

# Acute-phase proteins and oxidative stress in patients undergoing coronary artery bypass graft: comparison of cardioplegia strategy



Dariusz Plicner<sup>1</sup>, Jarosław Stoliński<sup>1</sup>, Anna Rzucidło-Hymczak<sup>2</sup>, Bogusław Kapelak<sup>1,3</sup>, Anetta Undas<sup>3</sup>

<sup>1</sup>Department of Cardiosurgery, John Paul II Hospital, Kraków, Poland

<sup>2</sup>Department of Infectious Diseases, John Paul II Hospital, Kraków, Poland

<sup>3</sup>Institute of Cardiology, Jagiellonian University Medical College, Kraków, Poland

Kardiologia i Torakochirurgia Polska 2017; 14 (1): 16-21

## Abstract

**Introduction:** Several strategies are still being introduced to cardiac surgery techniques to reduce the signs of the inflammatory response and oxidative stress. Many efforts have been made to develop the best possible method for myocardial protection.

**Aim:** To assess the effect of the cardioplegia strategy on the systemic inflammatory response and oxidative stress.

**Material and methods:** A group of 238 consecutive, elective on-pump coronary artery bypass graft patients (CABG; 183 men, aged 64.6 ± 8.1 years) were prospectively studied. Patients were enrolled in two groups: with warm blood cardioplegia ( $n = 124$ ) and with cold crystalloid cardioplegia ( $n = 114$ ). In each group, pre- and postoperative levels of plasma C-reactive protein, fibrinogen, interleukin 6 and 8-iso-prostaglandin  $F_{2\alpha}$  (8-iso-PGF<sub>2 $\alpha$</sub> ) were measured.

**Results:** All studied markers significantly increased 18–36 h following CABG and then decreased in 5–7 postoperative days but remained above baseline levels. No differences in terms of studied markers and clinical outcomes were noted for the different types of cardioplegia. Regression analysis showed a significant correlation between preoperative level of oxidative stress measured by 8-iso-PGF<sub>2 $\alpha$</sub>  and postoperative myocardial infarction as well as in-hospital cardiovascular death ( $p = 0.047$  and  $p = 0.041$  respectively).

**Conclusions:** This study extends previous reports by showing that the type of cardioplegia does not affect the systemic inflammatory response or oxidative stress, which are associated with the CABG procedure. It might be speculated that preoperative screening of oxidative stress could be helpful in identifying patients at increased risk of an unfavorable course after CABG.

**Key words:** coronary artery bypass graft, cardioplegia, inflammatory response, oxidative stress.

## Streszczenie

**Wstęp:** Ciągłe wprowadzane są nowe techniki chirurgiczne i anestezjologiczne mające na celu zmniejszenie odpowiedzi zapalnej i stresu oksydacyjnego po operacjach kardiologicznych. Podjęto wiele badań, których celem było stworzenie możliwie najlepszej metody ochrony mięśnia sercowego.

**Cel:** Ocena wpływu metody ochrony mięśnia sercowego na odpowiedź zapalną i stres oksydacyjny.

**Materiał i metody:** W badaniu prospektywnym wzięto udział 238 kolejnych chorych poddanych planowemu pomostowaniu aortalno-wieńcowemu (CABG; 183 mężczyzn, średni wiek: 64,6 ± 8,1 roku). Pacjenci zostali przydzieleni do dwóch grup – w pierwszej wykorzystano ciepłą kardioplegicę krwistą ( $n = 124$ ), a w drugiej chłodną kardioplegicę krystaliczną ( $n = 114$ ). W każdej grupie oznaczono przed- i pooperacyjnie poziomy białka C-reaktywnego, fibrynogenu, interleukiny 6 oraz 8-iso-prostaglandyny  $F_{2\alpha}$  (8-iso-PGF<sub>2 $\alpha$</sub> ).

**Wyniki:** Wszystkie badane markery wzrosły istotnie pomiędzy 18. a 36. godziną po CABG, a następnie zmniejszyły się w 5.–7. dobie po operacji, lecz ich poziom ciągle pozostawał wyższy niż wyjściowy. Nie odnotowano istotnych różnic w zakresie badanych markerów oraz w przebiegu klinicznym pomiędzy badanymi grupami. Analiza regresji wykazała istotną korelację pomiędzy przedoperacyjnym poziomem stresu oksydacyjnego, mierzonym 8-iso-PGF<sub>2 $\alpha$</sub> , oraz okołoperacyjnym zawładem mięśnia sercowego i śmiertelnością szpitalną (odpowiednio  $p = 0,047$  i  $p = 0,041$ ).

