Egyptian Journal of Anaesthesia

ISSN: (Print) 1110-1849 (Online) Journal homepage: https://www.tandfonline.com/loi/teja20

The cytokine balance during CABG surgery with and without cardiopulmonary bypass

Samia R. El Azab, Nagwa Doha, Ayman Rady, Abeer E. El-Sayed & Mahmoud Abd-Rabo

To cite this article: Samia R. El Azab, Nagwa Doha, Ayman Rady, Abeer E. El-Sayed & Mahmoud Abd-Rabo (2010) The cytokine balance during CABG surgery with and without cardiopulmonary bypass, Egyptian Journal of Anaesthesia, 26:4, 281-286, DOI: 10.1016/j.egja.2010.05.003

To link to this article: https://doi.org/10.1016/j.egja.2010.05.003

Egyptian Journal of Anaesthesia (2010) **26**, 281–286

Egyptian Society of Anesthesiologists

Egyptian Journal of Anaesthesia

www.elsevier.com/locate/egja
www.sciencedirect.com

Research Article

The cytokine balance during CABG surgery with and without cardiopulmonary bypass

Samia R. El Azab [a,b], Nagwa Doha [c,*], Ayman Rady [c], Abeer E. El-Sayed [d], Mahmoud Abd-Rabo [e]

[a] *Department of Anaesthesiology & Intensive Care, King Fahd Specialist Hospital, Burraydah, Saudi Arabia*
[b] *Department of Anaesthesiology & Intensive Care, Al Azhar University for Girls, Cairo, Egypt*
[c] *Department of Anaesthesiology, Al Monofia University, Egypt*
[d] *Department of Microbiology & Immunology, Faculty of Medicine, Suez Canal University, Egypt*
[e] *Department of Cardiothoracic Surgery, Zagazig University, Egypt*

Received 15 April 2010; accepted 19 May 2010

KEYWORDS

Inflammatory response;
Off-pump CABG;
Cytokines;
Cardiac surgery

Abstract *Background:* We investigated the cytokine response during coronary artery bypass grafting (CABG) surgery with and without cardiopulmonary bypass (off-pump) and the effect on patient's outcome in the early postoperative period.
Methods: Eighteen patients were studied, 9 patients undergoing off-pump surgery (group 1) and 9 patients with CPB (group 2). Demographic and preoperative characteristics were comparable in both groups. Plasma levels of TNF-α, IL-6, IL-8, IL-10, IL-4, tumour necrosis soluble receptors-1 (TNFsr-1) and tumour necrosis soluble receptors-2 (TNFsr-2) were measured before skin incision (*T*0), before revascularization (*T*1), after revascularization (*T*2), 2 h (*T*3) and 24 (*T*4) hours after skin closure. Levels of myocardial enzymes were also measured in the first postoperative morning.
Results: Serum levels of TNF-α and IL-8 increased in group 2 at *T*3 and *T*4 more than at *T*0 ($p < 0.05$). IL-6 increased in both groups with higher levels in group 2 than in group 1 at *T*3 (773 ± 331 vs 315 ± 189 pg/ml; $p < 0.05$). IL-10 was higher in group 2 than in group 1 at *T*2 (115 ± 119 vs 13 ± 4 pg/ml; $p < 0.001$) and at *T*3 (212 ± 171 vs 31 ± 29 pg/ml; $p < 0.05$). At

* Corresponding author. Address: Department of Anesthesiology and Critical Care, Menoufyia University Hospital, Shebin Elkom, Egypt. Tel.: +20 0106235642.
E-mail address: nagwamohameddoha@yahoo.com (N. Doha).

Peer review under responsibility of Egyptian Society of Anesthesiologists.
doi:10.1016/j.egja.2010.05.003

Production and hosting by Elsevier

*T*3 levels of TNFsr-1 and TNFsr-2 were higher in group 2 than in group 1 (TNFsr-1 4858 ± 1325 vs 2089 ± 584 pg/ml; $p < 0.01$ and TNFsr-2 4971 ± 63 vs 3801 ± 738 pg/ml; $p < 0.05$). Production of IL-4 did not increase in neither group. The length of ICU stay was less in group 1 than in group 2 (52 ± 33 vs 26 ± 11 h; $p < 0.05$) as well as was the length of hospital stay (7.1 ± 0.4 vs 5.3 ± 0.5 days; $p < 0.001$).

