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Systemic inflammatory response after off-pump coronary artery bypass surgery: comparison of median sternotomy and minimally invasive techniques

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Background: The small difference in the magnitude of the inflammatory response between on-and off-pump coronary artery bypass surgery (CABG) could be caused by the fact that both surgical options require comparable invasive surgical access. The aim of the current study was to assess how systemic inflammatory response is influenced by extent of surgery trauma during CABG.

Material and Methods: We studied 52 consecutive patients undergoing, elective and isolated off-pump CABG procedure. Patients were divided into two groups: 35 patients who underwent conventional median sternotomy off-pump CABG (OPCAB) and 17 subjects who underwent minimally invasive direct coronary artery bypass surgery (MIDCAB). In venous blood samples drawn before the surgery, 18-36 h and 5-7 days after CABG, we examined the following inflammatory markers: C-reactive protein (CRP), fibrinogen and interleukin 6 (IL-6).

Results: The studied groups were comparable in demographic, clinical characteristics, and inflammatory markers levels at baseline. In the postoperative period, all analyzed markers were significantly lower in the MIDCAB patients compared with those after OPCAB. 18-36 h after surgery, levels of the analyzed markers were: CRP 34.0 vs 152.2 mg/L, p<0.0001; fibrinogen 4.5 vs 5.5 g/L, p=0.021, respectively. 5-7 days after the CABG, levels of the studied markers were: CRP 2.3 vs 47.3 mg/L, p<0.0001; fibrinogen 4.3 vs 7.4 g/L, p<0.0001; IL-6 2.8 vs 13.6 pg/mL, p=0.0004, respectively.

Conclusions: This study provides additional evidence that extended surgical trauma largely contributes to enhanced inflammatory response after CABG surgery.

Wprowadzenie: Niewielkie różnice w natężeniu odpowiedzi zapalnej pomiędzy klasycznymi operacjami pomostowania aortalno-wieńcowego (CABG) z lub bez użycia krążenia pozaustrojowego, mogą być spowodowane podobną, w obu technikach, rozległością urazu chirurgicznego. Celem badania była ocena wpływu wielkości urazu chirurgicznego na odpowiedź zapalną u chorych poddanych CABG.

Materiał i Metodyka: Badaniem objęto 52 kolejnych chorych, u których wykonano planową, izolowaną operację CABG bez użycia krążenia pozaustrojowego. Pacjenci zostali podzieleni na dwie grupy. U 35 chorych wykonano operację z dostępu poprzez pełną sternotomię (OPCAB), natomiast u 17 pacjentów wykonano operację techniką małoinwazyjną (MIDCAB). We krwi obwodowej oznaczono trzykrotnie (przed operacją, pomiędzy 18 i 36 godziną oraz pomiędzy 5 a 7 dobą po operacji) stężenia białka C-reaktywnego (CRP), fibrynogenu oraz interleukiny-6 (IL-6).

Wyniki: Dane demograficzne oraz przedoperacyjne cechy kliniczne i stężenia badanych markerów zapalnych były podobne w obu analizowanych grupach. W okresie pooperacyjnym, wszystkie badane markery były istotnie niższe u chorych z MIDCAB w porównaniu z grupą OPCAB. W 18-36 godzinie po operacji, stężenia analizowanych markerów wynosiły odpowiednio: dla CRP 34,0 vs 152,2 mg/l, p<0,0001; dla fibrynogenu 4,5 vs 5,5 g/l, p=0,021. Pomiędzy 5 a 7 dobą po operacji, stężenia badanych markerów wynosiły odpowiednio: dla CRP 2,3 vs 47,3 mg/l, p<0,0001; dla fibrynogenu 4,3 vs 7,4 g/l, p<0,0001; dla IL-6 2,8 vs 13,6 pg/ml, p=0,0004.

Wnioski: Przedstawione badanie dostarcza dodatkowych dowodów o wpływie rozległości urazu na natężenie odpowiedzi zapalnej u pacjentów po operacjach CABG.

