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Changes in the Coagulation System During Surgical Revascularization with and Without Cardiopulmonary Bypass

Zmiany w układzie krzepnięcia i fibrynolizy u pacjentów poddanych rewaskularyzacji wieńcowej z zastosowaniem i bez zastosowania krążenia pozaustrojowego

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Abstract

Background. The OPCAB technique is a well-known alternative to CABG performed with CPB; however, it has been widely discussed whether either technique is superior to the other.
Objectives. The aim of the study was to analyze changes in the coagulation system of patients after CABG with and without CPB.
Material and Methods. Twenty patients (16 male and 4 female, 47–79 years of age) undergoing first-time elective coronary artery bypass grafting were operated with the use of CPB (CPB group) and without it (OPCAB group). Fibrinogen, D-dimer, TAT, prothrombin, and F1+2 concentrations were measured after the induction of anesthesia and 8 hours and 24 hours after surgery.
Results. Initial concentration of TAT was lower in the OPCAB (5.41 μg/l) than in the CPB group (16.66 μg/l, $p = 0.01$). D-dimer concentration appeared to be initially higher in the OPCAB (1128 ng/ml) than in the CPB group (448.8 ng/ml, $p = 0.03$). Platelet count significantly decreased in the CPB group ($p = 0.02$), while in the OPCAB group this did not take place; moreover, when hemodilution was taken into account, an increase was observed. In both the groups the fibrinogen concentration increased ($p = 0.001$ for CPB and $p = 0.00007$ for OPCAB); however, the rise was higher 8 ($p = 0.04$) and 24 ($p = 0.03$) hours after surgery in the OPCAB group. Fibrinogen, prothrombin, and F1+2 concentrations did not vary in either group.
Conclusions. The presented data suggest that there are no significant differences in the activation of the coagulation system in patients undergoing CABG performed with and without CPB (**Adv Clin Exp Med 2007, 16, 4, 507–512**).

Key words: revascularization, coagulation, fibrinolysis, OPCAB, CPB.

Streszczenie

Wprowadzenie. Metoda OPCAB jest powszechnie znaną alternatywą chirurgicznej rewaskularyzacji wieńcowej z użyciem krążenia pozaustrojowego, chociaż wyższość jednej z technik nad drugą jest wciąż przedmiotem dyskusji.
Cel pracy. Analiza zmian w układzie krzepnięcia u pacjentów poddanych zabiegowi CABG z użyciem i bez użycia krążenia pozaustrojowego.
Materiał i metody. Badaniem objęto 20 pacjentów (16 mężczyzn i 4 kobiety w wieku 47–79 lat) poddanych pierwszorazowo planowej chirurgicznej rewaskularyzacji mięśnia sercowego z zastosowaniem maszyny płuco-serce (grupa CPB) i bez jej użycia (grupa OPCAB). Próbki krwi pobierano od pacjentów po indukcji znieczulenia (1), 8 godzin (2) i 24 godziny po zabiegu (3) i oznaczano stężenia fibrynogenu, d-dimerów, TAT, protrombiny i F1+2.
Wyniki. Wyjściowe wartości stężeń TAT były istotnie mniejsze w grupie OPCAB (5,41 μg/L) niż w grupie CPB (16,66 μg/L; $p = 0,01$). Stężenie wyjściowe d-dimerów natomiast w tej grupie okazało się statystycznie istotnie większe (1128 ng/ml) w porównaniu z CPB (448,8 ng/ml; $p = 0,03$). Liczba płytek krwi w grupie CPB zmniejszyła się istotnie w stosunku do wartości wyjściowych ($p = 0,02$), w grupie OPCAB nie obserwowano tego zjawiska,

a nawet po uwzględnieniu rozcieńczenia krwi stwierdzono istotny ich wzrost w 24 godz. od zakończenia zabiegu chirurgicznego. W obu badanych grupach stwierdzono istotne zwiększenie wartości stężenia fibrynogenu (dla CPB $p = 0{,}001$; dla OPCAB $p = 7.12 \times 10^{-05}$). Wzrost ten był istotnie większy w grupie OPCAB w 8 godz. ($p = 0{,}04$) i w 24 godz. od zakończenia zabiegu ($p = 0{,}03$). Nie stwierdzono istotnych statystycznie różnic między stężeniami kompleksów TAT, F1+2, ATIII między obu grupami podczas całego okresu badawczego.
Wnioski. Przedstawione dane sugerują, że nie ma istotnych różnic w aktywacji układu krzepnięcia i fibrynolizy u pacjentów poddawanych rewaskularyzacji wieńcowej z użyciem i bez użycia krążenia pozaustrojowego (**Adv Clin Exp Med 2007, 16, 4, 507–512**).