Conclusion: Off-pump procedure evoked a lower cytokine response than CABG with CPB. This minimised myocardial damage and shorten the stay in the ICU and the hospital.

1. Introduction

The use of beating heart coronary artery bypass grafting or off-pump (OP-CAB) surgery has become more popular and widely used. One of the chief reasons for contemporary interest in the OP-CAB is the desire to minimise the inflammatory response and to avoid the deleterious systemic effects of the extracorporeal circulation. Despite the theoretical advantage, however, it has been reported that OP-CAB also elicits marked systemic inflammatory response [1,2], even to a similar degree as in on-pump coronary artery bypass graft surgery (CABG) [3–5].

Studies concerning the different inflammatory and cytokine responses between CABG surgery with and without CPB are also conflicting. In two published studies it was found that the levels of IL-6 were comparable in the two groups [6,7], while Struber et al. reported lower IL-6 levels in the off-pump group [8]. Further, Wei et al. [9] and Orhan et al. [10] found that the TNF-α production did not differ in patients undergoing CABG with or without CPB but other studies revealed that levels of TNF-α were lower in OP-CAB surgery [11,12]. Most of the previous studies were concerned mainly with the pro-inflammatory cytokines. To our knowledge there is no study reporting the inflammatory with the anti-inflammatory cytokine responses of two groups of patients undergoing multivessel CABG surgery with and without CPB. We designed a prospective randomised study to investigate plasma levels of the inflammatory cytokines TNF-α, IL-6 and IL-8 and the anti-inflammatory cytokines IL-10, IL-4, TNFsr-1 and TNFsr-2 response during and after CABG with and without CPB and the effect on the early postoperative patient's outcome and the length of stay in the ICU an the hospital.

2. Patients and methods

Eighteen patients undergoing elective CABG surgery were randomised for this study. The study was approved by the Ethical Committee of of King Fahd Specialist Hospital – Burraydah and all patients gave their informed consents. Exclusion criteria were severely impaired left ventricular function (ejection fraction <40%), pulmonary disease, severe systemic non-cardiac disease, renal or liver impairment, insulin dependent diabetes, recent myocardial infarction (<6 weeks), infectious disease before operation or patients under corticosteroid or other immunosupressive treatment. On the morning of the operation, patients were randomly selected to either group 1 or group 2; group 1 (9 patients) for off-pump CABG and group 2 (9 patients) for conventional CABG with CPB. Cardiac medications including beta-adrenergic blocking agents, calcium-channel blocking agents and nitrates were continued until the morning of surgery.

All patients were premedicated with lorazepam 40 μg kg^{-1} orally the night of the operation and morphine sulphate 70 μg kg^{-1} and scopolamine 8 μg kg^{-1} intramuscularly 1 h before the operation. Anaesthesia was induced with sufentanil 2 μg kg^{-1} and midazolam 0.15 mg kg^{-1} and maintained with sufentanil 1.0 μg kg^{-1} h^{-1} and midazolam 0.12 mg kg^{-1} h^{-1}. In the two groups tracheal intubation was facilitated with pancuronium bromide 0.1 mg kg^{-1}. A bolus dose of sufentanil 0.5 μg kg^{-1} was given before skin incision. No acute normovolaemichaemo dilution was allowed, and no corticosteroids were given before, during or after the operation. Patients were ventilated with oxygen/air (inspired oxygen fraction = 0.5) with a tidal volume of 5–7.5 ml kg^{-1} aiming at normocapnia. After completion of surgery patients were transferred to the intensive care unit.

