Could Pentraxin 3 Be a New Diagnostic Marker for Excessive Inflammatory Response in Cardiac Surgery?

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Abstract

Background   The aim of this study was to compare the dynamics of two inflammatory response biomarkers pentraxin 3 (PTX3) and C-reactive protein (CRP) after cardiac surgery with particular regard to different postoperative clinical manifestation of inflammatory response.

Patients and Methods   In this study, 42 patients undergoing open heart surgery with the use of cardiopulmonary bypass were included and divided in two groups according to the extent of clinical manifestation of inflammatory response: Group A ($n = 21$)—patients with different severity of systemic inflammatory response syndrome (SIRS) and Group B ($n = 21$)—patients with uneventful postoperative period (no SIRS). The serum levels of PTX3 and CRP were evaluated and compared at the following time points: before and at the end of surgery, 6 hours, 1st, 3rd, and 7th day after surgery.

Results   The dynamics of CRP levels were comparable between both groups and showed the classical characteristics after cardiac surgery with a peak on the 3rd postoperative day (113 vs. 132 mg/L). In contrast, the dynamics of PTX3 showed an earlier increase of serum levels with the peak on the 1st postoperative day in both groups (36.3 vs. 42.7 ng/mL). Importantly, a significant difference of PTX3 levels was found on the 3rd postoperative day (31.1 vs. 7.0 ng/mL; $p < 0.006$) between the two groups showing significantly delayed decrease of PTX3 levels in patients with SIRS (Group A).

Conclusion   This study demonstrates considerably different dynamics of PTX3 levels after cardiac surgery in patients with SIRS and patients without SIRS, thus it may be indicative to start the appropriate therapy.

Keywords
► SIRS
► postoperative care and complications
► cardiac surgery

Introduction

Cardiac surgery is well established for development of systemic inflammatory response.[1,2] The crucial point is to achieve the physiological level of the inflammatory response during postoperative period. In majority of patients, this response has no clinical manifestation. In minority of patients, it can result in a systemic inflammatory response syndrome (SIRS) with the risk of organ failure or even death.[3–5] This undesirable reaction is based on the individual

genetic predisposition together with the exposition of patients to the danger stimuli, both endogenous and exogenous origin. Endogenous danger stimuli are induced especially by oxidative stress associated with ischemia/reperfusion injury.[6] Patients are heavily exposed to microbial danger patterns, which are penetrating into the body due to mucosal barrier failure. Danger signals are identified by the pattern recognition molecules (PRMs),[7] which are classified into two major groups: (1) cell-associated receptors and (2) fluid-phase molecules. Fluid-phase PRMs are essential effectors and modulators of the innate immunity including collectins, ficolins, and pentraxins.[8,9] Pentraxins are pivotal components of the innate immune system and important acute phase reactants. On the basis of the primary structure, pentraxins are divided into two groups: short and long pentraxins.[10] C-reactive protein (CRP) is prototypic short pentraxin, whereas pentraxin 3 (PTX3) represents the long pentraxin arm of the family.[11] CRP is synthesized in the liver and is barely detectable in the plasma of healthy human adults (≤ 3 mg/L). Its concentration increases by as much as 1,000-fold in several pathological conditions with maximum at approximately 48 hours.[12] PTX3 is synthesized locally at the inflammatory site by both somatic and immune cells. PTX3 plasma levels are very low in normal conditions (≤ 2 ng/mL)[13] increasing rapidly in several pathological conditions and reaching peak values after 6 to 8 hours.[14]

Based on the current knowledge, it seems there is only slight increase of the PTX3 in patients during and after uncomplicated coronary artery bypass grafting (CABG) surgery with no signs of SIRS. The inherent pro-inflammatory/anti-inflammatory response is able to deal with this clinical situation without relevant deviations of plasma PTX3 levels. In occurrence of eventful postoperative course with clinical manifestation of excessive inflammatory response it is still unknown, if the timely increase of PTX3 plasma levels can anticipate an oncoming (multiple) organ failure, so that proper treatment may be instituted as early as possible.[6]

The aim of this study was to compare the dynamics of two inflammatory response biomarkers (PTX3 and CRP) in two groups of patients with different clinical manifestation of inflammatory response after cardiosurgical procedure (patients with different severity of SIRS and/or its complication vs. patients with uneventful postoperative course—no SIRS) to identify cardiosurgical patients at the risk of development of excessive inflammatory response.

