Predictors of infection after pulmonary endarterectomy for chronic thrombo-embolic pulmonary hypertension

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Abstract

Objective: Pulmonary endarterectomy (PEA) is an effective and potentially curative treatment for chronic thrombo-embolic pulmonary hypertension (CTEPH). The postoperative course after PEA is accompanied by a number of complications, which contribute to the high rate of early postoperative mortality. Markers allowing the early detection of infectious complication during the postoperative period may be of major clinical importance. The aim of the prospective study was to analyse a predictive value of five inflammatory markers to recognise inflammatory complications accompanying PEA before the first clinical signs of infection.

Methods: Eighty-two patients with CTEPH, who underwent PEA using cardiopulmonary bypass (CPB) and deep hypothermic circulatory arrest (DHCA), were included into the study. Procalcitonin (PCT), tumour necrosis factor-α, interleukin (IL)-6, IL-8 and C-reactive protein arterial concentrations were measured before sternotomy and repeatedly up to 72 h after the end of surgery. Haemodynamic parameters, infectious and non-infectious complications were recorded.

Results: Postoperative course was uncomplicated in 59/82 patients (group 1). Fourteen out of 82 patients (group 2) developed an infection in the first 3 days after surgery (bronchopneumonia, n = 9; bacterial sepsis, n = 5). Nine out of 82 patients (group 3) developed non-infectious complications in the same period. PCT and IL-6 were the only significant independent predictors of infection in days 1–3 after PEA. The area under receiver operating characteristic (ROC) curve calculated for PCT to predict postoperative infection was 0.83 (95% confidence interval (CI): 0.74–0.92) compared with 0.74 (95% CI: 0.68–0.81) for IL-6. With the cut-off 2.3 ng ml⁻¹, the test characteristics of PCT were as follows: sensitivity, 86%; specificity, 83%; negative predictive value, 92%; and positive predictive value, 84%.

Conclusions: The increase in PCT and IL-6 may allow patients at increased risk of infection after PEA to be identified, allowing earlier institution of antibiotic treatment. These changes that occur before infection can be detected clinically. This finding may make the daily monitoring of PCT post-PEA useful.

Keywords: Cardiopulmonary bypass; Infection; Inflammatory mediators; Procalcitonin; Surgery complications

1. Introduction

Pulmonary artery endarterectomy (PEA) is a potentially curative surgical procedure for patients with chronic thrombo-embolic pulmonary hypertension (CTEPH), whose prognosis would otherwise be very poor [1]. After successful endarterectomy, both pulmonary artery pressure and pulmonary vascular resistance drop and the cardiac output increases [2–4].

The postoperative course after PEA is accompanied by a number of specific complications, which contribute to the relatively high rate of early postoperative mortality, which ranges from 5% to 23% [5]. PEA is associated with
haemodynamic instability in the perioperative course due to systemic vasodilatation that may be resistant to vasopressor therapy [6]. The common causes of death include pulmonary reperfusion oedema, right ventricular failure and infectious complications [7].

In patients undergoing PEA, markers allowing the early detection of infectious complications during the postoperative period are of major clinical importance. Assicot et al. [8] reported procalcitonin (PCT) as a highly specific marker for the diagnosis of clinically relevant systemic bacterial infections and sepsis. Over the last decade, PCT has become useful as a tool for the rapid diagnosis of sepsis. A major advantage of PCT compared with both inflammatory cytokines and acute-phase proteins is its early and specific increase in response to severe systemic bacterial infections and sepsis.