2.1. Off-pump technique (group 1)

A standard median sternotomy was performed. A retractor (CTS/Guidant Cupertino California) was placed and the pericardial edges were lifted. Three to four deep pericardial sutures were placed on the left sided pericardium posterior of the phrenic nerve to rotate and displace the heart anteriorly and to the right. As an additional measurement, when necessary for the haemodynamic status, the patient was tilted to the right and placed in Trendelenburg position. Traction on the right sided pericardial edge sutures was regulated according to surgical needs. The temperature of the patient was maintained above 36 °C by a warming mattress and by warming the intravenous fluid administration. The ultima access platform/stabiliser (CTS/guidant Cupertino California®) was used for presenting and stabilising the coronary arteries. After dissecting the left internal mammary artery (LIMA) from its origin to below the bifurcation, the patient was heparinized with 200 IU kg^{-1} IV as a bolus followed by an infusion of 2000 IU h^{-1} to maintain the activated coagulation time (ACT) >300 s (Hemochron 801® International Technidyne Corp; Edison, NJ). Distal anastomoses were performed first. In all cases the LIMA anastomosis to the diagonal branch(s) and/or left anterior descending (LAD) were routinely performed first before the right internal mammary (RIMA) or vein graft anastomosis to the right coronary artery (RCA), inferior and posterior arteries. The proximal vein graft anatomises were performed using a side-beating clamp while maintaining the systolic blood pressure <100 mm Hg. The distal anastomoses were made under local ligation of the coronary vessel with prolene 5–0, a FloCal® shunt was used for all distal anastomoses. After the last proximal anastomosis the heparin was reversed by protamine sulphate. Inotropic support with dopamin and/or noradrenaline was used when indicated.

2.2. Cardiopulmonary bypass technique (group 2)

Routine median sternotomy was performed and the pericardial edges were lifted. After dissecting of the LIMA from its origin to below the bifurcation, the patient was heparinized with a bolus of 300 IU kg^{-1} IV to achieve an ACT >450 s. Additional increments of heparin were administered during the procedure to maintain the ACT >450 s. Cardiopulmonary bypass was instituted using a Cobe hollow fibre membrane oxygenator. The circuit was primed with 1100 ml (500 ml gelofusine + 500 ml Ringer's solution + 100 ml mannitol). The CPB flow was maintained at 2.4 L min^{-1} m^{-2}, and mild hypothermia of 32 °C was accomplished. Cold cardioplegic solution was given after cross-clamping for myocardial protection (800–1000 ml initially and 200–300 ml after every 30 min through the aortic root and 100 ml after every distal anastomosis through the vein graft). The distal vein graft anastomoses were performed first, while the distal LIMA anastomoses to the diagonal branches and or LAD were performed last. The proximal vein graft anastomosis was performed under side clamping of the aorta. After declamping, the heart was defibrillated, if needed, then the patient was rewarmed to a rectal temperature of at least 34 °C. After weaning of the CPB and decanulation the heparin was reversed with protamine sulphate. Inotropic support with dopamin and/or noradrenaline was used during weaning when indicated.

2.3. Cytokine measurements

Blood sampling for determination of TNF-α, IL-6, IL-8, IL-10, IL-4, TNFsr-1 and TNFsr-2 was performed at the following time points; after induction of anaesthesia and before skin incision (*T*0), before starting revascularization in group 1 or before cardiopulmonary bypass in group 2 (*T*1), at the end of revascularization in group 1 or at the end of CBP in group 2 (*T*2), 2 h (*T*3) and 24 h after skin closure (*T*4). Samples were collected in tubes containing lithium heparin (VenoJect®, Terumo, Europe NV, Leuven, Belgium). The samples were immediately centrifuged at 1000*g*, and the plasma was stored at −70 °C until assays were performed. Enzyme-linked immunosorbent assays were used to measure IL-10, IL-4, TNFsr-1 and TNFsr-2 (R&D Systems Inc., Minneapolis, USA). IL-6, IL-8 and TNF-α were also determined by enzyme-linked immunosorbent assays (Immulite®, DPC, Los Angeles, USA). All assays were performed according to the manufacturers instructions.

2.4. Postoperative management

All patients followed standard care and processes on the ICU and postoperative ward until discharge from the hospital. On arrival to the ICU, haemodynamic and ventilation criteria were recorded every 15 min before extubation and hourly until discharge from ICU. Patients were weaned from mechanical ventilation as soon as they were haemodynamically stable, responded to verbal stimulation, completely rewarmed and when blood loss did not exceed 100 ml/h. Postoperative pain management was achieved with doses of piritramide i.v. boluses of 5–10 mg. The time to extubation, postoperative fluid and blood transfusion requirement, the need for inotropic support, the presence of postoperative complications, the length of stay in the ICU and the hospital were recorded. On the first postoperative morning myocardial enzymes including, creatine kinase (CK), creatine kinase MB fraction (CK-MB), lactate dehydrogenase (LDH), aspartate aminotransferase (AST) were measured. Patients were discharged from the ICU on the first morning, if they were haemodynamically stable, had normal blood gases under spontaneous respiration and acceptable cardiac enzymes. They were discharged home from the hospital when they were able to perform basic routine tasks independently.