Patients and Methods

Study Population and Clinical Characteristics
The institutional review board approved the study and an informed consent was obtained from each patient.

A series of 42 patients undergoing open heart surgery with the use of cardiopulmonary bypass (CPB) at our institution between May 2010 and July 2012 was included in the study. Patients were divided into the following groups according to the extent of clinical manifestation of inflammatory response: Group A ($n = 21$)—patients with different severity of SIRS and/or its complications and Group B ($n = 21$)—

patients with uneventful postoperative period (no SIRS). SIRS was defined by at least two of following criteria: core temperature $> 38°C$ or $< 36°C$; heart rate > 90 beats/min; respiratory rate > 20 breaths/min or $PaCO_2 < 32$ mm Hg; white blood cells $> 12,000/mm^3$, $< 4,000/mm^3$, or $> 10\%$ immature (band) forms and always presence of clinical signs of hypoperfusion and/or organ dysfunction[15] with the need for multiple vasoactive therapy and glucocorticoids (GCs) administration to maintain a mean blood pressure > 70 mm Hg. Patients with preoperative GCs and nonsteroid anti-inflammatory drugs therapy and patients with preoperatively diagnosed infection were excluded from the study.

A prospective collection of patients' clinical data was performed. Demographic data and preoperative clinical characteristics, according to the postoperative course, are summarized in ►**Table 1**.

Anesthesiological Management
All patients were anesthetized according to the standardized protocol. Food and fluid intake was discontinued at midnight on the day preceding surgery. Anesthesia was induced using thiopental, propofol, midazolam, or etomidate, where appropriate. Muscle relaxation was achieved with rocuronium. Anesthesia was maintained with isoflurane and intermittent administration of sufentanil. Volume-controlled ventilation with FiO_2 0.5 was employed. Mean arterial pressure was kept above 70 mm Hg by norepinephrine administered as required.

Surgical Technique
After median sternotomy and pericardiotomy, a heparin was administered intravenously (4 mg/kg of body weight) to maintain an activated clotting time above 480 seconds. CPB was then established by ascending aorta or subclavian artery cannulation (depending on the distal extension of the aortic disease) and by two-stage venous cannulation of the right atrium or direct bicaval venous cannulation, where appropriate. After initiation of CPB, the pump flow was maintained at targeted rate of 2.4 L/min/m². After cross-clamping the aorta, cardiac arrest was achieved by administration of cold blood cardioplegic solution (St. Thomas solution, Ardeapharma, Sevetin, Czech Republic; ratio 4:1) in antegrade fashion (10–15 mL/kg of body weight). The heart was cooled topically and cardioplegia repeated every 25 minutes. The patient's temperature was allowed to drift to 34 to 35°C. Mean arterial pressure during CPB was maintained at 50 to 70 mm Hg, hematocrit was above 0.20. The acid–base status was kept using the α-stat perfusion strategy. After termination of CPB, heparin was neutralized with protamine sulfate at 1:1 ratio.