**Wnioski:** Przedstawione badanie poszerza wcześniejsze doniesienia, że rodzaj kardioplegii u pacjentów poddanych CABG nie wpływa istotnie na poziom odpowiedzi zapalnej oraz stresu oksydacyjnego. Przedoperacyjny pomiar stresu oksydacyjnego może być pomocny w rozpoznaniu pacjentów o zwiększonym ryzyku niekorzystnego przebiegu pooperacyjnego.

**Słowa kluczowe:** pomostowanie aortalno-wieńcowe, kardioplegia, odpowiedź zapalna, stres oksydacyjny.

**Address for correspondence:** Dariusz Plicner MD, John Paul II Hospital, 80 Prądnicza St, 31-202 Kraków, Poland, phone: +48 12 614 30 75, 501 499 845, fax: +48 12 423 39 00, e-mail: plicner@outlook.com

**Received:** 30.12.2016, **accepted:** 14.02.2017.

## Introduction

The protective effect of cardioplegia is related to myocardium metabolism reduction, thereby increasing cardiac capacity for prolonged ischemia during cardiosurgery procedures. Although the heart is protected during surgery by cardioplegic solution, temporary myocardial ischemia and then reperfusion result in exacerbation of the systemic inflammatory response, which is a result of, among other things, surgical trauma, manipulation of the heart, cardiopulmonary bypass, pericardial suction or genetic predisposal [1, 2]. Despite cardioplegia, myocardial production of reactive oxygen species still occurs. Imbalance between reactive oxygen species generation and elimination results in oxidative stress, which is an important cause of the systemic inflammatory response and in consequence leads to ischemia-reperfusion injury [2].

Since Denis Melrose introduced elective, chemical cardiac arrest in the 1950s, many efforts have been made to develop the best possible method for myocardial protection. The two main types of cardioplegic solutions predominantly used in coronary artery bypass graft (CABG) surgery are warm blood cardioplegia and cold crystalloid cardioplegia. There is an ongoing discussion about the effectiveness and side effects of cardioplegic solutions [3]. To our knowledge, there are few studies comparing the inflammatory response and oxidative stress in different type of cardioplegia [4–6].

## Aim

Therefore, the aim of this study was to analyze the impact of cardioplegia strategy on C-reactive protein (CRP) and fibrinogen, as well as interleukin 6 (IL-6) as the main stimulus for production of these acute-phase proteins in the liver. Furthermore, we evaluated the influence of the type of cardioplegia on 8-iso-prostaglandin  $F_{2\alpha}$  (8-iso-PGF $_{2\alpha}$ ) as a marker of oxidative stress.

## Material and methods

### Patients

The study was performed in accordance with the Declaration of Helsinki and with the consensus guidelines expressed by the STROBE statement. The patients were recruited between January and March 2008. We studied 238 consecutive patients undergoing primary, elective and isolated CABG using cardiopulmonary bypass (CPB). A subset of this cohort was analyzed in our previous studies [7, 8]. Indications for CABG were consistent with the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery guidelines on myocardial revascularization [9]. The exclusion criteria were signs or symptoms of acute infections, presence of extensive dental disease, concomitant diseases such as autoimmune disorders or cancer, acute coronary syndrome, or percutaneous coronary intervention within 1 month before the enrolment, and liver or renal insufficiency. Patients were categorized into two groups: with warm blood and cold crystalloid cardioplegia. The choice of the type of cardioplegia was based on the

surgeon's preference. Clinical outcomes showed no associations with surgery performance. All data were collected prospectively. Additionally, we correlated the perioperative values of inflammatory and oxidative stress markers with the clinical outcomes after CABG surgery, i.e. postoperative myocardial infarction (PMI) and in-hospital cardiovascular death. The PMI was defined as a serum creatine kinase-myocardial band (CK-MB) concentration greater than or equal to 5 times the upper limit of normal ( $\geq 85$  U/l), and new Q waves present, or the CK-MB value had to be greater than or equal to 10 times the upper limit of normal ( $\geq 170$  U/l) (with or without new Q waves) or new regional wall motion abnormalities demonstrated by transesophageal echocardiography [10]. In-hospital cardiovascular death was defined as death occurring during the same hospitalization period as the CABG surgery.