2.5. Statistical analysis

Calculations were performed on a personal computer using SPSS version 16.0.

The groups were tested for differences with Student's *t*-test for continuous variables and Fisher's exact test for catigorical variables. For comparing cytokine levels between the two groups at each time point Mann–Whitney *U*-test was used. Repeated measures analysis of variance together with Bonferroni adjustment was used for multiple within-group comparisons. In all cases p value less than 0.05 was considered to indicate statistical significance.

3. Results

Demographic data and the preoperative clinical characteristics were comparable in both patient groups (Table 1). The intraoperative course was uneventful and the intraoperative characteristics were comparable in both patient groups (Table 2). In all patients complete revascularization was achieved.

3.1. Cytokine response

Levels of TNF-α and IL-8 (Fig. 1) were usually low at all times of measurement in group 1 while both cytokines increased at *T*2 and remained high at *T*3 in group 2. Levels of TNF-α were higher in group 2 than in group 1 at *T*3 (93 ± 93 vs 12 ± 7 pg/ml; $p < 0.01$) and levels of IL-8 were higher in group 2 at *T*2 (154 ± 256 vs 13 ± 10 pg/ml; $p < 0.05$) and at *T*3 (719 ± 842 vs 27 ± 24 pg/ml; $p < 0.01$). Levels of IL-6 (Fig. 1) increased in both groups at *T*2 and peaked at *T*3, but they were higher in

Table 1 Demographic and preoperative characteristics of patient groups.

	Group 1 (off-pump)	Group 2 (off-pump)
Age (years)	62 ± 6	63 ± 7
Height (cm)	175 ± 11	174 ± 8
Weight (kg)	80 ± 12	85 ± 14
Sex (m/f)	6/3	6/3
NYHA[a] class (II/III/IV)	2/3/4	2/4/3
Smoking (N/Y)[b]	4/5	6/3
Diabetes (N/Y)[b]	8/1	7/2
Hypertension (N/Y)[b]	7/2	7/2
Number of affected vessels	3.2 ± 0.2	2.8 ± 0.7

The data are shown as mean ± SD for the continuous variables and as numbers for categorical variables. No significant differences between groups.

[a] NYHA, New York Heart Association.

[b] N, no; Y, yes.

Table 2 Intra-operative characteristics of patient groups.

	Group 1 (off-pump)	Group 2 (off-pump)	*p* Value
Number of grafts	4.2 ± 0.8	4.3 ± 0.9	0.958
Intraoperative blood intake (ml/kg)	2 ± 3	2 ± 3	0.600
Intraoperative fluid intake (ml/kg)*	52 ± 8	73 ± 13	0.002
Total surgical time (min)	229 ± 70	190 ± 53	0.216
CPB[a] time (min)	–	114 ± 19	–
Aorta cross-clamping time (min)	–	74 ± 13	–

The data are shown as mean ± SD.
[a] CPB, cardiopulmonary bypass.
* There is difference between groups.

