Procalcitonin Kinetics After Heart Transplantation and as a Marker of Infection in Early Postoperative Course

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ABSTRACT

Introduction. Procalcitonin (PCT) is a biomarker of systemic infection. Specificity of PCT is decreased because PCT is also elevated after heart transplantation (HTx). There is no established normal range of serum PCT concentrations after HTx yet.

Our aim was to determine the course of PCT concentrations in patients after HTx in the early postoperative period, if we can discriminate postoperative increase in values from infectious complications.

Results. Of 39 patients we diagnosed infection in 11. These patients develop acute kidney injury significantly more often than in control group (group C) (5 in infection group [group I] and 2 in group C, $P < .05$), and 1 patient died within 30 days in group C. Seven patients developed primary graft dysfunction (3/4 + ECMO [extracorporeal membrane oxygenation], respectively, group I/group C) and 2 neurologic disorders in group I. Reoperation due to bleeding was 3 in each group. During the 14 days after HTx, serum PCT concentrations increased with maximum on the second postoperative day (group C: 30.6 ± 15.3 ng/mL; group I: 24.9 ± 44.3 ng/mL). Normal values for PCT were reached on day 8 in group C and 11 in group I. Mean PCT levels were similar: 8.7 ± 5.7 ng/mL vs 11.9 ± 13.1 ng/mL in group I vs group C, respectively. Patients in group I stayed longer in the intensive care unit.

Conclusions. Despite increase in serum concentration of PCT in early postoperative course after HTx there is no marker of infection. Trends in PCT serum concentration may be a valuable tool in diagnosis of infection in patients after HTx, but further investigation is needed.

PROCALCITONIN (PCT), the precursor of the hormone calcitonin, is produced under normal conditions in the C cells of the thyroid gland and K cells of the lung [1,2]. In healthy subjects, PCT levels are usually below the detection threshold [3]. Several reports show the superiority of PCT over other biomarkers in diagnosing systemic infection either in normal or immunocompromised populations. For solid organ transplant recipients, immunosuppression is necessary. Infectious complications in pharmacologically immunosuppressed patients following organ transplantation remain a major cause of morbidity

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Table 1. Demographic Data and Comorbidities

	With Infection	Without Infection	*P*
Age, y	52 ± 7.2	47.6.4 ± 10.5	.22
Hypertension	3 (27%)	6 (21%)	.32
Diabetes mellitus	7 (64%)	19 (68%)	.12
Ischemic cardiomyopathy	3 (27%)	7 (25%)	.21
Nonischemic cardiomyopathy	8(73%)	21(75%)	.42
Renal impairment	4 (36%)	5 (18%)	.74
Neurological disorders	2 (18%)	5 (18%)	.26
Sex, male	10 (91%)	21 (81%)	.048

and mortality. Bacterial infections in this special population necessitate early identification, timely therapeutic intervention, and urgent treatment [1–4]. Unfortunately, the specificity of PCT in predicting a bacterial complication has been decreased by the fact that PCT is also elevated after major surgery where bacterial infection is ruled out. However, monitoring the postoperative course, even if PCT values are elevated, does not limit the utility of PCT as a diagnostic tool [5]. The investigators therefore think that a reference range of every type of surgery should be established. As a consequence, PCT kinetics and its nonspecific increase during the following first few days will help to monitor patients at risk [6]. According to Mandershahian and colleagues there is no established normal range of serum PCT concentrations after heart transplantation (HTx) yet. We do not know which cut-off value can be a discriminating parameter for infectious complications [5].

The aim of our study was to determine course of PCT concentrations in patients after heart transplantation in the early postoperative period, if we can discriminate postoperative increase in values from infectious complications.

MATERIAL AND METHODS

We retrospectively analyzed 41 consecutive adult orthotopic HTx performed in Silesian Centre for Heart Disease in 2017. Patients who died within 48 hours after grafting (n = 2) were excluded from the study. Of the 39 heart transplant recipients, 11 (10M/1F) in group I had infection in the post-transplant period and 28 (23M/5F) in group C without infection. The reason for heart failure were ischemic cardiomyopathy in 3 patients in group I and 7 in group C. Eight patients in group I and 21 in group C had nonischemic cardiomyopathy. Additionally 4 patients in group I and 5 in group C had diagnosed renal impairment, 7 had diabetes mellitus in group I and 19 in group C, before transplantation. Infections were diagnosed according to clinical signs and confirmed by biological cultures. PCT plasma levels were measured once daily, and we analyzed up to 14 days of stay. Patients in group I were more often males. Demographic data are collected in Table 1. The institutional research ethics board reviewed and approved the study. Individual resignation for consent was granted.