Dodatkowe słowa kluczowe: pomostowanie aortalno-wieńcowe, uraz chirurgiczny, odpowiedź zapalna

Introduction

Activation of systemic inflammation which occurs after coronary artery bypass graft surgery (CABG) may result from a number of factors including the use of cardiopulmonary bypass, cardioplegic myocardium arrest, retransfusion of pericardial blood collected intraoperatively, surgical trauma, preexisting comorbidities or genetic predisposition [1,2]. The role of assessing the size of the inflammatory response after CABG is vital as systemic inflammation results in heightened activation of blood coagulation, impairment of physiological anticoagulant mechanisms, and inhibition of fibrinolysis. It therefore influences the development of several adverse postoperative outcomes such as: perioperative myocardial infarction, renal, pulmonary and neurological complications, bleeding and multiple organ dysfunction [3,4]. To reduce the extent of systemic inflammation after CABG, procedures which avoid cardiopulmonary bypass as well as new methods of myocardial protection and less invasive techniques have been studied and implemented in clinical practice in recent years. Which part of the procedure plays the most important role in the development of inflammatory response after CABG is still the subject of scientific debate and the results are inconclusive [5,6]. Our previous studies validated the concept that during CABG surgery mechanisms other than cardiopulmonary bypass or type of myocardial protection play a role in the systemic inflammatory response [7,8]. During the early postoperative period, cardiopulmonary bypass is the major determinant of the onset of the inflammatory response, but in the later phases, the surgical trauma itself could play a major role [3,9].

The aim of this study was to assess how the systemic inflammatory response is influenced by the extent of surgery trauma during CABG. For this purpose, white blood count (WBC), acute phase proteins (C-reactive protein (CRP) and fibrinogen) and interleukin 6 (IL-6), the main stimulus for production of these proteins, were evaluated in patients who underwent conventional median sternotomy off-pump CABG (OPCAB) and patients who underwent minimally invasive direct coronary artery bypass surgery (MIDCAB). We hypothesized that general surgical trauma, derived from surgical access may play an important role in systemic inflammatory response after CABG.

Methods

Patients

Study protocol was approved by the local Research Ethics Board and all participating patients signed an informed consent. The study was performed in accordance with the Declaration of Helsinki.

We studied 52 consecutive patients who underwent primary, elective and isolated off-pump CABG procedure. Indications for CABG were consistent with the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery guidelines on myocardial revascularization. Exclusion criteria were: history of previous cardiac surgery, percutaneous coronary intervention within 1 month prior to surgery, renal or liver insufficiency and signs or symptoms of acute infections, presence of extensive dental disease, and concomitant diseases such as autoimmune disorders or cancer. Patients were divided into two groups: 35 patients who underwent OPCAB and 17 subjects upon which MIDCAB was performed.

Blood samples were drawn from an antecubital vein with minimal stasis after an overnight fast, before the start of any anesthesia or surgery related procedures, and examined for CRP and fibrinogen then checked again 18-36 h post-CABG and 5-7 days after surgery. WBC and IL-6 were measured twice, first before and then during the first 18-36 h after surgery or 5-7 days after CABG, respectively.

Surgical technique

Classical CABG was carried out through median sternotomy. Revascularization was performed on the beating heart using the Octopus system (Medtronic Inc., Minneapolis, USA) and a coronary flow-shunt was always passed into the coronary arteriotomy. Anticoagulation was accomplished by administration of heparin (500 IU/kg) and was monitored by means of an activated clotting time above 400 s. After all anastomoses were complete, anticoagulation was reversed by protamine chloride to a normal activated clotting time.

For MIDCAB surgery a double tube lumen tracheal tube was used allowing for separate lung ventilation. Surgery began with thoracoscopic harvesting of the left internal mammary artery (LIMA). A 10 mm thoracoscope was introduced through the trocar placed in the 5th intercostal space, electrocautery was introduced through the trocar placed in the 3rd intercostal space, and a grasper was introduced through the trocar placed in the 7th intercostal space in the anterior axillary line on the left side of the chest. Continuous carbon dioxide insufflation was applied during LIMA harvesting to keep the pressure in the left hemithorax around 10 mmHg. After LIMA was gathered, a minithoracotomy (6-8 cm) was made in the 4th intercostal space on the left side of the chest below the left nipple. The LIMA to left anterior descending coronary artery anastomosis was performed on the beating heart, under direct vision using Octopus heart stabilizer (Medtronic Inc., Minneapolis, USA) and an intracoronary shunt placed in the coronary artery. Careful haemostasis was performed and a single drain was placed in the left hemithorax before the minithoracotomy was closed. Patients from both groups received uniform postoperative care.

