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Production of Reactive Oxygen Species and Antioxidant Defense Systems in Patients after Coronary Artery Bypass Grafting: One-Week Follow-up Study*

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Objectives: Great cardiac surgery performed with cardiopulmonary bypass is associated with systemic inflammatory response which is characterised by an extensive overproduction of reactive oxygen species, too. This oxidative stress draws off the endogenous stores of antioxidant systems and usually evokes a decrease of antioxidant status of the organism. According to the recent observations, the new off-pump method is less harmful and evokes only moderate systemic inflammatory reaction.

Aim of study: Follow-up of patients with low and high left ventricular ejection fraction undergoing on-pump or off-pump cardiac surgery (coronary artery bypass grafting) in course of the first postoperative week.

Patients and methods: Forty-one patients were divided in four groups according to their left ventricular function (patients with low or high left ventricular ejection fraction) and to the surgical technique used (with or without cardiopulmonary bypass). Immediately before surgery and in course of the first postoperative week, samples of central venous line were drawn and some parameters of oxidative metabolism were analysed: plasma levels of total antioxidant status (TAS) and thiobarbituric acid reactive substances (TBARS) as well as the erythrocyte activities of superoxide dismutase (SOD) and glutathione peroxidase (GPx).

Results: Patients undergoing surgical myocardial revascularisation – regardless of the grade of their cardiac dysfunction or of the kind of surgical technique used – revealed a marked decrease of TAS even at the preoperative period that did not change substantially during the early postoperative period. In the group of patients with high left ventricular ejection fraction a tendency to further decrease of plasma levels of TAS was observed. Despite of negligible changes of the plasma levels of TBARS, during the short postoperative period markedly decreased activities of SOD and only non-significantly increased activities of GPx were demonstrated in the whole cohort of investigated patients.

Conclusions: Patients with coronary artery disease undergoing surgical revascularisation (coronary artery bypass grafting) revealed a marked decrease of antioxidant capacity before and after surgical event. The extensive treatment of these patients with antioxidant drugs and vitamins was recommended even in the preoperative period. *J Clin Basic Cardiol* 2005; 8: 33–6.

Key words: coronary artery bypass grafting, on-pump and off-pump cardiac surgery, antioxidant defense systems, thiobarbituric acid reactive substances

More or less expressive systemic inflammatory response is a regular pathophysiological reaction which is predominantly due to cardiopulmonary bypass (CPB) (on-pump technique) used in great cardiac surgery [1]. Nevertheless, there are also many other adverse events associated with this on-pump-technique – increased infection-related morbidity as well as neurologic, renal, and pulmonary dysfunctions [2]. Cardioplegia and subsequent reperfusion of the ischaemised heart evoke ischaemia-reperfusion injury and systemic inflammation response which are associated with increased production of cytotoxic reactive oxygen species (ROS). It has been demonstrated that this kind of substances may have some deleterious effects on heart function and that this negative influence of ROS can be attenuated by an increase of effective antioxidant defense of patient's organism [3].

Recently, some authors demonstrated that a novel method – cardiac surgery on beating heart which is performed without cardiopulmonary bypass (off-pump technique) – is generally considered – in comparison with the on-pump method – as more safe and less harmful for the patient with very low degree of postoperative morbidity and mortality [2, 4, 5]. Benefit of off-pump operation for CABG was also demonstrated by markedly lower levels of troponin T and CK-MB compared with the on-pump technique [6, 7]. Among the most important advantages of off-pump cardiac surgery is the alleviation of systemic inflammatory response which belongs to the deleterious concomitant events in patients undergoing car-

diac operations [8, 9]. Although operative trauma in off-pump surgery performed by full median sternotomy is similar to conventional on-pump technique, the ischaemia-reperfusion injury is considered to be reduced and some contact between cellular and humoral blood components and arteficial surfaces of extracorporeal circulation circuit is missing. This fact is important, since both last mentioned events are associated with leukocyte and endothelial activation as factors involved in the development of systemic inflammation response syndrome. Activated neutrophils through NADPH-oxidase systems and activity of myeloperoxidase generate ROS causing extracellular damage in order to facilitate migration of neutrophils into tissues [10, 11].

