Systemic Inflammation After On-Pump and Off-Pump Coronary Bypass Surgery: A One-Month Follow-Up

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Background. **This study sought to assess inflammation activation in the follow-up (up to one month) of coronary bypass surgery performed both on- (CABG) and off-pump (OPCAB).**

Methods. **Thirty patients, candidates for coronary surgery, were randomized to undergo CABG (n = 16) or OPCAB (n = 14). Blood samples were collected before the intervention, after protamine administration, and 4, 8, and 30 days after surgery.**

Results. **Plasma tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) levels significantly increased with respect to baseline from protamine administration up to eight postoperative days, whereas high-sensitivity C-reactive protein (hs-CRP) and fibrinogen increased after surgery up to eight postoperative days in both groups. On the other hand, neutrophil elastase levels were higher than baseline from protamine administration up to four postoperative days in CABG, and at the time point eight days after surgery in OPCAB. The only significant differences between CABG and OPCAB in inflammatory markers occurred intraoperatively, after protamine administration, when TNF-α and elastase levels were higher in CABG, whereas no differences were detected between CABG and OPCAB at any postoperative time point. Postoperative increases in fibrinogen and hs-CRP were positively correlated with increases in IL-6, but not with postoperative changes in TNF-α both in CABG and OPCAB.**

Conclusions. **After coronary bypass surgery, there is a protracted postoperative activation of inflammation persisting several days after surgery; this postoperative activation is not affected by the surgical strategy (on-pump or off-pump).**

(Ann Thorac Surg 2007;84:823–8)

Cardiopulmonary bypass (CPB) induces an inflammatory response in patients undergoing cardiac surgery, and this has been mainly attributed to the exposure of blood with the large artificial surface of the CPB circuit. In fact, early after coronary bypass surgery performed with CPB use, a sensible activation of the inflammatory pathways has been widely shown; when CPB is avoided (eg, off-pump coronary bypass surgery [OPCAB]), however, evidence suggests that activation of inflammation still occurs, but is slightly delayed with respect to on-pump bypass [1, 2].

However, information concerning the behavior of inflammatory markers is available only concerning the early hours after surgery, and data about the time course of inflammatory variables during the first month after surgery in both on-pump and off-pump surgery are still limited. This study has been designed in order to assess the levels up to one month after surgery of cytokines (plasma tumor necrosis factor-α [TNF- α] and interleukin-6 [IL-6]), neutrophil activation markers (neutrophil elastase), and acute phase proteins (high-sensitivity C-reactive protein [hs-CRP], and fibrinogen) in patients randomized to either CABG or OPCAB.

As the acute phase proteins fibrinogen and hs-CRP are well-established cardiovascular risk factors and important players in atherosclerosis [3–5], the relation between cytokine activation and postoperative changes in acute phase proteins has also been evaluated.

Patients and Methods

Patients

Thirty patients, candidates to elective primary surgical myocardial revascularization following the American

Accepted for publication April 16, 2007.

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This article has been selected for the open discussion forum on the CTSNet Web Site: http://www.ctsnet.org/sections/newsandviews/discussions/index.html

Published by Elsevier Inc

0003-4975/07/$32.00
doi:10.1016/j.athoracsur.2007.04.048

Heart Association/American College of Cardiology guidelines [6], and in whom both OPCAB and CABG were considered feasible, were enrolled during the time period January 2004 to June 2005 and randomized to undergo CABG (n = 16) or OPCAB (n = 14). Patients were individually randomized to undergo myocardial revascularization with either (1) a conventional on-pump operation or (2) an off-pump operation on the beating heart. The randomization codes were concealed in numbered, sealed, opaque envelopes. The treatment allocation for a patient was determined by opening the next envelope the evening before the operation. On-pump and off-pump surgeries were performed by four fully trained cardiac surgeons who had already performed a minimum of 100 off-pump operations.

In all cases the preoperative ejection fraction was greater than 0.30, and the left ventricular end-diastolic pressure was below 20 mm Hg. Preoperative exclusion criteria were age greater than 80 years, renal or liver disease, intake of drugs affecting platelet function, or coagulation or fibrinolysis within ten days prior to surgery, while intraoperative and postoperative exclusion criteria were excessive (> 1,000 mL/24 hours); postoperative bleeding or reexploration for bleeding, perioperative myocardial infarction, stroke or renal failure requiring dialysis. All patients gave informed consent to participate in this study that was approved by the Institutional Review Board of Centro Cardiologico Monzino IRCCS.