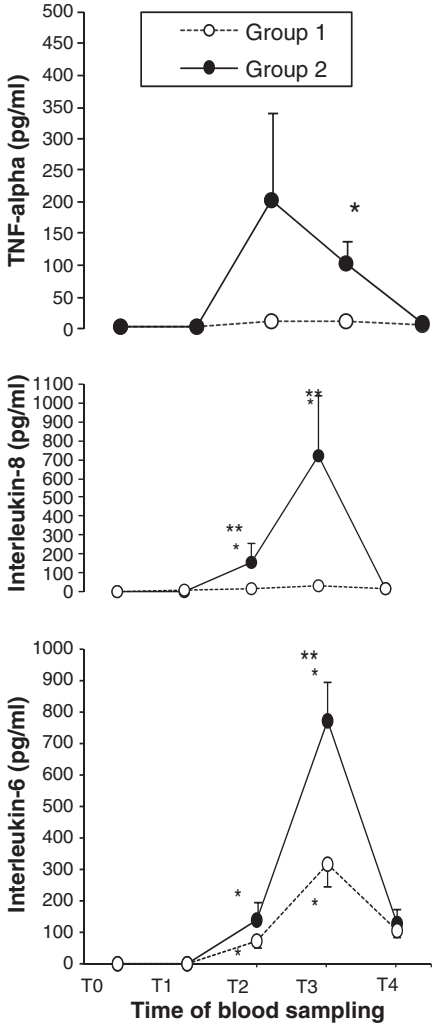

Figure 1 Data are expressed as mean ± SE. *T*0 = after induction of anaesthesia and before skin incision, *T*1 = before cardiopulmonary bypass or before starting revascularization in group 1, *T*2 = end of CBP or end of revascularization in group 1, *T*3 = 2 h after skin closure, *T*4 = 24 h after skin closure. *p value < 0.05 between two times in the same group. **p value < 0.05 between groups.

group 2 than in group 1 at *T*3 (773 ± 330 vs 315 ± 189 pg/ml; $p < 0.01$). Production of IL-10 (Fig. 2) was also significantly higher in group 2 than in group 1 at *T*2 (115 ± 119 vs 13 ± 4 pg/ml; $p < 0.01$) and at *T*3 (212 ± 171 vs 31 ± 29 pg/ml; $p < 0.01$). At *T*3 levels of TNFsr-1 and TNFsr-2 (Fig. 2) were higher in group 2 than in group 1, regarding to TNFsr-1 (4858 ± 1325 vs 2089 ± 584 pg/ml; $p < 0.01$) and TNFsr-2 (4971 ± 63 vs 3801 ± 738 pg/ml; $p < 0.05$). Production of IL-4 (Fig. 2) did not increase through all times of measurement in both groups.

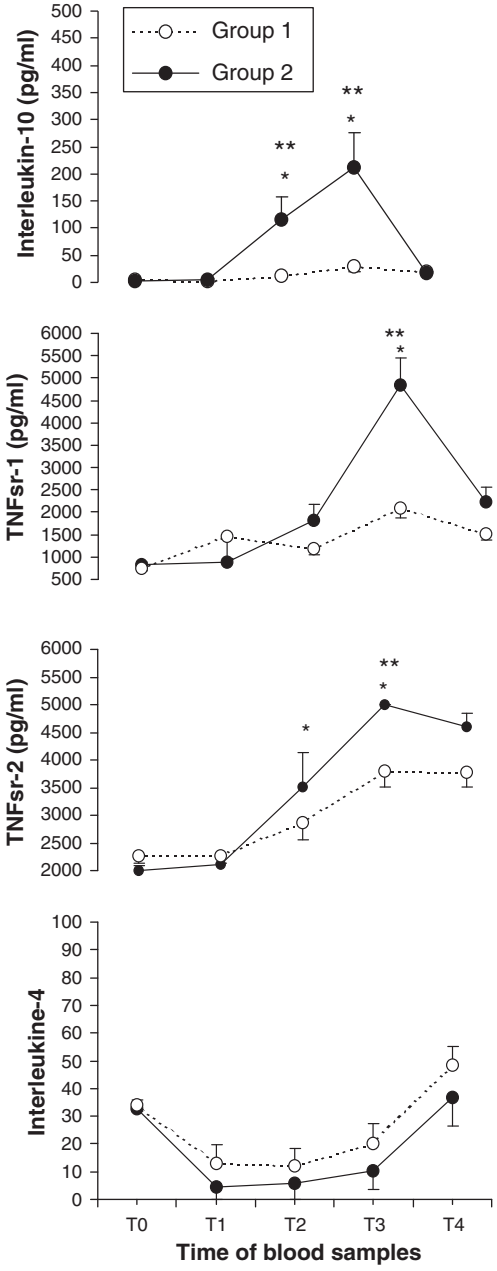

Figure 2 Data are expressed as mean ± SE. *T*0 = after induction of anaesthesia and before skin incision, *T*1 = before cardiopulmonary bypass or before starting revascularization in group 1, *T*2 = end of CBP or end of revascularization in group 1, *T*3 = 2 h after skin closure, *T*4 = 24 h after skin closure. *p value < 0.05 between two times in the same group. **p value < 0.05 between groups.