There is also evidence that high levels of PCT are associated with increased mortality and morbidity after cardiac surgery, and PCT may provide a valuable prognostic marker [9]. However, different non-infectious factors such as surgical stress intensity, duration of surgery and cardiopulmonary bypass (CPB) also contribute to raised PCT, postoperatively [10]. Dörge et al. [10] have disputed the detection of infectious complications during the postoperative period are of major clinical importance. Assicot et al. [8] reported procalcitonin (PCT) as a highly specific marker for the diagnosis of clinically relevant systemic bacterial infections and sepsis. Over the last decade, PCT has become useful as a tool for the rapid diagnosis of sepsis. A major advantage of PCT compared with both inflammatory cytokines and acute-phase proteins is its early and specific increase in response to severe systemic bacterial infections and sepsis.

The authors of the present study used the highly specific group of cardiosurgical patients undergoing PEA for the analysis of evolution of five inflammatory parameters during the first 72 h after surgical procedure — PCT, C-reactive protein (CRP), and three cytokines (tumour necrosis factor-α (TNFα), interleukin (IL-6) and IL-8). The authors hypothesised that PCT and/or other inflammatory markers have a predictive value to recognise patients with complications before first clinical signs of infection.

2. Material and methods

A prospective study was approved by the local research and ethics committee. All patients scheduled for isolated PEA between January 2005 and December 2009 were eligible.

2.1. Anaesthesia and surgical procedures

Thirty minutes before skin incision, the first prophylactic dose of sultamicillin 1.5 g (Unasyn, Pfizer, Roma, Italy) was given. The same dose was repeated every 3 h throughout the procedure and every 6 h postoperatively until postoperative day 2. A total intravenous anaesthesia using a combination of benzodiazepines, propofol, opioids and muscle relaxants, routinely used in our institution for PEA, was given to all study patients.

The standard approach for pulmonary endarterectomy was median sternotomy. CPB was established with cannulation of the ascending aorta and the inferior and superior vena cava. Deep hypothermic circulatory arrest (DHCA, 18–20 °C) was used to ensure optimum operating conditions and facilitate accurate endarterectomy. Endarterectomy was started with dissection in the right level of pulmonary artery and followed to the segmental branches. To achieve accurate visualisation during peripheral dissection, repeated periods of DHCA limited to 20 min were performed with re-establishment of CPB between them. Arteriotomy on the main pulmonary artery was started on the left side and continued to the left branch. After completion of endarterectomy on the both sides, CPB was recommenced along with controlled rewarming. Weaning from CPR was started with pressure control ventilation with positive end-expiratory pressure (PEEP), atrio-ventricular epicardial stimulation, stepwise increased filling of the right heart and reduction of pump flow together with low doses of norepinephrine. Dobutamine (Dobutrex, Lilly, Germany) was administered only if inotropic support was needed during or after weaning of CPB. Before the end of CPB, we used an ultrafiltration for haemoconcentration.

2.2. Monitoring

Radial and femoral artery cannulae, triple lumen central venous cannula, Swan–Ganz catheter and single lumen jugular bulb catheter were inserted for continuous monitoring of haemodynamic parameters and jugular bulb blood saturation. Left atrial catheter was surgically placed for both measurement and norepinephrine administration.

2.3. PCT, cytokine and CRP analysis

Arterial blood samples were drawn from femoral artery catheter before operation, after sternotomy, after DHCA, after separation from CPB and 12, 18, 24, 36, 48 and 72 h after the end of surgery. For all measurements, 5 ml of arterial blood was drawn into a vacutainer heparin tube and immediately centrifuged at 5000 rpm for 15 min. Plasma was stored at −80 °C until analysis. Plasma levels of PCT were detected by Kryptor test (Brahms AG, Hennigsdorf, Germany) in duplicates. The sensitivity of the analytic method was 0.02 ng ml^{-1}.

Plasma concentrations of TNFα, IL-6, IL-8 (ELISA, Immunotech, Paris, France) and CRP (Kryptor — TRACE technology, BRAHMS AG, Hennigsdorf, Germany) were measured in duplicates. The intra- and inter-assay coefficients of variation were below 5%.

Infectious and non-infectious post-surgical complications were recorded. Definitions of infections were based on the guidelines published from the Center for Disease Control and Prevention [11]. Sepsis was defined as a systemic inflammatory response syndrome (SIRS) in the presence of infection.

