Is C-reactive protein level before cardiac operations for the most common indications helpful in risk prediction of in-hospital postoperative complications?

Czy poziom białka C-reaktywnego przed operacjami kardiochirurgicznymi z najczęstszych wskazań pomaga przewidzieć powikłania w szpitalnym okresie pooperacyjnym?

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Abstract

Background: Studies on this topic use different CRP cut-off values and their results are divergent.
Aim: To answer the question: can preoperative CRP>5 mg/L predict either atrial fibrillation, or other complications in patients who underwent heart operation?
Material and Methods: 85 patients underwent operations: 59 for CAD (51 on, 8 off-pump), and 26 for valve diseases (aged from 21 to 78 years, 61 male, 24 female). 39 (45.8%) had increased CRP level (range: 6.7-131.2; 24.97±24.71 mg/L on average), and 46 (54.2%) had normal (range: 0-4.5; 1.78±1.11 mg/L on average; p<0.001).
Age, gender, preoperative EF and CRP, maximal CKMB, and WBC with neutrophil percentage at discharge were compared in two pairs of contrary groups: with/without complications, and with paroxysmal AF/sinus rhythm. Receiver operating characteristic (ROC) curves were drawn for both pairs of groups.
Results: Patients with complications were significantly older, and had significantly higher CKMB, whereas other parameters in these groups, as in all AF/sinus rhythm ones, did not differ. The ROC curves confirmed that preoperative CRP level does not discriminate between patients and there is no sense in looking for a cut-off point.
Conclusions: Increased preoperative CRP value cannot be a predictor of complicated early outcome after heart surgery. Better cut-off CRP predictive value cannot be found. Complications, except for AF, were depended on higher age, and myocardial injury represented by increased postoperative CKMB level. Despite a lack of statistical evidence, a delay of elective operations should possibly be considered in patients with very high CRP level.
Key words: C-reactive protein, heart surgery, atrial fibrillation, postoperative complications.

Streszczenie

Wstęp: Wyniki badań na ten temat są rozbieżne i używane są w nich różne wartości graniczne białka CRP.
Cel: Odpowiedź na pytanie: Czy przedoperacyjne CRP >5 mg/L zwiększa ryzyko migotania przedsionków i innych powikłań po operacjach serca?
Materiał i metody: Badano 85 chorych (w wieku od 21 do 78 lat, 24 kobiety i 61 mężczyzn), 59 operowanych z powodu choroby wieńcowej (51 w krążeniu pozaustrojowym, 8 bez niego) i 26 z powodu wad zastawkowych. 39 (45,8%) z nich miało zwiększone przedoperacyjne stężenie CRP (6,7–131,2; 24,97±24,71 mg/L), a 46 prawidłowe (0–4,5; 1,78±1,11 mg/L; p<0,001).
W dwóch parach przeciwstawnych grup chorych: 1) z napadowym migotaniem przedsionków i z rytmem zatokowym oraz 2) z innymi powikłaniami i bez powikłań porównano za pomocą odpowiednich metod statystycznych wiek, płeć, przedoperacyjne CRP i frakcję wyrzutową lewej komory oraz leukocytozę i odsetek granulocytów przy wypisie. Ponadto wyznaczono krzywe operacyjno-charakterystyczne (ROC) dla CRP w obu parach grup.
Wyniki: Pacjenci z powikłaniami byli starsi i mieli wyższe maksymalne CKMB (p<0,05) niż pacjenci bez powikłań, natomiast inne parametry nie były istotnie różne. Nie było różnic między chorymi z AF i rytmem zatokowym. Krzywe ROC potwierdziły, że przedoperacyjne CRP nie różnicuje chorych i nie ma sensu poszukiwanie innego punktu granicznego.
Wnioski: Podwyższone przed operacją stężenie CRP nie prognozuje powikłanego wczesnego okresu pooperacyjnego. Nie można też znaleźć lepszej prognostycznie wartości granicznej. Powikłania, z wyjątkiem FA, występowały u chorych starszych i z uszkodzeniem mięśnia sercowego, obrazowanego przez CKMB. Mimo braku dowodów statystycznych należy rozważyć opóźnienie operacji planowych u chorych z bardzo wysokim CRP.

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Słowa kluczowe: białko C-reaktywne, operacje serca, migotanie przedsionków, powikłania pooperacyjne.