The CPB circuit consisted of noncoated tubing, a hard shell venous reservoir (Dideco SrL, Mirandola, Italy), a cardiotomy suction device, a hollow fiber membrane oxygenator (Dideco SrL, Mirandola, Italy), a roller pump with nonpulsatile flow (Stöckert S3, Sorin Group, München, Germany), and an arterial line filter (Dideco SrL). The extracorporeal circuit was primed with 500 mL of Ringer's lactate, 500 mL of rheodextran, 5,000 IU heparin, 80 mL of natrium bicarbonate ($NaHCO_3$ 8.4%), 20 mL of 10% magnesium sulfate, and

Table 1 The preoperative data

	Group A	Group B	p value
Number of patients	21	21	
Age, median (range), y	68 (38–82)	62 (27–76)	0.232
Female gender	6 (28.6%)	9 (42.9%)	0.334
Mean BMI ± SD	28 ± 5	29 ± 4	0.848
Hypertension	16 (76.2%)	16 (76.2%)	1.000
Dyslipidemia	12 (57.1%)	11 (52.4%)	0.757
DM	6 (28.6%)	3 (14.3%)	1.000
COPD	5 (23.8%)	0	0.048
Atrial fibrillation	9 (42.9%)	1 (4.8%)	0.009
Previous cardiac surgery	3 (14.3%)	2 (9.5%)	1.000
Logistic EuroSCORE I, median (range), %	9.6 (1.5–37.9)	4.7 (0.9–16.8)	0.097
LV ejection fraction, %			
> 50	10 (47.6%)	17 (81.0%)	
30–50	9 (42.9%)	4 (19.0%)	0.057
< 30	2 (9.5%)	0	

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; LV, left ventricular; SD, standard deviation.
Note: Group A—patients with different severity of SIRS and/or its complications; Group B—patients with uneventful postoperative period.

mannitol (at 1 g/kg of body weight) and calculated to reach hematocrit level above 0.22.

It was a heterogenous group of operations, including alone CABG, valve surgery, aortic surgery, or combination of all of them.

Sample Collection and Data Acquisition

Blood samples were withdrawn from the subclavian or antebrachial vein into both BD Vacutainer EDTA and BD Vacutainer (BD, Plymouth, UK) with a thrombin additive tubes at the following time points: before surgery, at the end of surgery, 6 hours, 1st , 3rd, and 7th days after surgery. Plasma and serum were separated by centrifugation and stored at − 70°C. Plasma levels of PTX3 were determined with antihuman PTX3 ELISA kit (R&D Systems, Minneapolis, Minnesota, United States). Assay range was 0.15 to 200 ng/mL. Values above the standard curve range were extrapolated. CRP level in serum was measured using immunonephelometry. CRP was analyzed on Immage 800 (Beckman Coulter, Inc., Brea, California, United States) with Beckman Coulter CRP nephelometry kit. Detected range of values was 1 to 960 mg/L.

Early Postoperative Management

Immediately after operation, all patients were transferred to the cardiosurgical intensive care unit (ICU). They were fully anesthetized, required full mechanical ventilation, and treated for hypothermia. An adequate management of potential complications was maintained. Due to the hemodynamic status, the different fluid and vasoactive drug therapy was necessary. The patients in Group A were treated with norepinephrine and at least one of inotropic drugs (dobutamine, milrinone, levosimendan). On the basis of the clinical mani-

festation of SIRS and/or its complications (signs of hypoperfusion and/or organ dysfunction), a glucocorticosteroids therapy was initiated from the operation day to the 3rd postoperative day. The type of GCs, dose, and duration of therapy was defined at discretion of an independent physician in charge. The dose ranged from 200 to 5,200 mg of hydrocortisone equivalent (median 700 mg) administrated continuously or intermittent. The patients in Group B were treated with no vasoactive drugs or GCs.

Statistical Analysis

Continuous and discrete variables were reported as mean ± standard deviation or median and range for data not normally distributed. Categorical and ordinal variables were reported using the number and percentage of observations. Continuous and discrete variables were compared using a two-sample *t*-test, Mann–Whitney or Kolmogorov–Smirnov test, where appropriate. Categorical and ordinal variables were compared using a Pearson *chi*-squared test or Fischer exact test, where appropriate. A *p* value < 0.05 was considered to indicate statistical significance. Statistical analysis was performed using the IBM SPSS Statistics software program (version 21.0.0.0 for MS Windows, IBM Corporation, Armonk, New York, United States) and Statistica 10 software (StatSoft, Inc., Tulsa, Oklahoma, United States).