3.2. Postoperative clinical outcome

In the ICU, no death or major complications occurred in both groups. Three patients in group 2 needed inotropic support versus 1 patient in group 1 ($p > 0.05$), atrial fibrillation was recorded in one patient in each group, myocardial infarction was also recorded in one patient in each group. Postoperative fluids and blood intake were comparable in both groups. The minimum and the maximum values of mean blood pressure, heart rate, cardiac index, haemoglobin content and haematocrit percent were comparable in both groups. Inspired oxygen fraction, PEEP level, mean inspiratory pressure and time to endotracheal extubation were comparable in both groups. On the first postoperative morning, group 2 had higher levels of CK-MB (53 ± 53 vs 16 ± 13 μg/L; $p = < 0.05$), LDH (281 ± 84 vs 176 ± 23 U/L; $p < 0.01$), AST (70 ± 40 vs 38 ± 13 U/L; $p < 0.05$). They also stayed longer in the ICU (52 ± 33 vs 26 ± 11 h; $p < 0.05$) as well as in the hospital (5 ± 0.5 vs 7 ± 0.4 days; $p < 0.001$).

4. Discussion

Our data revealed that when compared to conventional CABG, off-pump surgery is associated with reduced cytokine response. Moreover, the degree of postoperative myocardial damage seems low and length of stay in the ICU and the hospital was short.

Unlike Wei et al. [9] and Orhan et al. [10], but in agreement with others [11,12] we found significantly lower levels of TNF-α in the patients of off-pump group. However in a recent study it was found that levels of TNF-α did not differ between on-pump and off-pump CABG surgery [13]. TNF-α has an important role in myocardial ischaemia–reperfusion injury [14,15]. It is primarily produced by non-cardiac-activated macrophages in response to ischaemia and reperfusion [16]. Then the circulating TNF-α stimulates intracellular adhesion molecule-1 (ICAM-1) expression on cardiac myocytes [17], which in turn promotes adhesive interaction between transmigrated neutrophils and cardiac myocytes of the reperfused myocardium [18]. TNF-α is also known to trigger the release of all known mediators of inflammation including other cytokines and all metabolites of arachidonic acid. It damages the host by inducing and enhancing the production of reactive oxygen derivatives [19].

We noticed that the production of IL-8 was maintained low in the off-pump group at all measurements, although it increased significantly in the other group after the end of CPB to peak 2 h after skin closure. The clinical benefits of this finding can be expected because IL-8 is known to be one of the important mediators in ischaemia–reperfusion injury through effect on neutrophil activation and its adherence to the vascular endothelium [20]. Furthermore blocking of the IL-8 response by the administration of anti IL-8 antibodies prevents lung ischaemia–reperfusion injury in rabbits [21].

We found high levels of IL-6 in both groups, albeit higher in the CPB group, implying that the production of this cytokine might be influenced by the degree of surgical trauma and tissue damage rather than by the effect of CPB itself [7]. It has been suggested that IL-6 may be a more sensitive indicator of the degree of myocardial damage, and an association was found between the size of IL-6 response and cardiac morbidity [22]. High concentrations of IL-6 may impair cardiac function as a result of negative inotropic effects possibly due to impaired entry of calcium into myocardial cells [23]. Moreover, IL-6 may have anti-inflammatory effects through direct suppression of TNF as well as through the induction of natural antagonist of TNF [24].

The causal relationship between pro- and anti-inflammatory cytokines was exemplified in our study by the IL-10 response which followed the IL-8 response in both groups. This finding was previously reported in the results of Wan et al. when they found that the levels of IL-10 were proportional to the levels of IL-8 in patients of CABG surgery with and without CPB [7]. IL-10 increased only in the CPB group while it remained low throughout measurements in the off-pump group. IL-10 is a potent inhibitor of pro-inflammatory cytokines, suggesting that it may also have an important regulatory role in limiting the duration and extent of the acute inflammatory response [25].