Anesthesia

Patient management during and after surgery was the same in both groups of patients. All patients continued their cardiac medications until surgery. Patients received thiopentone, 3 to 5 mg/kg, and fentanyl, 1 μg/kg, as induction and were maintained with sufentanil boluses up to 4 to 5 μg/kg associated with propofol continuous infusion at 3 mg/kg/hour.

After orotracheal intubation, patients were ventilated with oxygen and air (fraction of inspired oxygen 50%), keeping partial pressure of carbon dioxide, arterial ($PaCO_2$) between 35 and 38 mm Hg. Rectal and cervical esophageal probes were employed for temperature monitoring, and acid-base equilibrium was maintained by the alpha-stat method.

After internal mammary takedown, systemic heparinization (300 IU/kg bovine lung heparin in both groups) was given and anticoagulation was assessed with celite activated clotting time, with a trigger level for additional heparin set at 440 seconds every 30 minutes during CPB (CABG) or during coronary anastomoses confection (OPCAB).

Upon completion of distal and proximal coronary anastomoses, heparin was antagonized with protamine sulfate at a 1:1 ratio (3 mg/kg) in both groups. The protamine dose was based on total heparin used during surgery. No patient received intra- or postoperative aprotinin administration, and in no patient a cell-saver was used.

CABG Surgery

A nonpulsatile roller pump, hollow-fiber oxygenator with integrated heat exchanger, arterial filter, open cardiotomy reservoir, and polyvinyl tubing system were used in all cases. Each operation was performed with tepid hypothermia and hemodilution. Blood flow during CPB was kept at 2.4 L/minute/m^2, and hematocrit at 18% to 25%. Myocardial protection was achieved by the administration of cold, multidose blood cardioplegia infused through the aortic root and the coronary sinus.

OPCAB Surgery

All OPCABs were performed through a midline sternotomy; mechanical stability of the coronary arteriotomy area was achieved with a suction stabilizer and a soft plastic coronary flow-shunt was always introduced into the coronary arteriotomy to maintain some degree of distal flow, to reduce myocardial ischemia, and to improve visualization of the anastomosis area. Coronary artery exposure was achieved with stay sutures applied on the left lateral side of pericardium or with deep pericardial stay sutures placed above the entry of the left lower pulmonary vein and laterally to the entry of the inferior vena cava (Lima stitch).

Follow-Up

All the patients were hospitalized until the eighth postoperative day. Then all patients underwent follow-up visit (physical examination, electrocardiogram, and blood collection) at the 30th postoperative day.

Blood Sampling

Blood collection was performed at baseline (the day before surgery), 5 minutes after protamine administration, and at 4, 8, and 30 days after surgical intervention. Plasma was prepared by centrifugation at 1,500*g* for 20 minutes at 4°C within 30 minutes from venipuncture, divided into aliquots, and frozen at −80°C until assayed. Samples were frozen and thawed only once. Fibrinogen levels were measured according to Clauss [7] (Fibrinogen-C, Instrumentational Laboratory, Milan, Italy) with a coagulometer (ACL 300, Instrumentational Laboratory, Milan, Italy). The IL-6, TNFα, neutrophil elastase, and hs-CRP levels were determined using specific commercially available enzyme-linked immunosorbent assay kits according to manufacturer's instructions (R&D System and Hyphen BioMed). High-sensitivity C-reactive protein was chosen as a method to assess CRP as it has been recently demonstrated that it is a potent predictor of future cardiovascular events at all levels of low-density lipoprotein cholesterol, all levels of the Framingham Risk Score, and all levels of severity of the metabolic syndrome. Moreover, hs-CRP appears to be implicated in acute coronary syndromes and provides prognostic information on vascular risk among several different subgroups of patients such as diabetics and patients with renal dysfunction [8, 9].

Table 1. Clinical Variables in the Study Population

Variable	CABG (n = 15)	OPCAB (n = 14)	*p*
Age (yrs.)	67 ± 3.1	66 ± 3.7	0.68
Male gender (%)	11 (73%)	12 (86%)	0.65
Previous MI (%)	7 (47%)	5 (36%)	0.71
Type I diabetes (%)	1 (7%)	1 (7%)	>0.99
Type II diabetes (%)	4 (27%)	3 (21%)	>0.99
COPD (%)	1 (7%)	3 (21%)	0.33
Hypertension (%)	12 (80%)	12 (86%)	>0.99
Echocardiographic EF	0.54 ± 0.028	0.56 ± 0.024	0.59
Preoperative hematocrit (%)	38 ± 1.1	39 ± 1.3	0.56
Diseased coronary vessels	2.7 ± 0.22	2.8 ± 0.19	0.74
Distal anastomoses	3.3 ± 0.39	3.1 ± 0.25	0.67
CPB time (min)	104 ± 7.4	—	—
Cross-clamp time (min)	86 ± 6.4	—	—
24-hour bleeding (mL)	495 ± 42	455 ± 53	0.57
Ventilation time (hour)	5.4 ± 1.01	4.7 ± 1.11	0.64

CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; CPB = cardiopulmonary bypass; EF = ejection fraction; MI = myocardial infaction; OPCAB = off-pump coronary artery bypass.

All the intraassay and interassay coefficients of variation were less than 6%. All data were normalized for hematocrit values.

Statistical Analysis

This study was powered to detect, with a power of 80% and an alpha error of 0.05, an inflammatory markers percent change from baseline equal to 1 standard deviation in any time point. Continuous variables are presented as means ± 1 standard error of the mean, categoric variables as percentage. Group differences in clinical variables between CABG and OPCAB were assessed by analysis of variance, χ^2, or Fisher exact tests when indicated.

General linear model analysis of covariance models were used for statistical analysis of time, group (CABG vs OPCAB), and interaction (time*group) main effects in inflammation markers. When time, group, or interaction effects were significant ($p \leq 0.05$), repeated measures analysis of covariance with Bonferroni correction was used to determine significant ($p \leq 0.05$) point-by-point differences.

Regression analysis with the computation of Pearson correlation coefficient was performed on log-transformed postoperative (time points: days 4, 8, and 30) changes with respect to baseline of cytokines (TNF-α, IL-6) with changes in acute phase proteins (fibrinogen and hs-CRP) in CABG and OPCAB groups, respectively; *p* values were corrected for within-subject repeated measurements by covariance analysis. A *p* value of 0.05 or less was considered statistically significant.

Results

Twenty-nine patients out of the 30 completed the study; there were no changes in group allocation after patients' randomization for any reason. One patient of the OPCAB group was excluded as he refused to participate in the study after surgery. No significant differences in clinical variables were detected between patients randomized to OPCAB or CABG (Table 1). All the patients had an uncomplicated postoperative course.