Recently, some authors have demonstrated a beneficial effect of off-pump coronary artery surgery in high-risk patients with low left ventricle function and in elder group of patients [12, 13]. Advantages of off-pump technique used in these patients were manifested by significant shorter ICU stay, better preservation of the renal function and reduction of the length of hospital stay in comparison with the CABG surgery performed with CPB [14].

The aim of the current study was to compare some biochemical parameters of oxidative stress and antioxidant defense systems in patients with high and low left ventricular function undergoing coronary artery surgery with and without cardiopulmonary bypass. Until now, these parameters were ana-

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lysed only during the operation and immediately after weaning of CPB. In this study we have concentrated our attention to the early postoperative period, since possible continuation of further increase in the production of ROS and the impairment of antioxidant could be of importance for the intensification of systemic inflammatory response and for some disturbances due to ischaemia-reperfusion injury.

Patients and Methods

Forty-one patients indicated for elective coronary surgery were included in this study. According to the previous exact clinical investigation patients were divided into four groups: patients with very low left ventricular ejection fraction (LVEF) undergoing coronary artery bypass grafting (CABG) by on-pump or off-pump technique and patients with high LVEF undergoing the same kinds of cardiosurgery. Clinical and perioperative characteristics of these patients are shown in Table 1.

Patients were pretreated and on-pump and off-pump cardiac surgery were performed by standard schedule and operative techniques used in our institute and described in our previous paper [15].

Twenty-four individuals without any clinical documented cardiovascular, hepatic or renal disturbances were investigated as control group (group C).

Samples of venous blood were collected immediately before surgery and then at the first, third, fifth, and seventh days of the early postoperative hospital stay of patients. Blood samples in plastic tubes containing lithium salt of heparin were immediately centrifuged in a refrigerated centrifuge (3,000 g – 5 minutes at 4 °C), blood plasma and pre-washed erythrocytes were then stored in a refrigerator at –20 °C until assay.

In the collected samples the following biochemical markers of reactive oxygen species (ROS) and antioxidant defense systems were estimated:

- plasma thiobarbituric reactive substances (TBARS) as representatives of ROS (on the basis of malondialdehyde concentration) [16]
- plasma total antioxidant status (TAS) (diagnostic set of RANDOX Laboratories, Ltd, U.K.)
- erythrocyte superoxide dismutase (SOD) activity (diagnostic set of RANDOX Laboratories, Ltd, U.K.)
- erythrocyte glutathione peroxidase (GPx) activity (diagnostic set of RANDOX Laboratories, Ltd, U.K.)

Plasma levels of TBARS and TAS were calculated with respect to the standard haematocrit value of 0.40. Erythrocyte activities of SOD and GPx were expressed in IU per gram of haemoglobin.

Data are presented as arithmetic means of individual measured values and their standard errors (S.E.M.) and statistically evaluated by two-tailed unpaired t-test (Statgraphics).

Results

There were no significant peri- and postoperative complications in any group of operated patients. After CABG the LVEF value raised significantly in the group of low-LVEF patients operated with off- as well as on-pump technique by 29 % ($p < 0.05$) and 37 %, resp. ($p < 0.01$). In the groups of patients with a high LVEF the postoperative LVEF values were not substantially different in respect to the preoperative values regardless of the operative technique used (Table 1).

Comparing the values of biochemical parameters in control group of individuals, a significant decreased level of TAS in all four groups of operated patients were demonstrated not only preoperatively (Table 2), but also in course of the first postoperative week without any tendency to draw closer to the control values (Table 3). On the other hand, we had found no significant differences in the TBARS levels of operated patients neither preoperatively nor in the course of early postoperative period (Table 4).

Table 1. Clinical characteristics of patients with low and high left ventricular ejection fraction (LVEF) undergoing coronary artery bypass grafting with or without cardiopulmonary bypass (CPB)

	Low LVEF		High LVEF	
	– CPB	+ CPB	– CPB	+ CPB
Patients (n)	9	8	10	14
Age (years)	58.6 ± 3.86	56.0 ± 2.04	52.6 ± 3.88	64.1 ± 2.19
N.Y.H.A. classification	4-III, 5-IV	4-III, 4-IV	4-II, 6-III	4-II, 9-III, 1-IV
LVEF (%) before	23.7 ± 2.06	25.1 ± 0.78	57.1 ± 2.29	50.8 ± 1.78
LVEF (%) after	30.6 ± 2.75 ^x	34.4 ± 1.98 ^{xx}	54.4 ± 2.88	53.4 ± 1.94
CPB (min)	–	84.7 ± 6.83	–	62.9 ± 5.11 ^x
Ao-cross clamp (min)	–	46.7 ± 3.49	–	38.6 ± 3.64
Grafts (n)	1.25 ± 0.02	3.13 ± 0.30	1.10 ± 0.01	2.79 ± 0.21