### Coronary artery bypass graft procedure

Surgical technique, anesthesia and perioperative management were uniform for all patients. All operations were performed on CPB consisting of a nonpulsatile roller pump (Jostra Medizintechnik AG, Hirrlingen, Germany) and an in-line arterial blood filter (Jostra Medizintechnik AG, Hirrlingen, Germany) under moderate systemic hypothermia (esophageal temperature, 32°C). Mean arterial pressure was maintained between 40 and 60 mm Hg and CPB blood flow was maintained at 2.0–2.4 l/min/m<sup>2</sup>. Anticoagulation was achieved by administration of heparin (500 IU/kg) before the onset of CPB and was monitored by means of the activated clotting time, which had to be above 400 s during CPB.

Cardiac arrest was accomplished by administration of antegrade, intermittent, cold crystalloid cardioplegia or antegrade, intermittent, warm blood cardioplegia. Patients obtaining crystalloid cardioplegia were given a first dose of 1000 ml of cardioplegia solution through the aortic root and were given more cardioplegia if cardiac arrest was not achieved. 500 ml of crystalloid cardioplegia was given the same way every 40 min or earlier in the case of premature heart activity. The cold crystalloid cardioplegia consisted of Ringer's solution (500 ml) to which 2.5 ml of 20% magnesium sulfate, 5 ml of 15% potassium chloride, 10 ml of 15% mannitol and 5.5 ml of 8.4% sodium hydrogen bicarbonate were added. The temperature of the cardioplegic solution was maintained at 4°C throughout the entire operative procedure. In patients with blood cardioplegia, warm (37°C) oxygenated blood was infused into the aortic root. A syringe pump containing 15% potassium chloride was connected to the cardioplegia circuit. Cardiac arrest was induced at a blood flow rate of 300 ml/min by continuous infusion of 180 ml/h of the syringe pump over a 3-minute time period. Cardioplegia was repeated through the aortic root for 2 to 3 min after the completion of each anastomosis or earlier in the case of premature cardiac activity.

### Laboratory investigations

Blood samples for IL-6, fibrinogen, high-sensitivity CRP and 8-iso-PGF $_{2\alpha}$  were drawn after an overnight fast, before

the start of any surgery-related procedures, 18–36 h after CABG (without IL-6) and 5–7 days postoperatively. A commercially available immuno-enzymatic assay was used to determine serum IL-6 (R&D Systems Inc., Minneapolis, USA) and plasma 8-iso-PGF<sub>2α</sub> (Cayman Chemicals, Ann Arbor, USA). The minimal detectable IL-6 concentration was 0.03 pg/ml. High-sensitivity CRP was measured by an immunoturbidimetric assay (Dade Behring, Marburg, Germany). Fibrinogen was determined using the Clauss method [11]. All measurements were performed by technicians blinded to the origin of the samples. Intra- and interassay coefficients of variation were < 7%.

### Statistical analysis

Descriptive statistics were described as numbers and percentages for categorical variables. Continuous variables were presented as mean and standard deviation ( $\pm$ ). The Shapiro-Wilk test was used to test the normality of continuous variables. To observe 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  $\chi^2$  test or Fisher's exact test was used to compare distributions of categorical variables between independent groups. The association between the concentrations of analyzed markers and PMI or in-hospital death was evaluated by logistic regression analysis. No multivariate logistic regression analysis was performed because of the low number of clinical endpoint events. Statistical analysis was performed with Statistica 10.0 (StatSoft, Tulsa, USA). Two-sided *p*-values of < 0.05 were considered statistically significant.

### Results

The mean age for all patients was 64.6  $\pm$  8.1 years. One hundred twenty-four patients were operated on using

blood cardioplegia and 114 underwent CABG using crystalloid cardioplegia. Patients' demographic data did not differ among groups (Tab. I). Aortic cross clamp time as well as CPB time were significantly longer in patients with blood cardioplegia (42.8  $\pm$  14.2 min vs. 38.9  $\pm$  13.8 min, *p* = 0.037 and 96.2  $\pm$  36.8 min vs. 83.0  $\pm$  29.5 min, *p* = 0.003, respectively), compared with the patients with crystalloid cardioplegia. Forty-seven (37.9%) patients with blood cardioplegia and 29 (25.4%) subjects with crystalloid cardioplegia needed transfusion of  $\geq$  3 units of blood products during the perioperative period (*p* = 0.039) (Tab. II).