Data Collection

Patient demographics, comorbidities, and complications were retrospectively analyzed using our institutional database and from the medical records. Baseline information was collected before orthotopic heart transplant. Patient demographic information and comorbidities including age, sex, diabetes, etiology of cardiomyopathy, indication for transplantation, height, and weight were also collected in order to calculate body mass index. We also collected number of neurologic, pulmonary, infectious complications, renal insufficiency, incidents of reoperations due to bleeding or tamponade, days of mechanical ventilation, and duration of intensive care unit (ICU) stay

Statistical Analysis

Data were analyzed using Statistica statistical software (StatSoft, Tulsa, Okla, United States). Categorical variables were treated as proportions, and continuous variables were reported as means and standard deviations. We compared the groups using independent-sample *t* tests for continuous variables and χ^2 and Fisher exact tests for categorical data. Complications during LVAD support were reported as event rates. A two-sided *P* value $< .05$ was considered as statistically significant.

RESULTS

Of 39 patients we diagnosed incidence of infections in 11 in postoperative course. These patients developed acute kidney injury significantly more often than in group C (5 in group I and 2 in group C, $P < .05$); 1 patient died within 30 days in group C. We noticed 7 patients with the use of intra-aortic counter pulsation and one on extracorporeal membrane oxygenation (ECMO) support (3/4 + ECMO, respectively, group I/group C) due to primary graft dysfunction and 2 neurologic disorders in group I. Reoperation due to bleeding was 3 in group I and 3 in group C. PCT kinetics during the 14 days after HTx had fluctuation. Serum PCT concentrations increased with maximum concentrations on the second postoperative day (group C: 30.6 ± 15.3 ng/mL; group I: 24.9 ± 44.3 ng/mL). From day 2, the levels of PCT decreased to reach a level of normal values for PCT on day 8 in group C and 11 in group I. Mean PCT levels were insignificantly different and were 8.7 ± 5.7 ng/mL vs 11.9 ± 13.1 ng/mL in group I vs group C, respectively. Patients in group I stayed longer in the ICU. Results are collected in Table 2 and Fig 1.

DISCUSSION

We retrospectively analyzed PCT plasma levels in patients in the early postoperative period after HTx in our study. There was no significant difference in PCT concentrations between groups with and without infectious complications.

Table 2. Results

	With Infection	Without Infection	*P*
Procalcitonin (ng/mL)	8.7±5.7	11.9±13.1	.44
Death in 30 days, n	0	1 (4%)	.16
Primary graft dysfunction, n	2 (20%)	5 (26%) (1 ECMO)	.52
Reoperation, n	3 (27%)	3 (20%)	.53
Neurologic disorders	2 (20%)	0	.16
ICU stay (d)	24±19	11±7	.004

Abbreviations: ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.

