberhoffer [21] also described this close correlation of PCT-concentrations to the severity of a bacterial infection. The prehormone was not elevated in surgical patients in the postoperative period and seems to be specific to septic complications [22]. However, in some clinical situations, the mechanism of PCT induction still remains obscure.

Today it is not always possible to distinguish a non-bacterial systemic inflammation or SIRS from systemic inflammation induced by microorganisms or bacterial endotoxins. The data of Al-Nawas indicate that without bacterial inflammation very low PCT-concentrations are found in patients with SIRS [23]. In contrast to CRP, IL-6, or other mediators of the inflammatory response, PCT is generally not induced by viral infections, operation trauma, autoimmune or allergic disorders, including allograft rejection or systemic inflammation [2]. Al-

Nawas furthermore showed that PCT determination in adult patients with sepsis is of high specificity and negative predictive value but of low sensitivity and positive predictive value at a threshold of 0.5 ng/ml.

The data of our patients show that a systemic bacterial infection causes a significant increase of PCT-concentrations, correlating to the severeness of the disease. If our patients suffered from a SIRS after ECC, we have not seen a PCT-elevation, so that consequently we were able to distinguish between a bacterial (sepsis) and a non-bacterial inflammation.

We conclude that PCT seems to be an early and specific marker of severe sepsis which could be very useful in diagnosis, monitoring and therapy. More clinical and experimental investigations are needed to understand the cellular origin and mechanism of PCT-synthesis.

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