As shown in Table III, in the whole group, mean IL-6 increased almost 6 times in 5–7-days after CABG (*p* < 0.0001). Mean fibrinogen increased by 50% 18–36 h after surgery (*p* = 0.01) and then continued to grow by 13% 5–7 days after the procedure (*p* = 0.05). As expected, CRP concentration increased markedly 18–36 h after CABG (*p* < 0.0001), and then decreased by 65% in 5–7 postoperative days (*p* = 0.001). Similarly, 8-iso-PGF<sub>2α</sub> increased by 30% 18–36 h following CABG (*p* = 0.05) and then decreased by 11% in 5–7 days after CABG (*p* < 0.0001). No differences in the studied markers were noted between the two types of cardioplegia.

There were no significant differences between analyzed groups regarding frequencies of occurrence of clinical endpoints. Of the 238 patients, 20 (8.4%) patients developed PMI, 11 (8.9%) patients from the blood cardioplegia group and 9 (7.9%) from the crystalloid cardioplegia group (*p* = 0.786). Eight (3.4%) patients died during the early postoperative period due to massive PMI. These were 4 (3.2%) patients from the blood cardioplegia group and 4 (3.5%) from the crystalloid cardioplegia group (Tab. IV). There were no differences in the preprocedural demographic and clinical data between the subjects with clinical endpoints and remaining patients (data not shown). Only 8-iso-PGF<sub>2α</sub> concentration was significantly higher in the PMI and in-hospital

Tab. I. Baseline characteristics of patients

Variable	All patients ( <i>N</i> = 238)	Blood cardioplegia ( <i>n</i> = 124)	Crystalloid cardioplegia ( <i>n</i> = 114)	<i>P</i> -value
Age [years]	64.6 $\pm$ 8.1	64.5 $\pm$ 8.2	64.6 $\pm$ 8.3	0.902
Male, <i>n</i> (%)	183 (76.9)	90 (72.6)	93 (81.6)	0.999
Peripheral vascular disease, <i>n</i> (%)	30 (12.6)	14 (11.3)	16 (14.0)	0.524
Diabetes mellitus, <i>n</i> (%)	69 (29.0)	36 (29.0)	33 (28.9)	0.988
Insulin, <i>n</i> (%)	33 (13.9)	19 (15.3)	14 (12.3)	0.515
Hypertension, <i>n</i> (%)	197 (82.8)	104 (83.9)	93 (81.6)	0.640
Previous myocardial infarction, <i>n</i> (%)	197 (82.8)	97 (78.2)	100 (87.7)	0.052
Hypercholesterolemia, <i>n</i> (%)	33 (13.9)	16 (12.9)	17 (14.9)	0.654
BMI [kg/m <sup>2</sup> ]	28.1 $\pm$ 4.1	28.1 $\pm$ 4.0	28.0 $\pm$ 4.1	0.850
LVEF (%)	52.2 $\pm$ 9.4	52.7 $\pm$ 9.7	51.5 $\pm$ 9.0	0.329
Previous PCI, <i>n</i> (%)	29 (12.2)	11 (8.9)	18 (15.8)	0.103
COPD, <i>n</i> (%)	11 (4.6)	7 (5.6)	4 (3.5)	0.433
EuroSCORE 1 (points)	3 (2–5)	3 (2–5)	3 (2–5)	0.965

Values are displayed as mean  $\pm$  standard deviation, number (percentage) or median with inter-quartile range. BMI – body mass index, LVEF – left ventricular ejection fraction, PCI – percutaneous coronary interventions, COPD – chronic obstructive pulmonary disease.