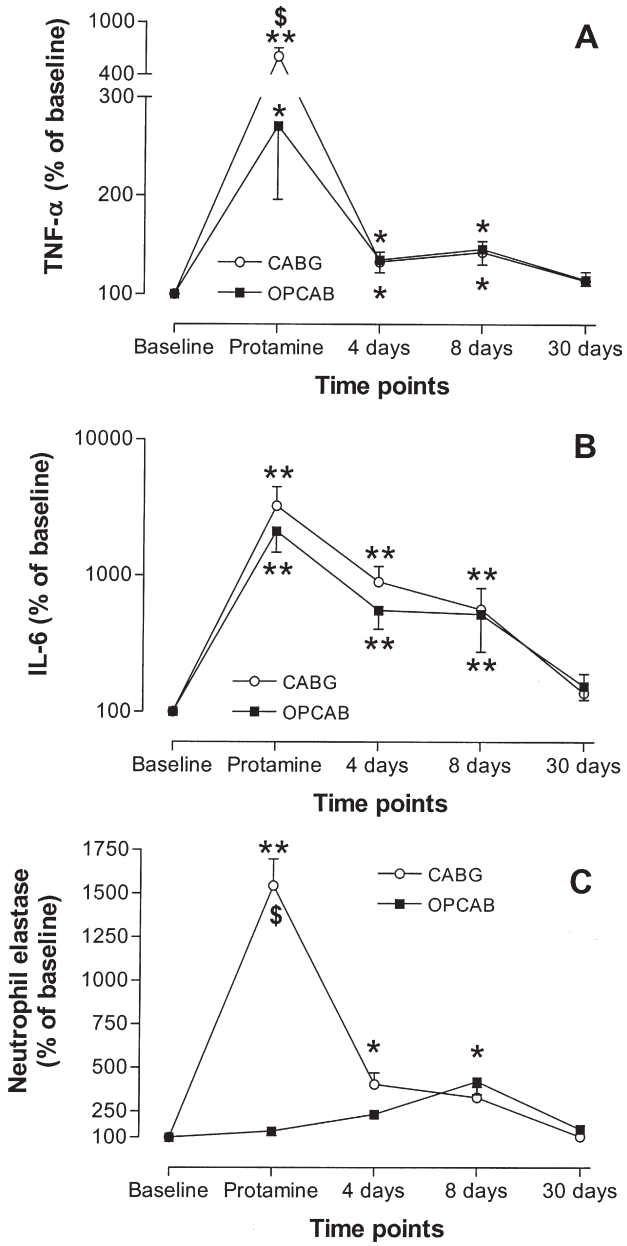

Fig 1. (A) Plasma TNF-α, (B) IL-6, and (C) elastase behavior over time. Means ± 1 standard error of the mean. Empty circles indicate patients assigned to CABG (n = 16), while filled squares indicate patients assigned to OPCAB (n=13). Note that the y axis of (B) is logarithmic. (= $p < 0.05$ vs baseline, ** = $p < 0.01$ vs baseline; $ = $p < 0.01$ CABG vs OPCAB; CABG = coronary artery bypass grafting; IL-6 = interleukin-6; OPCAB = off-pump coronary artery bypass; TNF-α = tumor necrosis factor-α.)*

Table 2. Inflammatory Markers Before, During, and After Surgery in CABG and OPCAB

Variable	Group	Baseline	Protamine	4 days	8 days	30 days	Main Effects Analysis of Covariance		
							Time	Treatment	Interaction
Tumor necrosis factor-α (pg/mL)	CABG	1.05 ± 0.09	6.4 ± 1.29[ab]	1.4 ± 0.09[c]	1.5 ± 0.11[c]	1.2 ± 0.11	0.0002	0.03	0.05
	OPCAB	0.96 ± 0.05	2.6 ± 0.78[c]	1.3 ± 0.13[c]	1.4 ± 0.13[c]	1.1 ± 0.07			
Interleukin-6 (*pg/mL*)	CABG	3.9 ± 0.67	127 ± 29.4[b]	35 ± 9.0[b]	22 ± 4.8[b]	5.4 ± 0.75	0.0002	0.19	0.21
	OPCAB	2.7 ± 0.34	57 ± 10.0[b]	15 ± 2.2[b]	14 ± 2.9[b]	4.2 ± 0.67			
Neutrophil elastase (ng/mL)	CABG	6.3 ± 0.67	98 ± 14.2[a,b]	18 ± 2.6[c]	15 ± 1.5	7.9 ± 1.05	<0.0001	0.01	<0.0001
	OPCAB	7.3 ± 0.41	10 ± 2.0	17 ± 1.2	28 ± 4.7[c]	12 ± 2.7			
hs-C-reactive protein (mg/dL)	CABG	3.2 ± 0.69	3.0 ± 0.71	75 ± 9.0[b]	45 ± 5.6[b]	5.4 ± 3.66	0.0017	0.13	0.16
	OPCAB	3.8 ± 0.74	2.5 ± 0.88	58 ± 6.5[b]	32 ± 5.2[b]	4.3 ± 1.04			
Fibrinogen (mg/dL)	CABG	429 ± 30	238 ± 17[c]	713 ± 22[c]	646 ± 23[c]	429 ± 18	<0.0001	0.42	0.73
	OPCAB	393 ± 17	256 ± 16[c]	728 ± 27[c]	645 ± 23[c]	385 ± 14			

[a] = Significant difference ($p < 0.01$, repeated measures analysis of covariance) between CABG and OPCAB groups; [b] = Significant difference ($p < 0.01$, repeated measures analysis of covariance) within each group as compared with baseline. [c] = significant difference ($p < 0.05$, repeated measures analysis of covariance) within each group as compared with baseline;

CABG = coronary artery bypass grafting; OPCAB = off-pump coronary artery bypass.

Cytokines and Neutrofil Activation

Baseline plasma TNF-α, IL-6, and elastase levels were similar in CABG and OPCAB patients. Analysis of covariance showed a significant effect of time for all these variables, and a significant effect of the treatment and of the interaction term for TNF-α and elastase. This implies that there are significant changes over time for all these markers, but for only TNF-α and elastase is there a significant effect of group assignment (CABG vs OPCAB). Point-by-point analysis showed significant intraoperative increases with respect to baseline in TNF-α and IL-6 both for CABG and OPCAB groups, but only TNF-α increase was significantly higher in CABG with respect to OPCAB, whereas changes in IL-6 levels did not differ between groups. Elastase levels increased intraoperatively with respect to baseline only in CABG patients and remained significantly higher than baseline up to four postoperative days, whereas in OPCAB there was a slower, progressive increase of elastase levels peaking eight days after surgery where the levels of this neutrophil activation marker were significantly higher than at baseline. Thirty days after surgery, TNF-α levels returned to baseline in both groups, whereas IL-6 was still higher than at