Introduce

C-reactive protein (CRP) is the first discovered acute phase protein (in 1930 by Tillett and Francis in the sera of patients with pneumonia) as a substance that reacted with the C polysaccharide of Pneumococcus [1]. Later it was revealed that it is produced mainly in hepatocytes and some also in adipocytes in any inflammation, from such causes as infection or tissue damage [2, 3]. Since the availability of automatic assays for CRP, despite its non-specific character, many investigators have tried to reveal its possible connection with suspected inflammatory origin of coronary disease, and its course. The results thus far are divergent. Some investigators say that increased preoperative CRP level can have predictive value of complicated outcome after coronary artery surgery on cardio-pulmonary bypass (CPB), while others have a different opinion [4-10]. Also, opinions on possible atrial fibrillation dependency on high preoperative CRP level are polarized [11-13]. We investigated previously CRP in on-pump coronary artery bypass grafting (CABG) [14], and in valve disease patients separately [15], but not in off-pump CABG patients (OPCAB), and not in a mixed group of patients.

Aim

The aim of the study is to reveal whether an increased level of preoperative CRP can have predictive value for serious complications, other than atrial fibrillation (AF), and AF itself in a mixed group of patients who underwent heart operation for the most common indications: coronary artery disease, and valve diseases.

Material and Methods

Clinical data

The study group consisted of 85 patients without left ventricular failure operated on in our department for common reasons: 59 cases of coronary artery disease (CAD) (69.4%), and 26 (30.6%) of aortic or mitral valve disease, which is representative for the whole capacity of the most frequent cardiac operation types. The age of patients ranged from 21 to 78 years. The male/female ratio was 61/24. The indications for the operation were established on the basis of clinical examination, echocardiography performed according to the standards of the Working Group on Echocardiography of the European Society of Cardiology, and coronary angiography. Patients with poor left ventricular function (ejection fraction less than 35%) were not included in the study. The patients were operated on via median sternotomy, and except for off-pump cases, on normothermic CPB, with cold crystalloid antegrade intermittent cardioplegia of St. Thomas Hospital type.

In the CAD group, 51 patients underwent operation on-pump, and 8 off-pump. Among the on-pump patients 10 had a history of acute coronary syndrome within 30 days before the operation.

In the on-pump group the number of grafts per patient was 3.2±0.8 on average. Left internal thoracic artery (LITA) for bypass to left anterior descendent coronary artery (LAD) was used as a gold standard in all but 3 of these patients, and 3 of them had 3 or 2 arterial grafts. For the rest of the grafts, portions of saphenous vein were used. All OPCAB patients had a sole LITA-LAD graft, except for one with an additional saphenous bypass graft (SBG) to the right coronary artery (RCA).

All 15 aortic valve patients required aortic valve replacement (AVR). As an additional procedure mitral annuloplasty was necessary in 1 patient. In 11 patients with mitral valve disease, mechanical valve replacement required 9, and mitral annuloplasty 2 patients. Additionally, 3 patients required tricuspid annuloplasty, and in one saphenous bypass graft to the right coronary artery was needed.

The patients' hospital medical records were reviewed, and all serious complications in the perioperative period were taken into consideration. Patients with at least one episode of paroxysmal AF were included in the AF group. Complications are shown in Table I.

Laboratory data

CRP was determined using the immunoturbidimetric method with latex molecules augmentation (CRPL2, COBAS® INTEGRA) before the operation. Maximal in-hospital creatine kinase MB isoenzyme (CK-MB) value (as a marker of myocardial injury), and white blood count (WBC), and neutrophil percentage at discharge (WBC, and %Neutrophil – as markers of level of inflammation) were determined by standard laboratory tests.

Statistical analysis

The patients were divided into two pairs of contrary groups: with complications (except for AF)/without them, and with postoperative paroxysmal AF (at least 1 episode)/patients with sinus rhythm. They were compared one versus another in pairs. Age, gender, preoperative left ventricular ejection fraction (EF) and CRP, maximal CKMB, and WBC with neutrophil percentage at discharge were analyzed. The statistical analysis for categorical data (gender) was based on chi-square test with Yates adjustment. Quantitative data were presented as mean ± standard deviation (SD). Normality was tested with Shapiro-Wilk's test. Differences between groups for continuous data were analyzed using Student's *t* test for independent samples (for variables normally distributed) or with Mann-Whitney's U tests (if the distributions of variables were different from normal).