**Tab. II.** Operative and postoperative characteristics of patients

Variable	All patients (N = 238)	Blood cardioplegia (n = 124)	Crystalloid cardioplegia (n = 114)	P-value
Aortic cross-clamp time [min]	40.9 ±14.1	42.8 ±14.2	38.9 ±13.8	0.037
CPB time [min]	89.9 ±34.1	96.2 ±36.8	83.0 ±29.5	0.003
Transfusion (red cells/platelets/plasma) ≥ 3 units, n (%)	76 (31.9)	47 (37.9)	29 (25.4)	0.039
Postoperative drainage [ml]	660 (460–905)	680 (500–930)	665 (465–870)	0.285
PMI, n (%)	20 (8.4)	11 (8.9)	9 (7.9)	0.786
In-hospital cardiovascular death, n (%)	8 (3.4)	4 (3.2)	4 (3.5)	0.903

Values are displayed as mean ± standard deviation, number (percentage) or median with inter-quartile range. CPB – cardiopulmonary bypass, PMI – postoperative myocardial infarction.

**Tab. III.** Changes of studied inflammatory response and oxidative stress parameters after coronary artery bypass graft

Variable	All patients (N = 238)	Blood cardioplegia (n = 124)	Crystalloid cardioplegia (n = 114)	P-value
IL-6 [pg/ml]:				
At baseline	2.1 (1.1–4.0)	2.1 (1.0–3.5)	2.1 (1.2–4.2)	0.110
5–7-days after CABG	14.6 (5.2–23.9)	16.4 (3.9–32.5)	14.0 (5.6–21.3)	0.739
Fibrinogen [g/l]:				
At baseline	4.2 ±1.2	4.2 ±1.2	4.2 ±1.1	0.994
18–36 h after CABG	6.3 ±1.7	6.7 ±1.8	5.7 ±1.6	0.479
5–7-days after CABG	7.1 ±1.4	7.1 ±1.5	7.0 ±1.3	0.585
CRP [mg/l]:				
At baseline	2.3 (1.5–4.7)	2.3 (1.5–4.8)	2.2 (1.6–4.6)	0.415
18–36 h after CABG	145.5 (102.2–183.8)	153.3 (122.4–180.2)	141.1 (89.8–195.4)	0.861
5–7-days after CABG	50.3 (28.3–80.5)	45.5 (27.1–85.9)	51.7 (29.9–70.1)	0.770
8-iso-PGF <sub>2α</sub> [pg/ml]:				
At baseline	358.4 ±39.3	358.3 ±38.2	358.4 ±41.3	0.994
18–36 h after CABG	466.9 ±42.5	466.4 ±42.9	467.7 ±42.3	0.867
5–7-days after CABG	417.2 ±47.8	424.1 ±49.1	410.4 ±46.0	0.189

Values are displayed as mean ± standard deviation or median with inter-quartile range. IL-6 – interleukin 6, CABG – coronary artery bypass graft surgery, CRP – C-reactive protein, 8-iso-PGF<sub>2α</sub> – 8-iso-prostaglandin F<sub>2α</sub>.

tal death group both before and after CABG, irrespective of the cardioplegia approach used. Inflammatory markers did not differ between patients with and without clinical endpoints, except IL-6, 5–7 days after the procedure (Tab. IV). Regression analysis showed a significant correlation between preoperative concentration of oxidative stress measured by 8-iso-PGF<sub>2α</sub>, and PMI as well as in-hospital cardiovascular death ( $p = 0.047$  and  $p = 0.041$ , respectively).

## Discussion

Our study compares the impact of warm blood cardioplegia versus cold crystalloid cardioplegia on inflammatory and oxidative stress markers as well as clinical outcomes after CABG. For the assessment of systemic inflammation, we measured CRP and fibrinogen as well as IL-6 as the main stimulus for CRP and fibrinogen production in the liver. 8-iso-PGF<sub>2α</sub> was analyzed as a stable and reliable biomarker of oxidative stress. In this study, neither cardioplegic solution was found to have a greater effect on inflam-

matory and oxidative stress markers after CABG surgery. Both cardioplegic solutions were associated with a similar, significant increase in the studied markers after the procedure. Moreover, our study failed to demonstrate any advantage of either cardioplegia in terms of PMI and in-hospital mortality. In addition, both clinical endpoints correlated only with pre- and postoperative levels of oxidative stress.