Blood sampling and biochemical measurements

Routine laboratory variables were determined using standard laboratory methods. CRP was measured by an immuno-turbidimetric assay (Dade Behring, Marburg, Germany). Fibrinogen was determined using the Clauss method [10]. A commercially available immuno-enzymatic assay was used to determine serum IL-6 (R&D Systems Inc., Minneapolis, USA). The minimal detectable IL-6 concentration was 0.03 pg/mL. All measurements were performed by technicians blinded to the origin of the samples. Intra- and inter-assay coefficients of variation were < 7%.

Statistical analysis

A descriptive statistic was described as numbers and percentages for categorical variables. Continuous variables were presented as mean and standard deviation (±) or as median with 25th, 75th percentiles inter-quartile range (IQR). The Shapiro-Wilk test was used to test the normal distribution. To detect the differences between the two independent groups, Student's t-test (for continuous normally distributed variables) or the Mann-Whitney U-test (for non-normally distributed variables) were used. The χ^2 test or Fisher's exact test were used to compare distributions of categorical variables between independent groups. No multivariate logistic regression analysis was performed because of low incidence of major adverse cardiovascular events in the groups studied. Data were analyzed using standard computer software (Statistica 10.0, StatSoft, Tulsa, USA). A two-sided p-value of less than 0.05 was considered statistically significant.

Results

Fifty two CABG patients were enrolled in the study of whom 35 patients underwent OPCAB and 17 subjects were operated on using the MIDCAB technique. The mean age for all patients was 63.8±8.7 years. The patient demographic data did not differ between the two groups, except for history of previous myocardial infarction, which was more common in patients from the OPCAB group (Tab. I). EuroSCORE I was similar between the analyzed groups.

We did not find significant differences between the groups in the number of grafts and levels of cardiac markers excluding creatine kinase, which were almost 3 times greater in OPCAB (p=0.036) (Tab. II).

Levels of the inflammatory markers are shown in Table III. There were no differences in preoperative values of the analyzed parameters between the two groups. In the OPCAB, CRP increased markedly to 152.2 mg/L 18-36 h after surgery (p<0.0001) and then decreased by 69 % in 5-7 days after CABG (p<0.0001). In the MIDCAB group the initial rise of CRP was not as high at only 34 mg/L (p<0.0001), and then their CRP decreased to normal range in 5-7 days after CABG (p<0.0001). Among the OPCAB patients, fibrinogen increased significantly by 25 % 18-36 h after surgery (p=0.02) and then grew to 34 % 5-7 days after the CABG (p =0.0003). By contrast, in the MIDCAB group, fibrinogen increased only by slightly more than 2 % 18-36 h post CABG (p<0.950) to reach a value below baseline in 5-7 postoperative days (p=0.457). In the OPCAB group, IL-6 increased more than 5 times in 5-7-

Table I
Baseline characteristics of patients.
Przedoperacyjna charakterystyka pacjentów.

Variable	All patients n = 52	OPCAB n = 35	MIDCAB n = 17	p
Age (years)	63.8±8.7	65.1±7.3	60.9±10.6	0.096
Male, n (%)	41 (78.8)	27 (77.1)	14 (82.3)	0.999
Diabetes mellitus, n (%)	21 (40.4)	14 (40.0)	7 (41.2)	0.988
Hypertension, n (%)	39 (75.0)	32 (91.4)	7 (41.2)	0.430
Previous myocardial infarction, n (%)	38 (73.1)	31 (88.6)	7 (41.2)	0.0001
Total cholesterol	4.9±1.0	4.8±0.8	5.0±1.4	0.617
BMI (kg/m^2)	27.3±3.5	27.9±4.0	26.1±1.4	0.079
ACE inhibitors, n (%)	43 (82.7)	29 (82.8)	14 (82.3)	0.500
Statins, n (%)	44 (84.6)	30 (85.7)	14 (82.3)	0.459
Beta-blockers, n (%)	48 (92.3)	32 (91.4)	16 (94.1)	0.549
COPD, n (%)	3 (5.8)	2 (5.7)	1 (5.8)	0.489
EuroSCORE I (points)	3 (2-5)	3 (2-5)	3 (2-5)	0.178