Statistical analysis was carried out using SPSS software (version 12.0) for Windows (SPSS, Chicago, IL, USA). The normal distribution of all data was examined using the Kolmogorov–Smirnov normality test to determine subsequent use of tests for statistical comparison. As variables were not normally distributed, the data were reported as medians and interquartile range. Mann–Whitney test was applied for the data comparison between groups. Bonferroni correction (multiple-comparison correction) was used to analyse simultaneous measurement at different time points. A multiple logistic regression model was used to test for independent predictors of infection in postoperative days 1–3. A receiver operator characteristic (ROC) analysis was implemented to assess the sensitivity and specificity of tested parameters. The optimum concentration for the calculation of positive and negative predictive accuracy was obtained from the ROC analysis.
Eighty-two patients were enrolled during the 5 years of the trial (Table 1). All patients underwent satisfactory clearance of intra-arterial obstruction, and there were no intra-operative deaths. No patients required allogenic blood transfusion.

Fifty-nine patients (group 1, 35 males/24 females) did not develop recognised postoperative infection as well as non-infectious postoperative complication, and all these patients were discharged home. Fourteen patients (group 2, seven males/seven females) did, however, develop a postoperative infection within 72 h after surgery. The first clinical signs of infection were recognised on day 2 (8/14 patients) or day 3 after surgery (6/14 patients). The diagnosis of bronchopneumonia (n = 9) and bacterial sepsis (n = 5) was based on standard clinical examination including chest X-ray examination and positive blood and/or sputum cultures. Gram-positive bacterial infection was revealed in three patients (Staphylococcus epidermidis, n = 2; Staphylococcus haemolyticus, n = 1), Gram-negative bacterial pathogens were found in nine patients (Klebsiella pneumoniae, n = 4; Pantoea agglomerans, n = 2; Pseudomonas aeruginosa, n = 2; Stenotrophomonas maltophilia, n = 1) and polymicrobial infection in two cases. In-hospital mortality for these patients was 3/14 (21%). In the first 72 h postoperatively, nine patients (five males/four females) revealed non-infectious complications as ventricular arrhythmia (n = 3), reperfusion oedema (n = 3), pneumothorax (n = 2) and lung bleeding (n = 1). These patients were defined as group 3.

Intra-operative data were analysed for all tested groups as described in Table 2. No significant differences among groups were found for CPB time, cross-clamp time or DHCA time. Plasma levels of PCT, CRP, TNF-α, IL-6 and IL-8 did not differ among groups preoperatively.

An uncomplicated course after PEA (group 1) was associated with a transient initial decline of PCT and subsequent elevation. Minimal PCT concentrations were found in blood samples collected after the last DHCA (Fig. 1).

### Table 1. Preoperative data (n = 82).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 (n = 59)</th>
<th>Group 2 (n = 14)</th>
<th>Group 3 (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of males (%)</td>
<td>47 (57%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>57.2 (8.4)</td>
<td></td>
<td></td>
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<tr>
<td>Mean pulmonary artery pressure (mm Hg)</td>
<td>55.8 (8.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac index (l min⁻¹ m⁻²⁻¹)</td>
<td>1.91 (0.37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>60 (9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary vascular resistance (dynes s cm⁻¹)</td>
<td>1112 (311)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Variables are absolute number or mean (standard deviation).