Systemic inflammatory response and enhanced reactive oxygen species formation could be a consequence of, among other things, surgical trauma, manipulation of the heart, cardiopulmonary bypass, pericardial suction or genetic predisposal [2]. Cardioplegic heart arrest and then reperfusion of the ischemic myocardium after CABG can further aggravate oxidative stress and the inflammatory response. In the experimental studies, cardiac myocytes, when exposed to ischaemia or myocardium arrested by cold crystalloid cardioplegia, have been shown to produce IL-6 [12–14]. Additionally, IL-6 and reactive oxygen species are also produced by the heart during the CABG procedure

**Tab. IV.** Changes of studied inflammatory response and oxidative stress parameters in patients with analyzed clinical endpoints

Variable	All patients (N = 238)	Patients without PMI (n = 218)	Patients with PMI (n = 20)	P-value	Survivors (n = 230)	In-hospital death (n = 8)	P-value
IL-6 [pg/ml]:							
At baseline	2.1 (1.1–4.0)	2.0 (1.2–4.6)	3.3 (1.9–3.9)	0.536	2.0 (1.1–3.9)	3.7 (2.6–4.4)	0.491
5–7-days after CABG	14.6 (5.2–23.9)	14.4 (5.9–22.1)	18.8 (11.2–32.7)	0.030	14.5 (5.2–23.8)	36.5 (18.2–49.7)	0.242
Fibrinogen [g/l]:							
At baseline	4.2 ±1.2	4.2 ±1.2	4.5 ±1.1	0.283	4.2 ±1.2	4.2 ±0.9	0.948
18–36 h after CABG	6.3 ±1.7	5.5 ±1.7	6.0 ±1.9	0.398	5.6 ±1.7	5.6 ±1.7	0.997
5–7-days after CABG	7.1 ±1.4	7.1 ±1.4	6.5 ±1.7	0.355	7.1 ±1.4	5.7 ±0.9	0.081
CRP [mg/l]:							
At baseline	2.3 (1.5–4.7)	2.3 (1.5–4.6)	2.6 (1.6–5.1)	0.958	2.2 (1.5–4.6)	3.3 (2.2–12.6)	0.546
18–36 h after CABG	145.5 (102.2–183.8)	144.3 (101.7–181.0)	170.4 (149.1–193.9)	0.213	144.8 (101.9–181.2)	181.6 (168.6–212.3)	0.072
5–7-days after CABG	50.3 (28.3–80.5)	48.3 (27.8–73.0)	85.3 (67.2–94.1)	0.174	49.2 (28.3–75.4)	94.0 (44.5–96.1)	0.265
8-iso-PGF <sub>2α</sub> [pg/ml]:							
At baseline	358.4 ±39.3	355.6 ±37.2	388.6 ±50.3	0.003	356.4 ±37.8	407.7 ±48.1	0.001
18–36 h after CABG	466.9 ±42.5	463.08 ±37.3	505.6 ±67.5	< 0.001	463.8 ±39.2	545.4 ±51.2	< 0.001
5–7-days after CABG	417.2 ±47.8	409.5 ±37.4	539.6 ±15.5	< 0.001	412.8 ±42.4	538.0 ±21.0	< 0.001

Values are displayed as mean ± standard deviation or median with inter-quartile range. IL-6 – interleukin 6, CABG – coronary artery bypass graft surgery, CRP – C-reactive protein, 8-iso-PGF<sub>2α</sub> – 8-iso-prostaglandin F<sub>2α</sub>.

[2, 12]. Some studies have shown that elevated IL-6 plasma concentrations are associated with negative inotropic effects and myocardial damage after reperfusion [15]. These studies are consistent with our findings. We also observed a significant increase of IL-6 after CABG, which was also irrespective of the type of cardioplegia.

Several strategies are still being introduced to cardiac surgery and anesthetic techniques to reduce the signs of the inflammatory response and oxidative stress [4, 9, 16]. These include, among others, reintroduction of off-pump CABG surgery during the first decade of the 21<sup>st</sup> century and introduction of different types of cardioplegia. The impact of cardiopulmonary bypass on systemic inflammation remains a matter of debate. Our previous study validated the concept that mechanisms other than cardiopulmonary bypass are responsible for the increased postoperative inflammatory response [8].