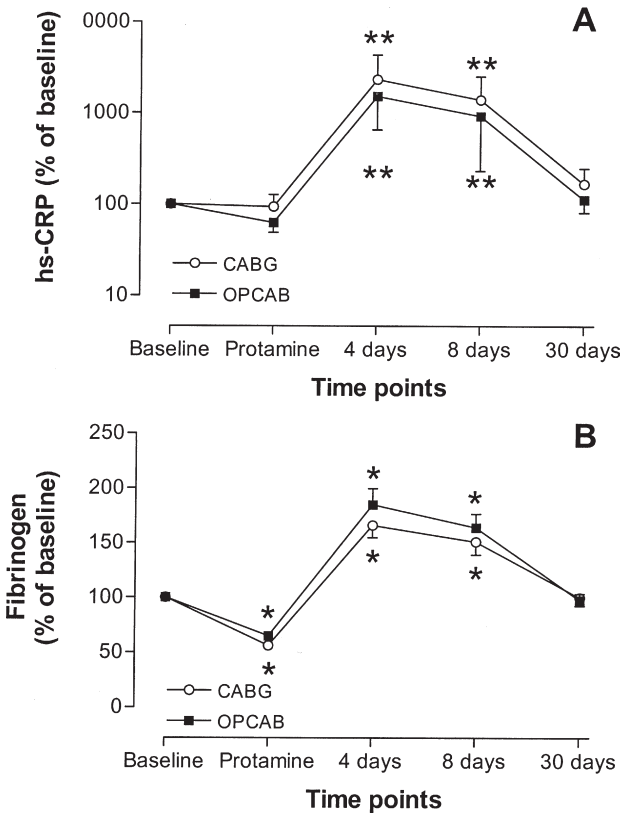

Fig 2. (A) Plasma hs-CRP and (B) fibrinogen behavior over time. Means ± 1 standard error of the mean. Empty circles indicate patients assigned to CABG (n = 16), while filled squares indicate patients assigned to OPCAB (n = 13). Note that the y axis of (A) is logarithmic. (CABG = coronary artery bypass grafting; OPCAB = off-pump coronary artery bypass; hs-CRP = high-sensitivity C-reactive protein.)

Table 3. (A) Correlations Between Perioperative Changes of Cytokines and of Fibrinogen

	CABG (n = 48)		OPCAB (n = 39)	
	Correlation Coefficient	*p* Value	Correlation Coefficient	*p* Value
Interleukin-6	0.744	<0.001	0.654	0.002
TNF-α	0.160	0.28	0.176	0.31

(B). Correlations Between Perioperative Changes of Cytokines and of High-Sensitivity C-Reactive Protein

Interleukin-6	0.770	<0.001	0.507	0.010
TNF-α	−0.057	0.69	0.267	0.12

CABG = coronary artery bypass grafting; OPCAB = off-pump coronary artery bypass.

baseline in both groups (+38% and +55% in CABG and OPCAB, respectively); the increases, however, not being statistically significant. After 30 days elastase levels returned to baseline in CABG patients, whereas they were higher than at baseline in OPCAB (+47%), although this was not statistically significant. No statistically significant differences were detected between CABG and OPCAB in any of the postoperative time points (from 4 to 30 postoperative days) (Fig 1; Table 2).

Acute Phase Proteins

Baseline plasma hs-CRP and fibrinogen levels were similar in CABG and OPCAB patients. Analysis of covariance showed a significant effect of time for both these variables, but no effect for the treatment and interaction terms was observed. This implies that there are significant changes over time for all these markers, but no effect of group assignment (CABG vs OPCAB). Point-by-point analysis showed no intraoperative changes in hs-CRP levels, whereas a significant decrease in fibrinogen levels was observed in CABG (−44%) and OPCAB (−35%) (Fig 2; Table 2). Postoperatively, point by point analysis showed significant increases with respect to baseline for both variables at the fourth and eighth postoperative day, with no differences between CABG and OPCAB groups. After 30 days, fibrinogen levels returned to baseline in both groups, whereas hs-CRP levels were still higher than at baseline, although this was not statistically significant (hs-CRP +69% and +13% in CABG and OPCAB, respectively).