### Table 2. Intra-operative data.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 (n = 59)</th>
<th>Group 2 (n = 14)</th>
<th>Group 3 (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of CPB (min)</td>
<td>331 (53)</td>
<td>348 (62)</td>
<td>334 (55)</td>
</tr>
<tr>
<td>Cross-clamp time (min)</td>
<td>122 (20)</td>
<td>120 (21)</td>
<td>119 (22)</td>
</tr>
<tr>
<td>DHCA time (min)</td>
<td>41.0 (7.8)</td>
<td>43.8 (7.1)</td>
<td>43.0 (6.2)</td>
</tr>
<tr>
<td>Minimum temperature (°C)</td>
<td>17.1 (0.7)</td>
<td>17.0 (0.8)</td>
<td>17.1 (0.7)</td>
</tr>
</tbody>
</table>

Variables are means (standard deviation). DHCA: deep hypothermic circulatory arrest. CPB: cardiopulmonary bypass. No significant differences on p < 0.05 were revealed among groups.

Initial decrease of PCT appeared to correlate with the decreased haematocrit due to haemodilution on CPB (r = 0.78, p < 0.01). PCT increased postoperatively from 0.21 ng ml⁻¹ (0.16–0.29) reaching a peak level 24 h after the end of surgery (2.00 ng ml⁻¹, 1.70–2.54). As expected, all inflammatory cytokines and CRP increased after surgery. TNF-α rose from 20 ng l⁻¹ (12–45) to a maximum of 218 ng l⁻¹ (140–411). IL-6 rise was maximal 12 h postoperatively from 20 ng l⁻¹ (416–645) with subsequent decline (Fig. 2). CRP showed prolonged elevation with a peak level 48 h after the end of surgery (55 mg l⁻¹, 39–72) (Fig. 3). Postoperative peak values of PCT and IL-6 correlated closely (r = 0.81, p < 0.01), as well as peak values of PCT and CRP (r = 0.72, p < 0.01).

In patients developing a postoperative infection (group 2), the levels of PCT were significantly higher 12 h postoperatively in relation to both group 1 (p = 0.019) and group 3 (p = 0.028) (Fig. 4). Similarly, IL-6 plasma concentrations 12 h postoperatively differed between group 1 and group 2 (p = 0.030) and between group 2 and group 3 (p = 0.036) (Fig. 5). The elevation of PCT anticipated the onset of infection in 12/14 patients with a time interval of 12–24 h before first clinical signs of infection. For TNF-α, IL-8 and CRP, there were no significant differences among groups on p < 0.05 at 12 h after the end of surgery (Table 3). No tested inflammatory parameter, including PCT and IL-6, distin-

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**Fig. 1.** PCT plasma concentrations in uncomplicated patients (group 1) (median and interquartile range). The same setting used for Figs. 1–3: Box and whisker plot depicting the mean values, interquartile range and full range. *Statistically significant differences to preoperative values, p < 0.05.

**Fig. 2.** IL-6 plasma concentrations in uncomplicated patients (group 1) (median and interquartile range).
guished group 1 and group 3 on \( p < 0.05 \) measured 12 h after the end of surgery.

Multiple logistic regression analysis revealed that PCT and IL-6 were the only significant independent predictors of infection on days 1–3 after PEA. The area under ROC curve used to predict postoperative infection for PCT was 0.83 (95% confidence interval (CI): 0.74–0.92) compared with 0.74 (95% CI: 0.68–0.81) for IL-6. For postoperative day 1, the optimum concentration of PCT for the calculation of positive and negative predictive accuracy as obtained from the ROC was 2.3 ng ml\(^{-1}\). With this cut-off, the test characteristics of PCT were as follows: sensitivity, 86%; specificity, 83%; negative predictive value, 92%; and positive predictive value, 84%. The optimum concentration of IL-6 for the calculation of predictive accuracy calculated from ROC was 646 ng l\(^{-1}\) with the following characteristics: sensitivity, 78%; specificity, 74%; negative predictive value, 84%; and positive predictive value, 86%.

In group 1, there was a weak correlation between maximum PCT concentrations and norepinephrine support (expressed as a time period in hours), \( k = 0.52, p < 0.05 \), in comparison with an expressive correlation between a norepinephrine support and IL-6 concentrations 12 h after surgery, \( k = 0.80, p < 0.01 \). Individual maximum doses of norepinephrine were without significant correlation to any of the inflammatory parameters. In group 2 and group 3, no relation between PCT levels and norepinephrine support was found on \( p < 0.05 \).