Statistical significance – LVEF before vs. after surgery or CPB low LVEF vs. high LVEF: ^x $p < 0.05$, ^{xx} $p < 0.001$

Table 2. Plasma levels of total antioxidant status (TAS) and thiobarbituric acid reactive substances (TBARS) as well as erythrocyte activities of superoxide dismutase (SOD) and glutathione peroxidase (GPx) in the control subjects (group C) and in patients with low and high left ventricular ejection fraction (LVEF) before cardiac surgery performed with or without cardiopulmonary bypass (CPB)

	Group C	Low LVEF		High LVEF	
		+ CPB	– CPB	+ CPB	– CPB
TAS (mmol/l)	1.83 ± 0.25	1.24 ± 0.13 ^a	1.05 ± 0.09 ^a	1.02 ± 0.05 ^b	1.14 ± 0.13 ^a
TBARS (mmol/l)	2.05 ± 0.09	2.42 ± 0.24	2.17 ± 0.24	2.28 ± 0.32	2.44 ± 0.24
SOD (IU/g Hb)	670.8 ± 20.93	N.E. 544.8	±18.72 ^b	528.0 ± 21.54 ^c	537.3 ± 30.02 ^b
GPx (IU/g Hb)	40.3 ± 3.98	38.8 ± 3.08	43.6 ± 3.96	44.8 ± 2.94	48.5 ± 2.94

N.E. – not estimated; Statistical significance vs. group C: ^a $p < 0.05$, ^b $p < 0.01$, ^c $p < 0.001$

Table 3. Total antioxidant status (mmol/l) of patients with low and high left ventricular ejection fraction (LVEF) undergoing coronary artery bypass grafting (CABG) surgery with and without cardiopulmonary bypass (CPB) in the course of early postoperative period

Days after CABG	Low LVEF		High LVEF	
	+ CPB	– CPB	+ CPB	– CPB
1	1.32 ± 0.13	1.13 ± 0.12	1.09 ± 0.04	0.90 ± 0.03
3	1.17 ± 0.12	1.27 ± 0.11	1.11 ± 0.04	0.91 ± 0.04
5	1.10 ± 0.08	1.16 ± 0.13	1.01 ± 0.05	0.87 ± 0.01
7	1.18 ± 0.09	1.05 ± 0.10	0.94 ± 0.05	0.91 ± 0.03

Table 4. Plasma levels of thiobarbituric acid reactive substances (mmol/l) in patients with low and high left ventricular ejection fraction (LVEF) undergoing coronary artery bypass grafting (CABG) surgery with and without cardiopulmonary bypass (CPB) in the course of early postoperative period

Days after CABG	Low LVEF		High LVEF	
	+ CPB	– CPB	+ CPB	– CPB
1	2.16 ± 0.28	1.96 ± 0.15	2.16 ± 0.24	1.96 ± 0.31
3	2.24 ± 0.27	1.93 ± 0.22	2.22 ± 0.16	2.06 ± 0.26
5	2.30 ± 0.41	1.86 ± 0.17	2.24 ± 0.20	2.15 ± 0.14
7	2.22 ± 0.21	1.93 ± 0.23	2.28 ± 0.20	2.13 ± 0.17

Unlike the non-significant changes of erythrocyte GPx activity (Table 5), a highly significant decrease of erythrocyte SOD activity in the three groups of patients (in patients with very low LVEF undergoing off-pump operation this parameter was not estimated) even preoperatively and also in the early postoperative period in comparison with the SOD activity in control subjects (Table 6) was found.