We found significantly raised levels of TNFsr-1 and TNFsr-2 in group 2. These endogenously released soluble receptors may compete with the cell-surface receptors for the binding of TNF, thus acting as physiological inhibitors [26]. In addition, the shedding of extracellular moiety of TNF receptors may decrease the sensitivity of these cells to TNF [27]. Whereas soluble TNF receptors are believed to be reliable markers for the activity in the TNF system [28], the biologic significance of these receptors is not yet fully understood. However it was found that high plasma levels of sTNF-RII were significantly associated with increased incidence of Coronary Heart disease [29].

In spite of the limited number of patients enrolled in our study, we could notice that the clinical outcome was better in the off-pump group as reflected by the lower myocardial enzymes and the shorter stay in the ICU and the hospital. The elevated myocardial enzymes in patients whom have been operated with CPB may be due to the high levels of pro-inflammatory cytokines in this group, although these patients were treated with cold cardioplegia. However the potential involvement of the inflammatory cytokines in postoperative myocardial dysfunction was previously supported by Hennein et al. [20] who found that postoperative left ventricular wall abnormalities were associated with high serum levels of IL-6 and IL-8. We think that prevention or attenuation of the cytokine response during off-pump operation should offer a means of substantially reducing potential morbidity.

In conclusion, this prospective randomised study suggests that in low-risk patients undergoing elective CABG, off-pump technique significantly reduces the inflammatory as well as the anti-inflammatory cytokine responses, decreases postoperative myocardial damage and shortens the length of stay in the ICU and the hospital. A larger prospective and randomised study should confirm the postoperative clinical benefits of the off-pump technique.

References

[1] Nesher N, Frolkis I, Vardi M, et al. Higher levels of serum cytokines and myocardial tissue markers during on-pump versus off-pump coronary artery bypass surgery. J Card Surg 2006;21:395–402.