4. Discussion

Among five tested inflammatory markers, PCT and IL-6 were the only significant independent predictors of infection in days 1–3 after PEA. PCT and IL-6 evolution anticipated first clinical signs of bronchopneumonia or bacterial sepsis with a time interval of 12–24 h. Moreover, both the parameters showed high specificity to distinguish inflammatory and non-inflammatory complications in this period. To our knowledge, this is the first report of PCT as a predictor of infection after PEA.

An infection, which was proved by standard clinical and laboratory examination, contributed substantially to mortality of our patients as 3/14 patients, who developed infectious complications, died.

Surgical patients, especially those after cardiac surgery, represent a major diagnostic challenge in terms of identification of infectious complication [12]. Due to the combination of local trauma, extracorporeal circulation (ECC) and pulmonary and myocardial reperfusion, cardiac surgery leads to substantial changes in the immune system [13]. At the same time, the prolonged use of central venous catheters and inotropes is associated with a high risk of the development of nosocomial infection [14,15].

Prolonged artificial ventilation (AV) is itself an important risk factor for post-surgical infection after PEA. In our patients, even in the group with uncomplicated post-operative course, the duration of AV was longer than usually documented in other cardiosurgical procedures. Moreover, the PEA patients are more susceptible to lung infection as a result of pulmonary reperfusion following the procedure.
leukocytes than other surgical procedures [10]. This is consistent with the findings of Franke et al. [21]. Cardiac surgery leads to a more pronounced activation of cytokines than other surgical procedures, and more invasive procedures are associated with higher PCT levels. PCT seems to be dependent on the surgical procedure, with PCT levels being highest in patients undergoing pulmonary endarterectomy (PEA) and lowest in patients undergoing routine cardiac surgery [18].

PCT is elevated in various surgical procedures (range: 0.5—7.0 ng ml\(^{-1}\)) and increases during the first 24 h after surgery. PCT levels peak around 24 h after the end of surgery with subsequent decline to half-life of PCT (18—24 h) in the absence of a further insult that may induce increased PCT production. The subsequent decline of PCT levels within a few days after uncomplicated PEA corresponded to the half-life of PCT [9,21,22].

Statistical significant differences between group 2 and group 3 on \(p < 0.05\) were not found. Abbreviations: AV: artificial ventilation; CRP: C-reactive protein; IL: interleukin; PCT: procalcitonin; TNF\(_a\): tumour necrosis factor \(\alpha\).

### Statistical Significant Differences

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF(_a) (ng l(^{-1}))</td>
<td>172 (135—316)</td>
<td>218 (154—498)</td>
<td>181 (145—318)</td>
</tr>
<tr>
<td>IL-8 (ng l(^{-1}))</td>
<td>431 (281—647)</td>
<td>508 (326—841)</td>
<td>439 (294—741)</td>
</tr>
<tr>
<td>CRP (mg l(^{-1}))</td>
<td>6.0 (3.1—9.1)</td>
<td>10.9 (3.6—21.3)</td>
<td>10.6 (7.2—17.4)</td>
</tr>
<tr>
<td>Leukocytes (10(^9) l(^{-1}))</td>
<td>12.2 (8.6—15.2)</td>
<td>14.0 (9.1—20.6)</td>
<td>13.1 (8.2—19.4)</td>
</tr>
<tr>
<td>AV time (h)</td>
<td>42.4 (37.1)</td>
<td>108.5 (52.7)*</td>
<td>104.3 (54.1)*</td>
</tr>
<tr>
<td>ICU stay (days)</td>
<td>8.1 (6.3)</td>
<td>22.8 (12.4)*</td>
<td>18.5 (7.4)*</td>
</tr>
</tbody>
</table>

References