Moreover, receiver operating characteristic (ROC) curves were drawn for both pairs of contrary groups to assess the prediction accuracy of CRP level. The main goal of the ROC analysis was to find the decision threshold (cut-off point of

Tab. I. Complications

Complication	In CABG	In OPCAB	In valve surgery	Total number
Atrial fibrillation (at least one episode)	15	1	12	28
Low cardiac output – catecholamine support (IABP)	20 (4)		9	29 (4)
Rethoracotomy for excessive bleeding	5		1	6
Prolonged mechanical ventilation (>24 hours)	3			3
Other pulmonary complications	4		4	8
Death	2		1	3
Ventricular fibrillation	1		1	2
Supraventricular tachycardia	1			1
AV block grade III/cardio stimulator	1			1
Delirium/agitation/disorientation	2			2
Stroke	1			1
Lower limb ischaemia – chronic	1			1
Femoral artery embolus	1			1
Transient renal insufficiency	1			1
Superficial surgery site infection		1		1
Positive native valve culture			2	2

CRP value) better than the higher border of normal CRP level = 5 mg/L.

The results were considered significant for $p<0.05$.

Results

Clinical results

Despite complications shown in Table I, the majority of patients quickly recovered and were discharged home in the second postoperative week, according to our policy. There were three in-hospital deaths (mortality rate 3.5%). In the CABG group one female patient died directly after the operation due to cardiogenic shock. She had preoperative CRP level = 49.6, and history of acute coronary syndrome before 30 days. A male patient died in the intensive care unit (ICU) on the 21st postoperative day due to neurological complications. He was operated on for unstable angina with preoperative CRP level = 10 mg/L. In the valve disease group one patient died 6 hours after aortic valve replacement, from low cardiac output and ventricular fibrillation. He had left ventricular mass = 391 g, and gradient through aortic valve = 112 mmHg; however, his CRP level before the operation was normal (4.0 mg/L).

Results of statistical analysis

The numbers of patients with normal (<5 mg/L) and with increased CRP level were almost equal to each other. There was a significant CRP difference ($p<0.001$) between 46 (54.2%) patients with normal CRP level (range: 0-4.5; 1.78±1.11 mg/L on average) and 39 (45.8%) patients with increased CRP level (range: 6.7-131.2; 24.97±24.71 mg/L on average).

Statistical comparison revealed that in the group with complications, patients were significantly older ($p=0.038$), and had higher maximal CKMB ($p=0.0084$), whereas their gender, preoperative CRP level, left ventricular ejection fraction, WBC and neutrophil percentage at discharge did not differ significantly from the group without complications. Interestingly, CRP was higher in the group without complications, although non-significantly. The results are shown in Table II.

Between the groups with AF and with sinus rhythm there were no significant differences in any of the investigated data, particularly in CRP level. The results are shown in Table III.

The ROC curve for patients with complications (analyzed variable – CRP) is shown in Fig. 1. Area under curve (AUC) value is 0.551, and $p=0.422$. This means that preoperative CRP level does not discriminate patients and there is no sense in looking for a cut-off point.

The ROC curve for patients with AF (analyzed variable – CRP) is shown in Fig. 2. The results (AUC=0.562; $p=0.357$) lead to the same conclusions as for patients with other complications.

Tab. II. Comparison of groups with and without complications

Variable	Complications		No complications		p
	Mean value	SD	Mean value	SD	
male/female	29/10		32/14		NS
age	61.46	12.87	58.65	9.05	0.0380
EF [%]	52.00	7.76	53.09	5.99	NS
CRP	10.81	12.18	13.76	25.58	NS
Max CKMB	73.53	56.80	44.83	40.00	0.0084
WBC	9.97	3.24	9.47	2.60	NS
% Neutrophil	70.87	9.62	67.37	8.99	NS

Tab. III. Comparison of groups with AF and with sinus rhythm

Variable	AF		Sinus rhythm		p
	Mean value	SD	Mean value	SD	
male/female	19/9		42/15		NS
age	62.04		58.91	11.84	NS
EF [%]	51.86		52.96	7.20	NS
CRP	12.35		12.41	18.45	NS
Max CKMB	55.91		52.27	47.02	NS
WBC	9.72		11.33	2.19	NS
% Neutrophil	72.38		73.97	9.33	NS