Little is known about the effects of blood and crystalloid cardioplegia on the systemic inflammatory response as well as the level of oxidative stress, and the results are inconclusive [4–6, 9]. The current findings provide evidence that there is no difference in systemic inflammatory response and level of oxidative stress between blood and crystalloid cardioplegia. Besides, among analyzed markers, only preoperative concentration of 8-iso-PGF<sub>2α</sub> positively correlated with occurrence of PMI and in-hospital mortality. On the other hand, we did not observe a correlation of PMI or mortality with type of cardioplegia. These conclusions appear to be similar to other studies [17, 18]. In contrast

to our outcomes, other authors observed a significant decrease of at least one analyzed clinical end point after using blood cardioplegia [19, 20]. Thus, the literature is far from conclusive, and additional studies are needed to assess the superiority of one cardioplegia over another. These discrepancies in the results could be explained at least partially by some differences in the composition of cardioplegic solutions, various patient characteristics and slightly different criteria for the diagnosis of PMI.

This study has several limitations. It is an analysis of data collected in a single center. The sample size of the analyzed group was limited and restricted to CABG patients. The IL-6, fibrinogen, CRP and 8-iso-PGF<sub>2α</sub> concentrations were measured just at two or three time points. It is likely that a stricter measurement schedule, with more time points, could more precisely visualize time-dependent changes in studied markers. The patients were enrolled before 2011, when a new model of risk evaluation was developed, and for all of them EuroSCORE I was calculated. The EuroSCORE I values were low as only elective, isolated CABG patients, without previous history of cardiac surgery and without renal or liver function impairment, were recruited. Thus, the results of this study cannot be extrapolated to high-risk or urgent patients, in whom an acute phase reaction is usually more powerful. Also, the influence of coronary artery disease severity and epicardial blood flow as well as platelet activation on the inflammatory response in different cardioplegia strategies was not analyzed [21–25]. The low incidence of PMI and in-hospital

mortality in our study render these clinical outcomes less reliable. Clinical aspects of different cardioplegia strategies were beyond the scope of this study, since a much larger cohort should be recruited for such analysis. Finally, our study was limited to the hospital stay. Long-term follow-up might provide new insights into the associations between the degree of oxidative stress and perioperative inflammatory response and prognosis after CABG surgery.

## Conclusions

Our study extends previous reports by showing that the type of cardioplegia does not affect specifically the systemic inflammatory response as well as oxidative stress reflected by changes in IL-6, fibrinogen, CRP and 8-iso-PGF<sub>2α</sub> following the CABG procedure. To our knowledge, this study is the first to assess these variables in patients undergoing CABG using different types of cardioplegia. It might be speculated that preoperative screening of oxidative stress could be helpful in identifying patients at increased risk of an unfavorable post-CABG course. Further, larger studies are needed to validate our observations.

## Disclosure

Authors report no conflict of interest.