Results

Surgical Data and Early Clinical Characteristics

The operative data according to the postoperative course are shown in ►**Table 2**. Briefly, a mitral and tricuspid valve surgery was performed in 67 and 53% (Group A) versus 24

Table 2 The operative and early postoperative data

	Group A	Group B	p value
Number of patients	21	21	
CABG	11 (52.4%)	8 (38.1%)	0.352
Aortic valve surgery	10 (47.6%)	15 (71.4%)	0.116
Mitral valve surgery	14 (66.7%)	5 (23.8%)	0.005
Tricuspid valve surgery	11 (52.4%)	3 (14.3%)	0.020
Surgery on the aorta	3 (14.3%)	6 (28.6%)	0.454
CPB time, median (range), min	130 (72–301)	110 (54–208)	0.450
Cross-clamp time, median (range), min	94 (43–242)	87 (37–180)	0.443
Chest tube output 24 h, median (range), mL	800 (300–3,050)	400 (150–2,000)	0.007
Re-exploration for bleeding or tamponade	2 (9.5%)	1 (4.8%)	1.000
Ventilation time, median (range), h	26 (5–265)	7 (3–20)	< 0.001
Reintubation	4 (19.0%)	0	0.107
ARDS	6 (28.6%)	0	0.021
Acute renal failure requiring dialysis	4 (19.0%)	0	0.107
Stroke	2 (9.5%)	0	0.488
Multiorgan failure	2 (9.5%)	0	0.488
Atrial fibrillation	16 (76.2%)	4 (19.0%)	0.001
DSWI	0	0	
ICU length of stay, median (range), h	119 (21–996)	45 (15–96)	< 0.001
Hospital length of stay, median (range), d	20 (12–90)	10 (8–53)	< 0.001
30-day mortality	0	0	

Abbreviations: ARDS, acute respiratory distress syndrome; CABG, coronary artery bypasses grafting; CPB, cardiopulmonary bypass; DSWI, deep sternal wound infection; ICU, intensive care unit.

Note: Group A—patients with different severity of SIRS and/or its complications; Group B—patients with uneventful postoperative period.

and 14% (Group B), respectively ($p = 0.005$ and $p = 0.02$). The CPB time/aortic cross-clamp time was 130/94 minutes in Group A versus 110/87 minutes in Group B, demonstrating no statistically significant difference between the groups ($p = 0.450$ and $p = 0.443$). Blood loss was 800 mL/24 hours in Group A versus 400 mL/24 hours in Group B ($p = 0.007$). There were significant differences between Group A versus Group B in ventilation time 26 versus 7 hours, ICU length of stay 119 versus 45 hours, and hospital length of stay 20 versus 10 days, respectively ($p < 0.001$ in all). Need of reintubation, occurrence of acute respiratory distress syndrome, acute renal failure requiring dialysis, stroke, or atrial fibrillation were more frequent in Group A, but not reaching a statistical significance. No death, acute myocardial infarction (AMI), or deep sternal wound infection occurred.

Samples Analysis—Pentraxin 3 and C-Reactive Protein

Serum Levels of PTX3
The preoperative serum level of PTX3 was 0.6 ng/mL in Group A and 0.4 ng/mL in Group B, respectively. Increased serum levels were observed after termination of surgery and the highest PTX3 level throughout the whole observation was measured on the 1st postoperative day (36.3 vs. 42.7 ng/mL;

$p > 0.60$). Afterward, the PTX3 levels were decreasing. On the 3rd postoperative day, the PTX3 levels remained substantially elevated in Group A (31.1 ng/mL) than in Group B (7.0 ng/mL). This was the only statistically significant difference in dynamics of PTX3 levels observed between the two groups ($p < 0.006$). Elevated serum levels of PTX3 remained as long as to the 7th postoperative day (4.8 vs. 2.7 ng/mL; $p < 0.15$) (►**Fig. 1**).