Słowa kluczowe: rewaskularyzacja, krzepnięcie, fibrynoliza, OPCAB, CPB.

Coronary vascular disease is a type of generalized atheromatic process in the coronary arteries and it is the leading cause of death in developed countries. Nowadays there are two main invasive methods of treating coronary vascular disease: angioplasty of the coronary arteries and surgical procedures [1]. It is worth noting that advances in interventional cardiological techniques have caused a rise in the number of high-risk patients qualified for surgical treatment. One of the routine methods of treating coronary vascular disease is surgical revascularization of the heart muscle with the use of cardiopulmonary bypass (CPB). Efforts to minimize the risk of complications have resulted in the introduction of the OPCAB technique (off-pump coronary artery bypass), which means performing the operation on a beating heart, i.e. without arresting it with cardioplegic solution and without the use of a heart-lung machine.

Although the necessity of performing such operations is without doubt, they are still connected with intra- and post-operative complications, such as bleeding, stroke, and myocardial infarction. Avoiding CPB results in a significant decrease in the number of neurological complications, but does not influence the number of thrombolic events or postoperative bleeding diathesis [4]. The success of a surgical treatment depends on the preservation of the subtle balance between bleeding on the one hand and intravascular coagulation on the other. A crack in the atheromatic plaque causes a local procoagulant state caused by contact of plasma and blood cells with the structures of the blood vessel wall (mainly collagen). In consequence of the activation of the coagulation cascade, this event leads to a generalized procoagulant state. If this occurs, the intensive whole-body atheromatic process is often connected with activation of the coagulation system [2]. Extracorporal circulation can be safely connected only after repression of the coagulation system. This is achieved by the administration of heparin, which may still result in the activation of a local or generalized inflammatory response [7]. In spite of full heparinization, the activation of coagulation, fibrinolysis, and an inflammatory response take place due to the contact of blood with the heart-lung machine's circuits [3, 9]. The consumption of coagulation factors may lead to increased postoperative bleeding [11] and, consequently, a rise in the requirement for transfusion in operated patients as well as the need for surgical re-exploration. These result in increased morbidity and mortality [12, 13].

The OPCAB technique demands half of the dose of heparin used for CABG with CPB. The neutralization of heparin's effect is achieved by protamine sulfate administration, which may cause stimulation of the complement system [6]. The reduced doses of heparin used in OPCAB procedures decrease the need for protamine, which results in a reduction in inflammatory response and a decrease in the activation of coagulation. The use of CPB during surgery is connected with hemodilution, which causes decreases in the concentrations of all the substances contained in blood, including coagulation factors. Surgical trauma (similar in both procedures) is connected with massive tissue impairment and extensive blood loss, which activates the coagulation system and leads to the consumption of its factors. Many researchers suggest that this mechanism is responsible for the hypercoagulable state during OPCAB [5, 8]. Numerous studies still have not definitively answered the question about the influence of the surgical technique on the coagulation system and the complications connected with it.

Material and Methods

Twenty patients qualified for first-time elective coronary surgery and operated on at the Department of Cardiac Surgery Silesian Piasts University of Medicine in Wrocław from November 2004 to May 2005 were studied. The trial was prospective and the non-randomized, patients were informed of the aim of the study and the methods used for the purpose of the research and they signed their consent. The patients were

Table 1. Demographic and preoperative features. Values: mean ± *SD* (range)

Tabela 1. Dane demograficzne i przedoperacyjne badanej grupy pacjentów. Wartości w tabeli: średnia ± odchylenie standardowe (rozpiętość cechy)

Feature (Cecha)	Total group (Cała grupa) n = 20	CPB group (Grupa CPB) n = 10	OPCAB group (Grupa OPCAB) n = 10	CPB/OPCAB p
Age – years (Wiek – lata)	66.45 ± 10.15 (47–79)	64.9 ± 11.36 (47–78)	68 ± 9.12 (54–79)	ns.
Sex – M/F (Płeć – M/K)	16/4	8/2	8/2	ns.
CCS	2.18 ± 0.75	2.0 ± 0.89	2.4 ± 0.55	ns.
EF (%)	55 ± 8.9 (40–68)	54.3 ± 11 (40–68)	56.5 ± 6 (50–65)	ns.

EF – ejective fraction.
CCS – Canadian Cardiovascular Society.

EF – frakcja wyrzutowa lewej komory.
CCS – Canadian Cardiovascular Society.

divided into two groups depending on the type of surgical procedure. In the CPB group, extracorporal circulation was used. In the OPCAB group the operation was performed on a beating heart without the use of CPB. Demographic and preoperative data of all patients are shown in Table 1.