Discussion

Generally, off-pump cardiac surgery belongs now to the very often used methods for coronary artery bypass grafting. Several authors demonstrated that this method – compared with the on-pump technique – is more safe and has many advantages especially in elder high-risk patients: it is associated with less postoperative complications and the majority of patients operated with off-pump technique have also a shorter ICU and hospital stay [14, 17–19]. On the other hand, the myocardial revascularisation of patients operated with off-method is more incomplete and this fact might be a future disadvantage [20]. Our presented data have confirmed this ascertainment: in the group of off-pump operated patients, the number of distal anastomoses was significantly lower compared with the patients undergoing coronary artery bypass grafting using cardiopulmonary bypass. In our study only one to two coronary artery bypass grafts were performed in the majority of patients operated by off-pump technique, regardless to their preoperative left ventricular function.

Reduction of ischaemia-reperfusion injury and blood circulation without contact with arteficial surfaces which is obligatory in on-pump method belong to the main merits of off-pump cardiac surgery. This situation is responsible for the decreased systemic antiinflammatory response of the organism and could be also one of the factors for decline of the ROS production by activated neutrophils and other competent cells. Therefore, we have turned our attention to the substances that represented the production of ROS and also to the pool of antioxidant defense systems of patients with different left ventricular function undergoing on-pump or off-pump coronary artery bypass grafting. These parameters – especially the production of lipid peroxides – have been already analysed by various authors, but only perioperatively

Table 5. Erythrocyte glutathione peroxidase activity (IU/g Hb) in patients with low and high left ventricular ejection fraction (LVEF) undergoing coronary artery bypass grafting (CABG) surgery in the course of early postoperative period

Days after CABG	Low LVEF		High LVEF	
	+ CPB	– CPB	+ CPB	– CPB
1	49.9 ± 6.07	38.4 ± 3.05	49.6 ± 3.11	50.9 ± 2.43
3	48.5 ± 4.66	45.4 ± 1.79	53.2 ± 2.94	56.2 ± 4.17
5	40.6 ± 4.84	52.5 ± 3.76	49.1 ± 2.10	49.1 ± 4.99
7	39.0 ± 1.63	48.2 ± 5.36	47.7 ± 2.85	48.8 ± 3.56

Table 6. Erythrocyte superoxide dismutase activity (IU/g Hb) in patients with low and high left ventricular ejection fraction (LVEF) undergoing coronary artery bypass grafting (CABG) surgery with and without cardiopulmonary bypass (CPB) in the course of early postoperative period

Days after CABG	Low LVEF		High LVEF	
	+ CPB	– CPB	+ CPB	– CPB
1	545.9 ± 25.95	N.E.	493.2 ± 26.04	540.5 ± 26.81
3	570.4 ± 19.66	N.E.	488.8 ± 29.21	555.4 ± 21.80
5	594.3 ± 31.04	N.E.	517.6 ± 19.49	555.8 ± 28.25
7	569.9 ± 33.11	N.E.	503.0 ± 30.83	554.7 ± 24.93

N.E. – not estimated

and during the very early postoperative period. In our study, the biochemical parameters of oxidative stress and of antioxidant capacity were analysed from the first to the seventh days after surgery. In all four groups of patients this time period was not characterised by ongoing increased production of ROS: during the seven days after surgery there were no significant differences of TBARS levels in comparison with their preoperative values and with the levels of this parameter in the control subjects.

On the other hand, we have found highly significant decreased levels of TAS in all patients investigated already preoperatively and in the further postoperative period. This finding of decreased antioxidant capacity of patients undergoing elective cardiac surgery agreed with our previous results obtained in patients with cardiomyopathies and in subjects before and after heart transplantation [21–23]. A decreased level of TAS was associated with the significant decreased erythrocyte superoxide dismutase activity, an enzyme that catalyses the removal of superoxide anion. These findings call attention on insufficient food intake of antioxidant substances in patients with moderate or severe impairment of heart function which is associated with the presence of increased oxidative stress.

Interestingly, we did not find any significant differences either in the levels of TBARS or in antioxidant defense systems in patients with very low and high left ventricular function undergoing on-pump or off-pump coronary artery surgery. We suggest that this situation reflects the long-lasting inadequate antioxidant reserves in the whole cohort of investigated patients.

We conclude that the long-lasting increase in production of reactive oxygen species in patients with cardiomyopathies and heart failure significantly exhausted their antioxidant reserves which could be an additional mechanism in worsening the course of present disease. Therefore, we propose to insert the regular and sufficient intake of antioxidant substances (i.e. antioxidant vitamins, coenzyme Q₁₀) in the long-term treatment schedule of these patients.

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