Serum Levels of C-Reactive Protein
A similar dynamics of the CRP levels was observed in both groups, but did not significantly differ between the two groups during the whole observation period. Baseline levels of serum CRP were 0.6 mg/L in Group A and 0.4 mg/L in Group B. They increased 6 hours after surgery, reaching the peak of 113 versus 132 mg/L on the 3rd postoperative day ($p = 0.615$). The elevated CRP serum levels remained as long as to the 7th postoperative day (26.0 mg/L in Group A vs. 26.2 mg/L in Group B; $p = 0.73$) (►**Fig. 2**).

Comparison of Pentraxin 3 and C-Reactive Protein Serum Levels
The increase of PTX3 level started immediately after the surgery termination and reached the maximum on the 1st
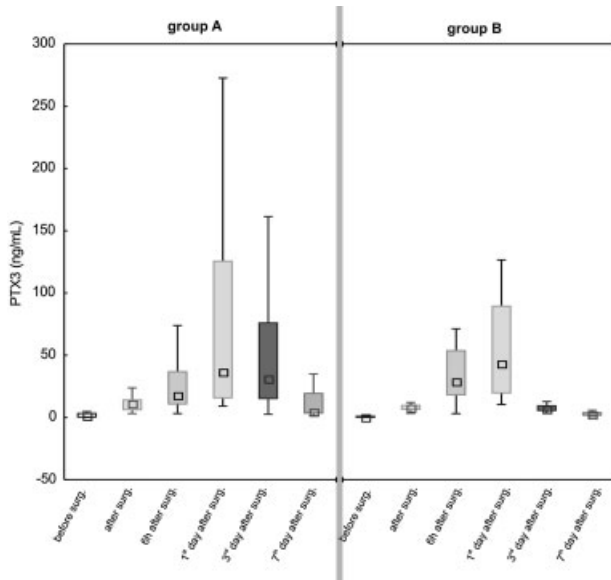
Fig. 1 PTX3 levels in serum of patients undergoing cardiac surgery (Group A—patients with different severity of SIRS and/or its complications; Group B—patients with uneventful postoperative period). The level of PTX3 differed significantly on the 3rd postoperative day between the two groups ($p < 0.006$). The PTX3 levels remained more elevated in Group A up to the 7th postoperative day ($p < 0.15$). Squares display median, boxes are quartiles, and whiskers display the range of nonoutlier values. PTX3, pentraxin 3; SIRS, systemic inflammatory response syndrome.
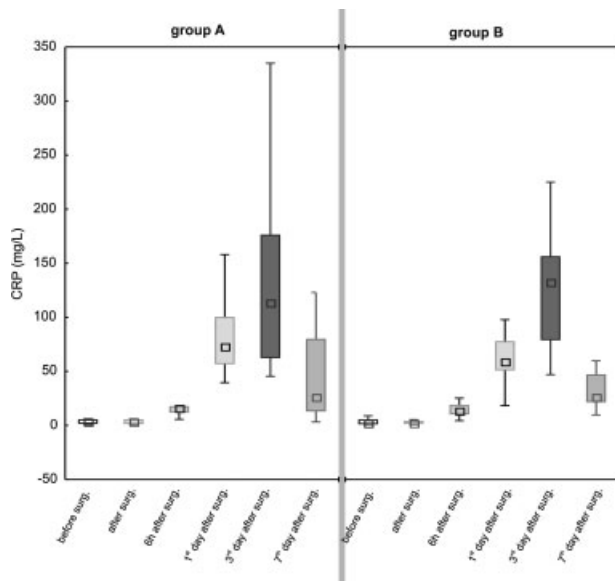

Fig. 2 CRP levels in serum of patients undergoing cardiac surgery (Group A—patients with different severity of SIRS and/or its complications; Group B—patients with uneventful postoperative period). The level of CRP did not differ significantly at all time points between the two groups. Squares display median, boxes are quartiles, and whiskers display the range of nonoutlier values. CRP, C-reactive protein; SIRS, systemic inflammatory response syndrome.