Surgical Technique

In both types of surgery, midline sternotomy was performed. Then the left internal mammary artery (LIMA) was harvested as well as the saphenous vein. In patients qualified for the CPB group, a cardiopulmonary bypass was used. Therefore the patients were administered heparin in a dose of 300–400 IU/kg body weight (bw) to achieve an activated coagulation time (ACT) exceeding 400 s. The next step was cannulation of the ascending aorta and the right atrium and connection of the CPB. The heart was arrested by warm blood cardioplegia (Calafiore protocol). The surgery was performed in normothermia. After the anastomoses were accomplished, the patient was weaned from the CPB and deheparinization was obtained by the administration of protamine sulfate in a dose of 1 mg per 100 IU heparin used.

In the patients of the OPCAB group, after harvesting the LIMA and the saphenous vein, heparin was administered in a dose of 150 UI/kg bw and an ACT level of 250 s was achieved. Local stabilization of the anastomosis site was achieved with the use of a tissue stabilizer (Octopus device, Medtronic). Deheparinization was started and continued until obtaining the initial ACT values (100–120 s).

In all patients, chest closure was performed with metallic sutures and the drainage of the left pleural cavity and pericardial cavity was left. Blood samples were obtained three times: after the induction of anesthesia, 8 h after surgery, and 24 h after surgery. The following parameters were measured: prothrombin, INR, antithrombin III (ATIII), fibrinogen, D-dimers, thrombin-antithrombin complex (TAT), prothrombin fragments F1+2, red blood cell count (RBC), white blood cell count (WBC), hemoglobin (HGB), hematocrit (HCT), platelet count (PLT), activated partial thromboplastin time (APTT), and thrombin time (TT). Postoperative complications, length of stay in the intensive care unit, and the magnitude of bleeding were also analyzed. The laboratory tests were performed with the use of the ELISA method (Enzygnost F1+2 micro and Enzygnost TAT micro, Dade Behring).

Statistics

All the data were statistically analyzed. The differences were evaluated by multivariate analysis of variance supplemented by the Wilcoxon rank test and the Kruskal-Wallis, Friedman, and chi-squared tests. They were considered significant at p values less than 0.05.

Results

There were no significant diversities in the two groups with regard to demographic features (Table 1) and the basic initial parameters (RBC, WBC, HGB, HCT). A higher concentration of D-dimers was noted in patients operated with the OPCAB technique (p = 0.03) and a lower concentration of TAT complexes in this group compared with the CPB group (p = 0.01) (Table 2).

Table 2. Laboratory test results

Tabela 2. Wyniki badań laboratoryjnych

	OPCAB			CPB		
	1	2	3	1	2	3
RBC M/µl	4.44	3.68	3.73	4.33	3.77	3.23
WBC K/µl	6.68	9.96	9.96	6.28	10.51	10.36
HGB g/dL	13.31	10.88	11.12	13.2	11.12	9.92
HCT %	40.82	34.03	34.47	40.28	35.09	30.05
PLT K/µl	227.7	172.2	198.9	208.1	134.46	139.6
PLT corr.	227.7	206.56	235.5	208.1	154.3	187.1
APTT s	35.7	448.31	38.08	30.96	38.43	36.01
TT s	44.48	18.68	15.1	18.94	21.42	15.187
Prothromb.%	84.3	72.1	87.1	88.3	74.5	92
INR	1.125	1.257	1.107	1.082	1.218	1.067
ATIII %	79.9	66.1	7.47	78.2	65.3	72.7
Fibrinogen mg%	396	368	927	341	281	655
D-dimers ng/ml	1128	1199	1214	448.8	960	747
TAT µg/l	5.41	22.42	6.02	16.66	14.75	5.06
F1+2 nmol/l	1.5	1.53	1.39	1.31	1.44	1.44

Table 3. Perioperative data

Tabela 3. Dane okołooperacyjne

	CPB	OPCAB	P
Time of surgery (Czas zabiegu) min	206 ± 22.71	164.5 ± 39.54	< 0.05
Time of CPB (Czas krążenia) min	76.5 ± 22.24	–	–
Time of Ao (Czas zaklemowania) min	34.6 ± 15.36	–	–
No. of grafts (Liczba pomostów)	2.6 ± 0.52	2.0 ± 0.82	ns.
Intensive care (Czas na OIOM) h	12.26 ± 3.75	13.27 ± 6.52	ns.
Bleeding in 24 hours (Krwawienie w ciągu 24 godz.) ml	403.5 ± 96.67	437 ± 158.68	ns.
Transfusions (Przetoczenia)	0.4 ± 0.84	0.4 ± 0.84	ns.
Amines (Aminy)	0.3	0.3	ns.