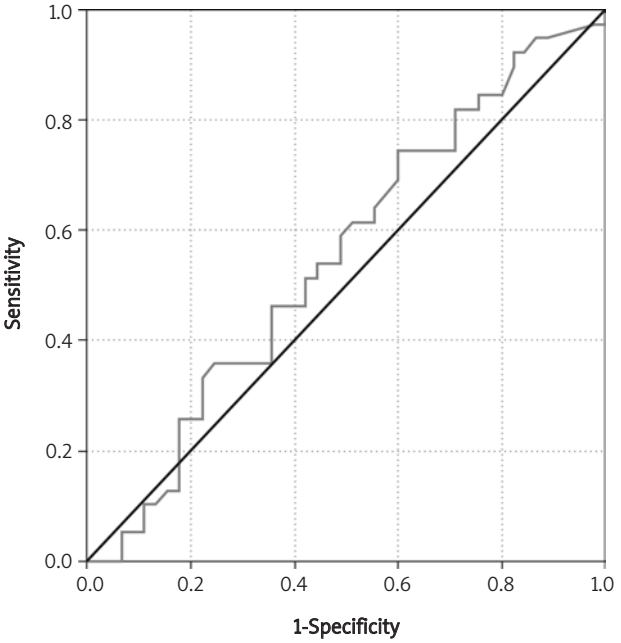

Fig. 1. ROC curve for patients with complications

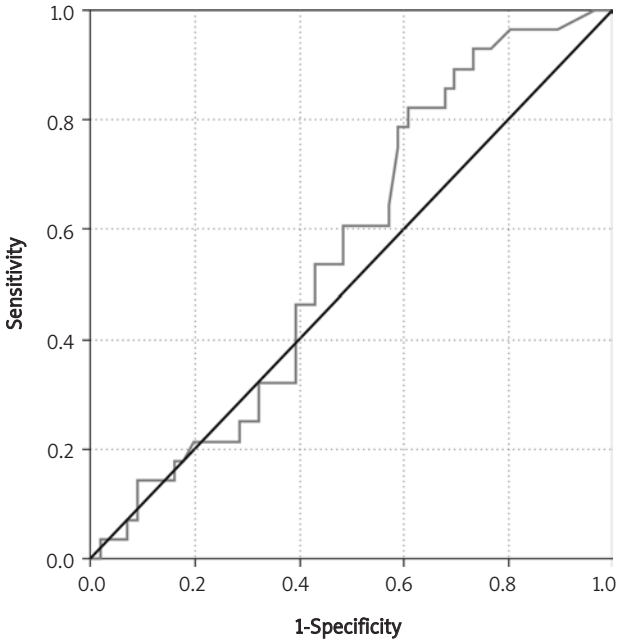

Fig. 2. ROC curve for patients with AF

Discussion

Increased CRP level is part of the non-specific acute-phase response to most forms of inflammation, infection, tissue damage, and neoplasm. Therefore for many years it was considered not to provide clinically useful information [2]. After CPB it is a part of the systemic inflammatory response (SIRS), and rises by many fold. Availability of automatic assays for CRP at low cost made it the most common investigated marker of inflammation. Against its acute-phase and non-specific nature, many investigators try to find a predictive value of just one pre-event measurement of CRP level for an outcome, for example in acute coronary syndrome. Introduction of the high sensitivity CRP test led to use of the somewhat misleading term "high sensitivity CRP". It is still the same CRP, but with a lower range of values, up to 3 mg/L. In our opinion, in this way CRP was forced to be transformed from an acute phase reactant into an indicator of chronic low grade inflammation. Until basic knowledge proves otherwise, this idea is too farfetched to the authors.

Therefore the cut-off values of CRP vary in different papers. The most common are: 5 mg/L, which is the established border of normal range, 10 mg/L (twice the previous one), and 3 mg/L (as the border of so-called high sensitivity CRP). The results of the torrent of cardiological investigations were reviewed by Biassuci [16].

Considering the aforementioned facts, there is nothing strange that opinions on the predictive value of preopera-

tive CRP levels in cardiac surgery patients are divergent. Boeken et al. [4], in 100 patients after CPB, found that in those with preoperative CRP level ≥5 mg/L without signs of an infection, occurrence of septic complications, need of catecholamine support, prolonged respiration and ICU stay were significantly higher. Fransen et al. [5] observed in 593 consecutive patients that risk of infection after cardiac surgery significantly correlated with preoperative CRP level. Cappabianca et al. [6] divided 597 patients after cardiac surgery into low and high inflammatory status groups depending on preoperative CRP level (cut-off value 5 mg/L). He found that in-hospital mortality, and rate of infectious complications were significantly higher in the second group. Moreover, Cappabianca observed lower survival of patients with high inflammatory status during 3-year postoperative follow-up despite surgical correction of cardiac disease. Biancari et al. [7] in multivariate analysis of 764 patients who underwent CABG showed that preoperative CRP of 10 mg/L or higher is an independent predictor of early postoperative death.