postoperative day in both groups. The release of CRP was delayed in comparison to PTX3 with the increase beginning 6 hours after surgery and peaking on the 3rd postoperative day in both groups. The serum levels of both biomarkers remained elevated as long as to the 7th postoperative day; however, the
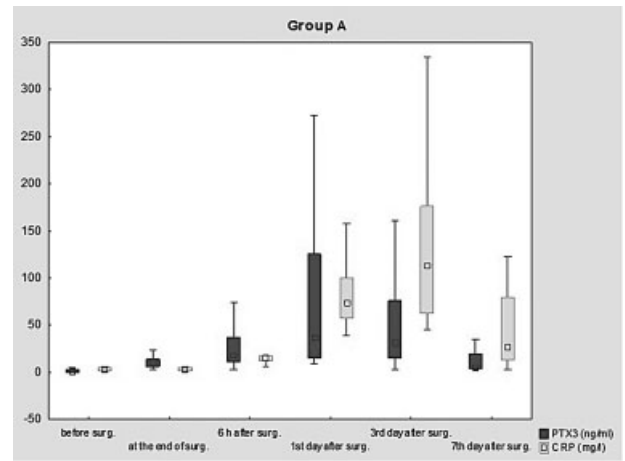
Fig. 3 PTX3 and CRP levels in serum of patients undergoing cardiac surgery within Group A—patients with different severity of SIRS and/or its complications. Plots show the early increase of PTX3 level and the delayed release of CRP. Both biomarkers remained elevated as long as to the 7th postoperative day; however, the decrease of CRP level was slow compared with the PTX level. Squares display median, boxes are quartiles, and whiskers display the range of nonoutlier values. CRP, C-reactive protein; PTX3, pentraxin 3; SIRS, systemic inflammatory response syndrome.

decrease of CRP levels was proportionally slow in both groups and the PTX3 level decrease even more significant in Group B (►**Figs. 3** and **4**).

Discussion

Cardiosurgical operation, especially with the use of CPB, served as a model of inflammatory response characterized by increased level of both proinflammatory and anti-
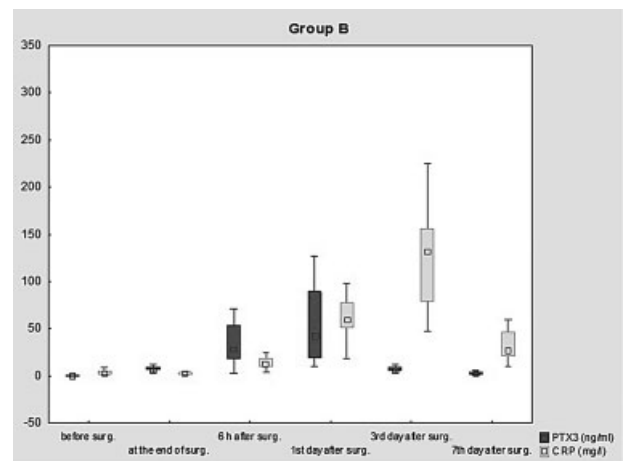

Fig. 4 PTX3 and CRP levels in serum of patients undergoing cardiac surgery within Group B—patients with uneventful postoperative period. Plots show the early increase of PTX3 level and the delayed release of CRP. Both biomarkers remained elevated as long as to the 7th postoperative day; however, the decrease of CRP level was slow compared with the PTX3 level (PTX3 level decrease even more significant in this group). Squares display median, boxes are quartiles, and whiskers display the range of nonoutlier values. CRP, C-reactive protein; PTX3, pentraxin 3.

inflammatory mediators.[1,2] An excessive inflammatory response can have clinical manifestation and lead to postoperative complications, organ dysfunction, or failure. An attempt is to recognize this unwanted reaction as soon as possible and to initiate the treatment to reduce the postoperative morbidity and mortality.