No significant differences in postoperative outcome in the two groups of patients were observed; the length of stay in the intensive care unit, postoperative bleeding, need for blood transfusion, and the amount of catecholamins administered did not reveal statistically significant differences (Table 3).

Platelet count decreased in both groups of patients in comparison with the initial values; however, when considering the hemodilution it appeared that the number of platelets slightly increased in the OPCAB group and decreased in the CPB group ($p = 0.02$):

$$\text{corrected PLT} = \text{PLT} \times \text{initial HCT/HCT}.$$

The average concentrations of ATIII and their variability did not differ in the two groups. No significant differences in F1+2 and TAT complex concentrations were noted. Fibrinogen concentration, initially a little higher in the OPCAB group, rose significantly in both groups ($p = 0.001$ for CPB, $p = 0.00007$ for OPCAB). The increase was relevantly greater in the OPCAB group. The D-dimer concentration remained constant in the OPCAB group, while in the CPB group it had doubled at the 8th hour and remained 1.6 times higher than the initial value 24 hours after surgery.

Discussion

This study presents preliminary results of comparing two techniques of surgical revascularization of the heart muscle, OPCAB and CABG with CPB, with regard to differences in the activation of coagulation and fibrinolysis. Disturbances in the activation of these systems connected with adaptation of CPB were studied because of bleeding complications disturbing recovery in patients undergoing CABG procedures [15]. Mariani et al. and Engelberger et al. independently studied coagulation system indicators in patients operated on with the OPCAB technique and showed essential growth in the activation of procoagulative factors 24 hours after surgery. These data may suggest the presence of increased risk of thrombosis in aortic-coronary anastomoses and the appearance of pulmonary thrombosis episodes in patients undergoing this type of surgery [18, 20].

Casati et al. observed that both techniques are connected with massive fibrinogen and ATIII consumption within the first 24 hours after surgery [8]. After analyzing the present data, distinct increases in the concentrations of fibrinogen in both studied groups were noted, with a fundamentally higher intensity of this process in the OPCAB group. No crucial differences in the concentration of ATIII were observed. Throughout the whole postoperative period a significant decrease in the platelet count was noticed only in the CPB group. Casati et al. noted a 24% drop in platelet count in patients from their CPB group considering hemodilution. The platelet count 24 h after surgery in the CPB group was still much higher than in the OPCAB group [8]. The above is contrary to the observations of Lo et al., who noticed a 40% drop in the number of platelets in the CPB group right after the surgery, but correction for hemodilution revealed no differences between the groups [17].

In the present study the concentration of D-dimers in the OPCAB group did not show an essential increase up to the end of the observation period, while in the CPB group the rise was twice as high as the initial values. The activation of fibrinolysis after the use of CPB has been described many times as a result of activation of the extrinsic as well as intrinsic pathways (factor XII and calicrein). Such a phenomenon was observed both by Casati et al. and Engelberger et al. [8, 18]. Vedin, noticing an increased level of D-dimers in a CPB group, suggested that apart from the increased activation of coagulation and fibrinolysis during the use of CPB, a higher D-dimer concentration may also be a result of administration of large doses of heparin [19].

Increases in the concentration of F1+2 in patients undergoing CABG with CPB has been commonly observed [7, 16, 17, 19], while in patients undergoing OPCAB procedure such results were not noted. This is probably due to less activation of coagulation and lower doses of heparin used. The results of the present study, however, do not show any differences in the concentration of F1+2 in the two studied groups. TAT concentration varied greatly in both groups. In the OPCAB group a significant rise in this parameter was observed at the three studied time periods, while in the CPB group a considerable decrease was noted.

Parolari et al. had different results. They noted continuous increases in TAT concentrations in both groups of patients [16]. The activation of coagulation and fibrinolysis takes place in patients undergoing both types of surgery to the same extent. However, these processes are delayed in the OPCAB group compared with the CPB group and, as other authors' observations show, achieve comparable intensity on the fourth day after surgery. These data suggest that avoiding CPB protects only from the early thrombotic complications [16, 17].

Numerous studies on the comparison of the two types of surgical revascularization of the heart muscle, OPCAB and CABG with CPB, suggest some clinical tendencies, such as reduced blood loss and less need for transfusion after OPCAB surgeries [14] as well as a smaller number of neurological complications and renal insufficiency symptoms in this group [10]. Nevertheless, it has not been definitely demonstrated that one of these techniques is superior to the other. This problem still needs further examination, and it is reasonable to continue this work on extended material and with longer observation times.

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