## References

- Collard CD, Gelman S. Pathophysiology, clinical manifestations, and prevention of ischemia-reperfusion injury. *Anesthesiology* 2001; 94: 1133-1138.
- Matata BM, Galinanes M. Cardiopulmonary bypass exacerbates oxidative stress but does not increase proinflammatory cytokine release in patients with diabetes compared with patients without diabetes: regulatory effects of exogenous nitric oxide. *J Thorac Cardiovasc Surg* 2000; 120: 1-11.
- Yamamoto H, Yamamoto F. Myocardial protection in cardiac surgery: a historical review from the beginning to the current topics. *Gen Thorac Cardiovasc Surg* 2013; 61: 485-496.
- van Boven WJ, Gerritsen WB, Driessen AH, Morshuis WJ, Waanders FG, Haas FJ, van Dongen EP, Aarts LP. Myocardial oxidative stress, and cell injury comparing three different techniques for coronary artery bypass grafting. *Eur J Cardiothorac Surg* 2008; 34: 969-975.
- Kalawski R, Baliński M, Bugajski P, Wysocki H, Olszewski R, Siminiak T. Stimulation of neutrophil activation during coronary artery bypass grafting: comparison of crystalloid and blood cardioplegia. *Ann Thorac Surg* 2001; 71: 827-31.
- Kalawski R, Deskur E, Bugajski P, Wysocki H, Siminiak T. Stimulation of neutrophil integrin expression during coronary artery bypass grafting: comparison of crystalloid and blood cardioplegic solutions. *J Thorac Cardiovasc Surg* 2000; 119: 1270-1277.
- Plicner D, Mazur P, Sadowski J, Undas A. Asymmetric dimethylarginine and oxidative stress following coronary artery bypass grafting: associations with postoperative outcome. *Eur J Cardiothorac Surg* 2014; 45: 136-141.
- Wypasek E, Stepień E, Kot M, Plicner D, Kapelak B, Sadowski J, Undas A. Fibrinogen beta-chain-C148T polymorphism is associated with increased fibrinogen, C-reactive protein, and interleukin-6 in patients undergoing coronary artery bypass grafting. *Inflammation* 2012; 35: 429-435.
- ESC/EACTS Guidelines on myocardial revascularization. Available at <http://www.escardio.org/Guidelines-&Education/Clinical-Practice-Guidelines/ESC-EACTS-Guidelines-in-Myocardial-Revascularisation-Guidelines-for>.
- Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *Eur Heart J* 2007; 28: 2525-2538.
- Clauss A. Gerinnungsphysiologische Schnellmethode zur Bestimmung des Fibrinogens. [Rapid physiological coagulation method in determination of fibrinogen]. *Acta Haematol* 1957; 17: 237-246.
- Sawa Y, Ichikawa H, Kagisaki K, Ohata T, Matsuda H. Interleukin-6 derived from hypoxic myocytes promotes neutrophil-mediated reperfusion injury in myocardium. *J Thorac Cardiovasc Surg* 1998; 116: 511-517.
- Dreyer WJ, Phillips SC, Lindsey ML, Jackson P, Bowles NE, Michael LH, Entman ML. Interleukin 6 induction in the canine myocardium after cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 2000; 120: 256-263.
- Suleiman MS, Zacharowski K, Angelini GD. Inflammatory response and cardioprotection during open-heart surgery: the importance of anaesthetics. *Br J Pharmacol* 2008; 153: 21-33.
- Zahler S, Massoudy P, Hartl H, Hahnel C, Meisner H, Becker BF. Acute cardiac inflammatory responses to postischemic reperfusion during cardiopulmonary bypass. *Cardiovasc Res* 1999; 41: 722-730.
- Szczurek W, Szyguta-Jurkiewicz B. Oxidative stress and inflammatory markers – the future of heart failure diagnostics? *Kardiochir Torakochir Pol* 2015; 12: 145-149.
- Guru V, Omura J, Alghamdi AA, Weisel R, Fremes S. Is blood superior to crystalloid cardioplegia? A meta-analysis of randomized clinical trials. *Circulation* 2006; 114: 331-338.
- Jacob S, Kallikourdis A, Sellke F, Dunning J. Is blood cardioplegia superior to crystalloid cardioplegia? *Interact Cardiovasc Thorac Surg* 2008; 7: 491-498.
- Dar MI. Cold crystalloid versus warm blood cardioplegia for coronary artery bypass surgery. *Ann Thorac Cardiovasc Surg* 2005; 11: 382-385.
- Zeng J, He W, Qu Z, Tang Y, Zhou Q, Zhang B. Cold blood versus crystalloid cardioplegia for myocardial protection in adult cardiac surgery: a meta-analysis of randomized controlled studies. *J Cardiothorac Vasc Anesth* 2014; 28: 674-681.
- Zalewski J, Bogaerts K, Desmet W, Sinnaeve P, Berger P, Grines C, Danays T, Armstrong P, Van de Werf F. Intraluminal thrombus in facilitated versus primary percutaneous coronary intervention: an angiographic substudy of the ASSENT-4 PCI (Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention) trial. *J Am Coll Cardiol* 2011; 57: 1867-1873.
- Zalewski J, Zmudka K, Musialek P, Zajdel W, Pieniazek P, Kadzielski A, Przewlocki T. Detection of microvascular injury by evaluating epicardial blood flow in early reperfusion following primary angioplasty. *Int J Cardiol* 2004; 96: 389-396.
- Bochenek M, Zalewski J, Sadowski J, Undas A. Type 2 diabetes as a modifier of fibrin clot properties in patients with coronary artery disease. *J Thromb Thrombolysis* 2013; 35: 264-270.
- Pastuszczyk M, Kotlarz A, Mostowik M, Zalewski J, Zmudka K, Undas A. Prior simvastatin treatment is associated with reduced thrombin generation and platelet activation in patients with acute ST-segment elevation myocardial infarction. *Thromb Res* 2010; 125: 382-386.
- Zalewski J, Durak M, Lech P, Gajos G, Undas A, Nessler J, Rosławiecka A, Zmudka K. Platelet activation and microvascular injury in patients with ST-segment elevation myocardial infarction. *Kardiol Pol* 2012; 70: 677-684.