On the other hand, some authors have the reverse point of view. Gaudino et al. [8], in a prospective study of 113 patients undergoing coronary surgery, did not observe any correlation between preoperative CRP level of 5 mg/L or higher and postoperative outcome. Kangasniemi et al. [9], who retrospectively analyzed 843 patients after coronary surgery, showed no impact of preoperative CRP level of 10 mg/L or higher on early postoperative outcome; however, he observed its influence on worse long-term overall survival (mean follow-up of 12 years).

Correspondingly, opinions on possible inflammatory postoperative causes of AF are also polarized. Ahlson et al. in a group of 524 patients, from whom 182 had at least one episode of postoperative AF, showed no correlation of its occurrence with preoperative and postoperative CRP concentrations, which did not differ between the groups [11]. Also, Hogue et al. [12] did not find any correlation between preoperative CRP level and rate of postoperative occurrence of atrial fibrillation in 141 women undergoing on-pump cardiac surgery. On the other hand, Lo et al. in a group of 73 on-pump and 79 off- pump CABG patients with arterial revascularisation found that the majority of those with postoperative AF had preoperative CRP>3.0 mg/L, and considered this level as risk of this complication [13].

Clearly, the lower the CRP cut-off value that was admitted, the higher the fraction of patients (and complications) who were included in the high level CRP group.

In two previous studies of ours [14, 15] on smaller and homogeneous groups of patients (one study on CABG, one on valve diseases) we found no correlation between preoperative high CRP level (which at that time we arbitrarily considered as >10 mg/L, that is twice as high as the higher normal value limit, for better differentiation of patients) and early postoperative outcome. Moreover, in the valve patients group there were also no correlations of occurrence of AF and other complications with maximal postoperative CRP level (which in comparison to the preoperative one, rose postoperatively by many fold in every patient, achieving a maximal level usually in the first 48 hours), or with CRP level at discharge, still significantly higher than the preoperative one [15].

Considering in-hospital mortality, we cannot be so sure, because there are not enough cases to draw any separate statistical analysis. However, high preoperative CRP level in two patients who died had a clear cause in recent acute coronary syndrome and unstable angina. Most probably that fact, and not CRP level itself, increased operative risk. We cannot do anything more for these patients but treat them surgically without delay. The third deceased patient had normal preoperative CRP.

CRP is a non-specific, acute phase inflammatory indicator/mediator, with a half-life of 19 hours, so it does not surprise us that no direct connection between its preoperative level and any early postoperative complication was found in our studies. Moreover, the role of CRP is still not fully recognized, and despite known pro-inflammatory activity, for example complement activation, its anti-inflammatory features can be speculated on the basis of our previous study [15]. The fact that despite very high postoperative level of CRP, almost all patients not only survive without any severe damage, but significantly improve over a week or two in comparison to preoperative status, suggests that in the acute phase it should be helpful rather than harmful, or at least indifferent. It was also revealed that CRP enhances the anti-inflammatory path of damaged cell death in the way of apoptosis, promotes phagocytosis, and prevents lysis [16], thus contradicting autoimmunization [16].

Therefore we share Pepys and Hirschfield's point of view: "CRP values can never be diagnostic on their own and can only be interpreted at the bedside, in full knowledge of all other clinical and pathological results. However, they can then contribute powerfully to management, just as universal recording of the patient's temperature, an equally nonspecific parameter, is of great clinical utility" [2].

On the other hand, practice, especially in surgery, often precedes theory. Because we know that in every patient the operation increases CRP level by many fold, it may be reasonable to consider a delay in elective operations in persons with very high CRP level. How high we do not know, but if the CRP level is about 50 mg/L, or higher, it probably should be taken into consideration.

Conclusions

Increased preoperative CRP value (>5 mg/l) cannot be a predictor of complicated early outcome after heart surgery for most common indications in patients without poor left ventricular function, operated on with normothermic CPB and cold crystalloid cardioplegia, or off-pump. Moreover, no better cut-off CRP value for prediction of complications can be found. Complications, except for AF, depended on higher age, and myocardial injury represented by increased postoperative CKMB level. However, despite the lack of statistical evidence, a delay of elective operations should possibly be considered in patients with very high CRP level.