[2] Rastan AJ, Bittner HB, Gummert JF, et al. On-pump beating heart versus off-pump coronary artery bypass surgery—evidence of pump-induced myocardial injury. Eur J Cardiothorac Surg 2005;27:1057–64.
[3] Parolari A, Camera M, Alamanni F, et al. Systemic inflammation after on-pump and off-pump coronary bypass surgery: a one month follow-up. Ann Thorac Surg 2007;84:823–8.
[4] Rasmussen BS, Laugesen H, Sollid J, et al. Oxygenation and release of inflammatory mediators after off-pump compared with after on-pump coronary artery bypass surgery. Acta Anaesthesiol Scand 2007;51:1202–10.
[5] Franke A, Lante W, Fackeldey V, et al. Pro-inflammatory cytokines after different kinds of cardio-thoracic surgical procedures: is what we see what we know? Eur J Cardiothorac Surg 2005;28:569–75.
[6] Czerny M, Baumer H, Kilo J, Lassnigg A, Hamwi A, Vukovich T, et al. Inflammatory response and myocardial injury following coronary artery bypass grafting with or without cardiopulmonary bypass. Eur J Cardiothorac Surg 2000;17:737–42.
[7] Wan S, Izzat MB, Lee TW, Wan IWP, Tang NLS, Yim APC. Avoiding cardiopulmonary bypass in multivessel CABG reduces cytokine response and myocardial injury. Ann Thorac Surg 1999;68:52–7.
[8] Struber M, Cremer JT, Gohrbandt B, Hagel C, Jankowiski M, Volker B, et al. Human cytokine responses to coronary artery bypass grafting with and without cardiopulmonary bypass. Ann Thorac Surg 1999;68:1330–5.
[9] Wei M, Kuukasjarvi P, Laurikka J, Kaukinen S, Iisalo P, Laine S, et al. Cytokine responses and myocardial injury in coronary artery bypass grafting. Scand J Clin Lab Invest 2001;61(2):161–6.
[10] Orhan G, Sargin M, Senay S, Yuksel M, Kurc E, Tasdemir M, et al. Systemic and myocardial inflammation in traditional and off-pump cardiac surgery. Tex Heart Inst J 2007;34(2):160–5.
[11] Schulze C, Conrad N, Schutz A, Egi K, Reichenspurner H, Reichart B, et al. Reduced expression of systemic proinflammatory cytokines after off-pump versus conventional coronary artery bypass grafting. Thorac Cardiovasc Surg 2000;48(6):364–9.
[12] Matasa BM, Sosnowski AW, Galinanes M. Off-pump bypass graft operation significantly reduces oxidative stress and inflammation. Ann Thorac Surg 2000;69(3):785–91.
[13] Javadzadegan H, NezamiNGhobadi K, Sadighi A, Abolfathi AA. Nader5 N.D. High-sensitivity C-reactive protein (hs-CRP) and tumor necrotizing factor-alpha (TNF-α) after on and off-pump coronary artery bypass grafting. HSR Proc Intensive Care Cardiovasc Anesth 2010;2:27–33.
[14] Zhang C, Xu X, Potter BJ, Wang W, Kuo L, Michael L, et al. TNF-α contributes to endothelial dysfunction inischemia/reperfusion injury. Arterioscler Thromb Vasc Biol 2006;26:475–80.
[15] SaitoY, Watanabe Y, Mishina H, Watanabe K, Yano T, Kobayashi T, et al. Reduction in Myocardial Ischemia-reperfusion Injury in Group IV Cytosolic Phospholipase A2-deficient Mice Partly Due to Inhibition of TNFα-mediated Pathway to Cell Injury. Circulation 2009;120:1058.
[16] Xiong W, Taggar JM, Knispel R, Worth J, Persidsky Y, Baxter BT. Blocking TNF-α attenuates aneurysm formation in a murine model. J Immunol 2009;183:2741–6.
[17] Ikeda U, Ikeda M, Kano S, Shimada K. Neutrophil adherence to rat cardiac myocyte by proinflammatory cytokines. J Cardiovasc Pharmacol 1994;23:647–52.
[18] Youker KA, Hawkins HK, Kukielka GL, Perrard JL, Michael LH, Balantyne CM, et al. Molecular evidence for induction of intracellular adhesion molecule-1 (ICAM-1) in the viable border zone associated with ischemia–reperfusion injury of the dog heart. Circulation 1994;89:2736–46.
[19] Ferrari R. The role of TNF in cardiovascular disease. Pharm Res 1999;40(2):97–105.
[20] Hennein HA, Ebba H, Rodriguez JL, Merrick SH, Keith Fm, Bronstein MH, et al. Relationship of the proinflamatory cytokines to myocardial ischemia and dysfunction after uncomplicated coronary revascularization. J Thorac Cardiovasc Surg 1994;108:626–35.
[21] Boyle EM, Kovacich JC, Hèbert CA, Canty TG, Chi E, Morgan EN, et al. Inhibition of Interleukin-8 blocks myocardial ischemia–reperfusion injury. J Thorac Cardiovasc Surg 1998;116:114–21.
[22] Cruickshanks AM, Oldroyd KG, Cobbe SM. Serum interleukine-6 in suspected myocardial infarction. Lancet 1994;343:974.
[23] Tilg H, Dinarello CA, Mier JW. IL-6 and APPs: anti-inflammatory and immunosuppressive mediators. Immunol Today 1997;18:428–32.
[24] Xing Z, Gauldie J, Gerard Cox G, Baumann H, Jordana M, Lei XF, Achong MK. IL-6 is an anti inflammatory cytokine required for controlling local or systemic acute inflammatory responses. J Clin Invest 1998;101(2):311–20.
[25] Opal SM, DePalo VA. Anti-inflammatory cytokines. Chest 2000;117:1162–72.
[26] Aggarwal BB, Natarajan K. Tumour necrosis factors: development during the decade. Eur Cytokine Netw 1996;72:93–124.
[27] Anderson JA, Knott AW, Wilson MA, Garrison RN, Sims DE, Edwards MJ. The effect of soluble tumour necrosis factor receptor-II on endotoxin-mediated hemodynamic instability. J Surg Res 1995;58:53–7.
[28] Bendtzen K. Cytokines and natural regulators of cytokines. Immunol Lett 1994;43:111–23.
[29] Shai I, Schulze MB, Manson JE, Rexrode KM, Stampfer MJ, Mantzoros C, et al. A prospective study of soluble tumor necrosis factor-receptor II (sTNF-RII) and risk of coronary heart disease among women with type 2 diabetes. Diabetes Care 2005;28:1376–82.