The current study is one of few to evaluate and compare the serum levels of PTX3 and CRP in patients undergoing cardiac surgery with different postoperative course. The CRP serum levels in our study were similar in both groups and do not correlate with the extent of excessive inflammatory response. On the contrary, we found statistically significant differences in PTX3 levels on the 3rd postoperative day between the two groups. The PTX3 levels remained more elevated up to the 7th postoperative day in the group of patients with eventful postoperative period (Group A), defined by the postoperative signs of hypoperfusion and/or organ failure (clinically manifested SIRS and/or its complications) with administration of multiple vasoactive agents and GCs therapy. However, we expected significant difference of the PTX3 serum levels between the groups already on the 1st postoperative day, this fact was not confirmed. The reason could be that cardiosurgical operations have generally more prolonged and complex postoperative course and therefore the potential complications due to excessive inflammatory response may occur later.

The dynamics of both biomarkers evaluated in our study were similar to that published by Kunes et al in a study comparing patients undergoing uncomplicated CABG with or without the use of CPB in 2007.[16] They described the peak of CRP levels on the 3rd postoperative day and the peak of PTX3 levels on the 1st postoperative day, respectively. Their patients have postoperatively no signs of excessive inflammatory response and the serum levels of PTX3 were not increased above the upper limit of normal at all. Another study showing similar dynamics of PTX3 in murine models of acute myocardial infarction (AMI) was published by Salio et al.[17] They found the PTX3 serum levels increase starting 8 hours after permanent coronary occlusion, peaked at 24 hours, and remained elevated up to 72 hours. Unlike, in a study published by Peri et al of 37 patients with AMI, the PTX3 peaked much earlier (median 7.5 hours) than CRP (median 24 hours) after AMI ($p = 0.001$).[18] The reason of the delayed PTX3 peak in our study may be caused by longer period between the two blood sampling points (6 hours after termination of surgery and the 1st postoperative day). In this timeframe, the real peak may have been hidden. On the contrary, in the study of Peri et al,[18] the first blood sampling point was defined at the coronary care unit admission, which is not always the time point of symptoms onset of an AMI. Taking this into consideration, the real peak may have been some hours later.

This study also showed significantly higher PTX3 serum levels than into the date published studies in adult cardiovascular medicine,[16,18–20] whereas the CRP levels are comparable to that published in cardiosurgical studies.[5,16,21] Based on our results, it seems the higher PTX3 levels may correlate to the complexity of the cardiac operation. This postulation

could be supported by results of Kunes et al, where only CABG patients ("on-pump" vs. "off-pump") with uneventful postoperative course were included.[16]

Doni et al indicated in their study that the regulation of PTX3 by GCs is dependent on the cell type, with inhibition in hematopoietic cells (macrophages and dendritic cells) and induction in nonhematopoietic cells (fibroblasts and endothelial cells). They concluded in vivo administration of GCs might increase the blood levels of PTX3 in mice and humans.[22] On the contrary, results published by Kunes et al do not correspond with this fact.[16] They found no significant PTX3 increase (above normal level of 2 ng/mL) in patients undergoing CABG with uneventful postoperative course, despite the patients in the CPB group were administered 500 mg methylprednisolone into the CPB priming solution (equivalent to 2,500 mg of hydrocortisone).

Study Limitations

This study has several limitations being primarily the definition and the clinical heterogeneity of SIRS. Obviously, we defined SIRS according to latest knowledge. However, the definition may be regarded as weak. Still, we think that this may be the most valid approximation to the problem. The PTX3 levels in Group A may be influenced by administration of GCs.

Conclusion

This study shows a significant difference in serum levels of PTX3 in patients with and without SIRS after open heart surgery. Consequently, this newly introduced biomarker may serve as an extension of the armamentarium of the clinician to diagnose and treat SIRS in the postoperative period. Based on current knowledge, the cutoff level of PTX3 for developing an excessive inflammatory response with clinical manifestation remains still unclear. Further studies are needed to elucidate the real diagnostic and prognostic value of PTX3.

Note

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Conflict of Interest

None.

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