Values are displayed as mean±standard deviation, number (percentage) or median with inter-quartile range. ACE inhibitors: angiotensin-converting-enzyme inhibitors; BMI: body mass index; COPD: chronic obstructive pulmonary disease; MIDCAB: minimally invasive direct off-pump coronary artery bypass surgery; OPCAB: conventional median sternotomy off-pump coronary artery bypass surgery.

Table II
Perioperative characteristics of patients.
Okolooperacyjna charakterystyka pacjentów.

Variable	All patients n=52	OPCAB n=35	MIDCAB n=17	p
Number of grafts	1.9±0.8	2.3±0.7	±0.0	0.956
Creatine kinase	247 (162-621)	471 (278-662)	167 (149-219)	0.036
Creatine kinase MB	31 (21-48)	20 (19-72)	35 (30-44)	0.224
Cardiac troponin I	1.31 (0.72-4.53)	2.00 (1.12-10.2)	0.76 (0.52-0.98)	0.410
In-hospital cardiovascular death, n (%)	1 (1.9)	1 (2.8)	0 (0.0)	0.491

Values are displayed as mean ± standard deviation, number (percentage) or median with inter-quartile range. MIDCAB: minimally invasive direct off-pump coronary artery bypass surgery; OPCAB: conventional median sternotomy off-pump coronary artery bypass surgery.

Table III
Changes of analyzed inflammatory response after coronary artery bypass graft surgery.
Zmiany stężeń analizowanych markerów zapalnych po operacjach pomostowania aortalno-wieńcowego.

Variable	All patients n=52	OPCAB n=35	MIDCAB n=17	p
CRP (mg/L)				
At baseline	2.1 (1.1-3.6)	3.1 (1.9-5.1)	0.9 (0.6-1.2)	0.088
18–36 h after CABG	112.7 (42.1-163.1)	152.2 (115.1-177.1)	34.0 (28.1-46.4)	<0.0001
5–7-days after CABG	15.2 (2.4-59.8)	47.3 (25.8-81.7)	2.3 (2.1-3.3)	<0.0001
Fibrinogen (g/L)				
At baseline	4.4±1.4	4.4±1.4	4.4±1.3	0.943
18–36 h after CABG	5.0±1.3	5.5±1.5	4.5±0.8	0.021
5–7-days after CABG	5.8±1.9	7.4±1.3	4.3±0.7	<0.0001
IL-6 (pg/mL)				
At baseline	1.9 (0.9-3.6)	2.6 (1.7-5.8)	1.4 (0.7-1.9)	0.232
5–7-days after CABG	6.7 (1.3-14.1)	13.6 (7.6-18.1)	2.8 (1.2-5.5)	0.0004
WBC				
At baseline	7.3±1.7	7.3±1.8	7.2±1.6	0.842
18–36 h after CABG	8.5±2.9	9.4±3.1	7.0±1.6	0.005

Values are displayed as mean±standard deviation or median with inter-quartile range.
CRP: C-reactive protein; IL-6: interleukin 6; MIDCAB: minimally invasive direct off-pump coronary artery bypass surgery; OPCAB: conventional median sternotomy off-pump coronary artery bypass surgery; WBC: white blood count.

days after procedure (p<0.0001). Among the MIDCAB patients, IL-6 increased only twice in 5-7 postoperative days (p=0.045). Lastly, WBC in the OPCAB surgery group increased by 30 % 18-36 h after CABG (p=0,002). In the MIDCAB group WBC did not change significantly (p=0.681) 18-36 h after the procedure. In the postoperative period, all analyzed markers were significantly lower in the MIDCAB group (Tab. III).