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References

1. Tillett WS, Francis T Jr. Serological reactions in pneumonia with a nonprotein somatic fraction of pneumococcus. J Exp Med 1930; 52: 561-585.
2. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest 2003; 111: 1805-1812.
3. Lau DC, Dhillon B, Yan H, Szmitko PE, Verma S. Adipokines: molecular links between obesity and atheroslcerosis. Am J Physiol Heart Circ Physiol 2005; 288: H2031-H2041.
4. Boeken U, Feindt P, Zimmermann N, Kalweit G, Petzold T, Gams E. Increased preoperative C-reactive protein (CRP) – values without signs of an infection and complicated course after cardiopulmonary (CPB) – operations. Eur J Cardiothorac Surg 1998; 13: 541-545.
5. Fransen EJ, Maessen JG, Elenbaas TW, van Aarnhem EE, van Dieijen-Visser MP. Enhanced preoperative C-reactive protein plasma levels as a risk factor for postoperative infections after cardiac surgery. Ann Thorac Surg 1999; 67: 134-138.
6. Cappabianca G, Paparella D, Visicchio G, Capone G, Lionetti G, Numis F, Ferrara P, D'Agostino C, de Luca Tupputi Schinosa L. Preoperative C-reactive protein predicts med-term outcome after cardiac surgery. Ann Thorac Surg 2006; 82: 2170-2178.
7. Biancari F, Lahtinen J, Lepojarvi S, Rainio P, Salmela E, Pokela R, Lepojärvi M, Satta J, Juvonen TS. Preoperative C-reactive protein and outcome after coronary artery bypass surgery. Ann Thorac Surg 2003; 76: 2007-2012.
8. Gaudino M, Nasso G, Andreotti F, Minniti G, Lacoviello L, Donatti MB, Schiavello R, Possati G. Preoperative C-reactive protein level and outcome following coronary surgery. Eur J Cardiothorac Surg 2002; 22: 521-526.
9. Kangasniemi O, Biancari F, Luukkonen J, Vourisalo S, Satta J, Pokela R, Juvonen T. Preoperative C-reactive protein is predictive of long-term outcome after coronary artery bypass surgery. Eur J Cardiothorac Surg 2006; 29: 983-985.
10. Verma S, Badiwala MV, Weisel RD, Li SH, Wang CH, Fedak PW, Li RK, Mickle DA. C-reactive protein activates the nuclear factor k-B signal transduction pathway in saphenous vein endothelial cells: Implications for atherosclerosis and restenosis. J Thorac Cardiovasc Surg 2003; 126: 1886-1891.
11. Ahlsson AJ, Bodin L, Lundblad OH, Englund AG. Postoperative Atrial Fibrillation is Not Correlated to C-Reactive Protein. Ann Thorac Surg 2007; 83: 1332-1337.
12. Hogue CW Jr, Palin CA, Kailasam R, Lawton JS, Nassief A, Dávila-Román VG, Thomas B, Damiano R. C-reactive protein levels and atrial fibrillation after cardiac surgery in women. Ann Thorac Surg 2006; 82: 97-102.
13. Lo B, Fijnheer R, Nierich AP, Bruins P, Kalkman CJ. C-Reactive Protein is a Risk Indicator for Atrial Fibrillation After Myocardial Revascularization. Ann Thorac Surg 2005; 79: 1530-1535.
14. Luigi M. Biasucci. DC/AHA Workshop on Markers of Inflammation and Cardiovascular Disease. Application to Clinical and Public Health Practice. Clinical Use of Inflammatory Markers in Patients With Cardiovascular Diseases. A Background Paper. Circulation 2004; 110: e560-e567.
15. Jander S, Walczak A, Bartczak K, Grychowska J, Gorzkiewicz G, Jaszewski R. Preoperative increased C-reactive protein level and early outcome after coronary artery bypass grafting. Clin Exp Med Lett 2007; 48: 33-35.
16. Bitner M, Nowak D, Jaszewski R, Sarniak A, Walczak A. C-reactive protein in operated acquired mitral and aortic valve diseases without left ventricular failure. Clin Exp Med Lett 2008; 49: 219-222.
17. Gershov D, Kim S, Brot N, Elkon KB. C-reactive protein binds to apoptotic cells, protects the cells from assembly of the terminal complement components, and sustains an antiinflammatory innate immune response: implications for systemic autoimmunity. J Exp Med 2000; 192: 1353-1363.