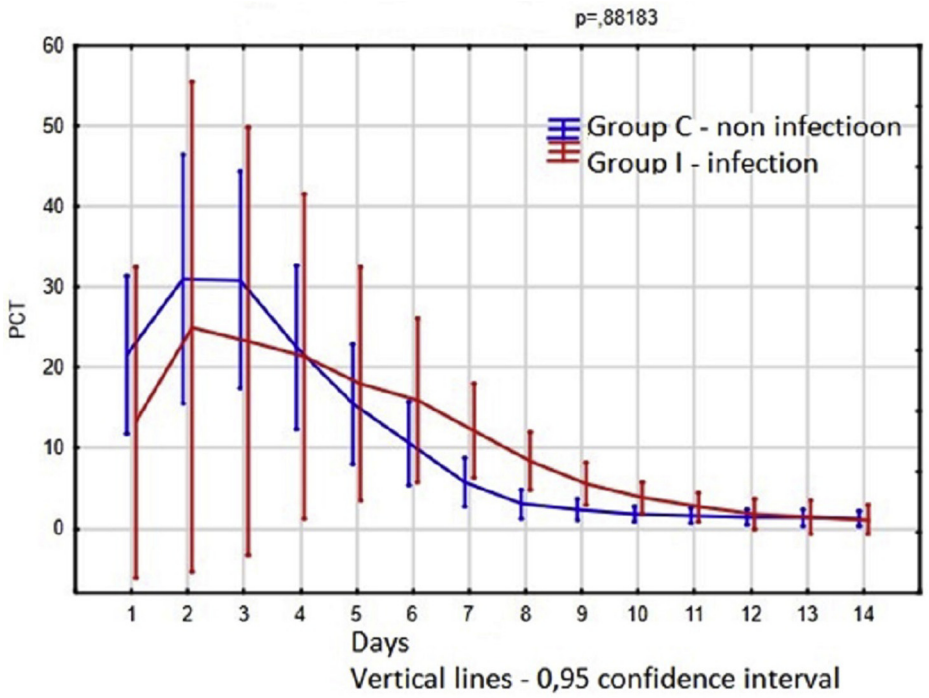

Fig 1. Daily PCT serum levels in patients with uncomplicated (n = 28) and complicated (n = 11) postoperative course. Day 1 = day of transplantation. Data are given as mean. The bars indicate 0.95 confidence interval. Serum PCT concentrations did not differ significantly between patients with and without complications.

High serum PCT levels are frequently seen after different types of surgery or transplant procedures due to many factors, such a surgical trauma, myocardial ischemia, translocation of bacterial endotoxins, high doses of catecholamines, or cardiopulmonary bypass. Early postoperative period is often associated with an inflammatory response and massive cytokine cascade activation, thus PCT can be elevated in the absence of bacterial infection [1–4].

PCT kinetics in recipients of organ transplants may be influenced by several factors, including surgery, the presence of underlying end organ disease, persistent immunosuppression, and type of immunosuppressive agents. This makes it more difficult to interpret than in nontransplant patients [7–9]. In heart and lung transplantation, PCT levels were high during the first day (usually 24-48 h) after surgical procedure and remained elevated during the subsequent days in patients with infection [5,6,10]. Madershahian et al showed in one study that PCT levels increased on the second day after surgery to 54.6 ± 8.8 ng/mL in patients with complications, compared with 9.1 ± 9.3 ng/mL in patients without complications; 75% of patients on the seventh day after surgery with no complicated course had a normal PCT value, whereas only 4% of patients with infectious and noninfectious complications had detection levels below the threshold [5]. Suberviola et al found that after lung transplantation in patients who did not receive induction therapy, PCT plasma levels reached their peak within the first 48 hours and stabilized in the first 7 days after transplantation [6].

PCT is a valuable biomarker for the identification of infectious complications, with a sensitivity of 77% and a specificity of 79% in meta-analysis by Wacker et al [11].

Guidelines recommend the cautious use of PCT with regard to clinical and other laboratory data [12]. Patients after transplantation should receive immunosuppressive therapy according to protocols, which may result in increased PCT concentrations.

There are several reports on extensively high PCT levels in kidney transplant patients after T-cell antibody infusion with no evidence of infection. Zazula et al showed that PCT levels increased without any signs of infection in patients undergoing orthotopic liver transplantation with antithymocyte globulin (ATG) administration [13]. Similar results were shown by Brodska et al and Sabat et al [14,15].

Franekova et all reported that PCT was able to differentiate between patients with and without septic complications in the early post-transplant period, but the administration of ATG significantly affects the level of PCT and may lead to difficulty in interpreting the results. Franekova et al described that presepsin is independent of ATG administration and was significantly higher in infected patients after HTx, thus, presepsin, not PCT, seems to be a valuable biomarker for the detection of infectious complications after HTx [16]. Madershahian et al also suggested that perioperative administration of immunosuppressive therapy is associated with significantly increased PCT levels, even in patients without infectious complications [17].

Our study has a limitation of the statistical analysis due to the low number of the patients. The results have to be confirmed in larger studies.

CONCLUSIONS

Despite increase in serum concentration of PCT in early postoperative course after heart transplantation, there is no marker of infection. Trends in PCT serum concentration may be a valuable tool in diagnosis of infection in patients after HTx, but further investigation is needed.

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