Discussion

In this study, we tested the hypothesis that the extent of surgery trauma may play an essential role in systemic inflammatory response after CABG. We therefore conducted a prospective, observational study to compare the influence of range of surgical trauma during off-pump CABG on systemic inflammatory response, measured by CRP, fibrinogen, IL-6 and WBC.

The study showed that a lower degree of surgical trauma during CABG plays an important role in reduction of systemic inflammatory response. Patients who underwent MIDCAB had significantly lower inflammatory markers in all postoperative time points. To the best of our knowledge this is the first study that compares these markers in patients who underwent MIDCAB and OPCAB. The analyzed groups were comparable in demographic, clinical characteristics, and inflammatory markers levels at baseline. Only the history of myocardial infarctions was more frequent among the classically operated patients. This can be explained by the fact that patients with more advanced coronary disease needed more than one by-pass and because of this could not be a candidate for MIDCAB surgery. As several studies have shown pleiotropic effects of statins, resulting not only from lipid-lowering, but also their anti-inflammatory properties, the analyzed groups were similar in terms of perioperative statins use [11].

Numerous studies have emphasized the important role of cardiopulmonary bypass in inflammatory response after CABG [12]. By contrast, our previous studies validate the concept that the cardiopulmonary bypass does not significantly affect systemic inflammatory response following CABG procedure [6,7,9]. A possible explanation for the small difference in the inflammatory response between on-and off-pump CABG may be that both methods share the necessarily invasive nature of surgical access. Surgical incisions made by classical sternotomy are highly traumatic and imposes significant injury to the tissues and produce a marked inflammatory response [4,13]. The acute phase response that occurs after tissue trauma is stimulated mainly by IL-6. This cytokine, the level of which reflects the degree of tissue damage, stimulates production in the liver of acute phase proteins, i.e. CRP and fibrinogen [14]. MIDCAB surgery causes less tissue injury than OPCAB procedures, so the increase of these inflammatory markers is more pronounced in conventional surgery. Also during lateral thoracotomy CABG, a more invasive method than MIDCAB, lower average concentrations of IL-6 were observed than in the OPCAB group [15]. Using less invasive techniques not only in CABG surgery but in atrial valve replacement procedures as well, likewise showed more clinical advantages [16]. In our study, clinical aspects of different CABG procedures were beyond the possibility of this research. A much larger cohort should be recruited for such analysis. The observation regarding influence of surgical trauma on inflammatory response is also consistent with reports from non-cardiac surgery [15,17]. In contrast to our observations, some reports observed that IL-6 also reflects the degree and duration of surgical trauma whereas CRP does not depend on the extension of trauma [18].

Because of a low incidence of major adverse cardiovascular events we did not correlate the perioperative values of inflammatory markers with the clinical outcomes after CABG. However, except for creatine kinase, the levels of cardiac markers after surgery were comparable between the two analyzed groups. Higher levels of creatine kinase which occurred in OPCAB patients can be explained by augmented rhabdomyolysis because of extensive surgery access rather than myocardial ischemia, as the concentration of creatine kinase MB and cardiac troponin I were similar in both groups.

Several limitations should be acknowledged in this study. The size of the study groups was limited. Therefore, lack of significant differences should be interpreted with caution. On the other hand, marked differences observed here strongly suggest that the impact of two surgical techniques is quite potent on the inflammation. Another limitation of our study is the short period of time in which postoperative inflammatory markers were monitored. It would of interest to assess the variables also within the first 24 hours and later after hospital discharge to better characterize the changes in these parameters as a function of time since the surgery. A study on a larger group of patients is needed to evaluate the prevalence of complications such as low cardiac output or perioperative myocardial infarction and their correlation with the inflammatory markers. Moreover, the influence of epicardial blood flow as well as platelet reactivity on inflammatory response after CABG was not analyzed [19,20]. Finally, this is an analysis of data collected in a single center. Long term follow-up may help to assess the associations between the degree of perioperative inflammatory response and prognosis after the two different CABG techniques analyzed.

In conclusion, our study adds to the concept that the extension of surgical trauma might play a crucial role in the development of inflammatory response after CABG surgery.

Conflict of interest

Authors report no conflict of interest.

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