Relation Between Postoperative Changes in Cytokines and Acute Phase Proteins

Postoperative changes in IL-6 were positively correlated with postoperative changes in fibrinogen and hs-CRP, and this was statistically significant both in CABG (Table 3A) and OPCAB (Table 3B). On the other hand, no relation was observed between postoperative changes in TNF-α with changes for fibrinogen and for hs-CRP both in CABG (Table 3A) and OPCAB (Table 3B).

Comment

Inflammation plays a critical role in cardiovascular diseases; epidemiologic and clinical studies have documented strong and consistent relations between inflammation markers and the occurrence of cardiovascular events, and elevated levels of TNF-α, IL-6, fibrinogen, and CRP have been shown to predict future vascular risk in a variety of clinical settings [3–5, 10]. Systemic inflammation is also now recognized to result in activation of coagulation, downregulation of physiological anticoagulant mechanisms, and inhibition of fibrinolysis. For instance, IL-6 affects the coagulation cascade at different levels, increasing tissue factor and factor VIII mRNA levels in monocytes and liver cell lines, enhancing platelet production, and increasing the transcription of fibrinogen gene [11]; some of these effects may also be mediated by other inflammatory markers such as C-reactive protein [12].

It is known that coronary artery bypass surgery elicits a sensible activation of inflammation in the early hours after surgery. Interestingly, some inflammatory markers (IL-1, IL-6, some leukocyte subsets) show similar behavior both in CABG and OPCAB, whereas others (TNF-α, IL-8, IL-10, and elastase) show earliest and highest peak levels in CABG during the time span between the final steps and the very early hours after the surgical procedure; afterwards, the differences in terms of inflammatory profile progressively fade and finally cancel out [1].

Data here reported, even with the limits of a relatively small sample size, support the concept that a sensible activation of inflammation occurs at the same extent in on- and off-pump and on-pump coronary surgery and lasts up to eight days after surgery. This supports the concept that, as previously reported for coagulation markers [13, 14], the inflammatory reaction occurring in the postoperative course of coronary bypass surgery is not related to the surgical strategy adopted, as the effect of coronary surgery performed on-pump on inflammatory markers is limited to the final phases of surgery and the very early hours thereafter. Thus, the use of cardiopulmonary bypass during surgery and all the consequences of cardiopulmonary bypass technology (including cardioplegic arrest of the heart and the related myocardial ischemia, as well as lungs ischemia due to lungs hypoperfusion during extracorporeal circulation), do not explain the occurrence of the protracted postoperative activation of the inflammatory system, but only the very early one, occurring soon after surgery. As a variety of novel minimally invasive extracorporeal circulation strategies such as centrifugal pumps, coated tubes, closed loop systems, or avoidance of shed blood recirculation have recently been developed demonstrating a beneficial effects on early inflammation [15, 16], it is possible that even this difference between CABG and OPCAB can be easily reduced in the near future.

Of note, some of the inflammatory markers we studied, namely IL-6 and hsCRP in both CABG and OPCAB groups, and neutrophil elastase in OPCAB patients, did not return to baseline levels even after 30 days, although differences did not reach statistical significance. This protracted period of activation of the inflammatory reaction parallels an increase in the risk of cardiovascular events that has been shown to occur more frequently early after surgery. In other words, these data add to the concept that the inflammatory reaction, together with the previously reported perturbation of the hemostatic-prothrombotic system, might play a substantial role in the risk to develop adverse cardiovascular events, which patients undergoing coronary surgery necessarily face in the postoperative period. Our findings indicate that actions should be taken to counteract the protracted inflammatory state that occurs both after CABG and OPCAB.

The postoperative increase in inflammatory markers, irrespective of the surgical strategy adopted, can also be read in the light of the relative long lasting prothrombotic state consequent to increases in tissue factor, thrombin generation, and fibrinolysis markers already docu-

mented in both CABG and OPCAB [13, 14]. These data, taken together, further support and expand the need of aggressive therapies targeted to modulate the occurrence of this protracted and prothrombotic and proinflammatory state occurring in the early weeks after coronary surgery.

Finally, the strong relation between postoperative changes in the levels of IL-6, but not of TNF-α, with that of C-reactive protein and fibrinogen, similar in CABG and OPCAB, suggests a link between these variables, albeit unaffected by the use of extracorporeal circulation, and, as a consequence, a possible link between inflammatory and hemostatic pathway activation. Indeed, fibrinogen, besides being an acute phase protein and a risk factor for future cardiovascular events, strongly affects hemostasis, blood rheology, platelet aggregation, and endothelial function. In conclusion, this study shows that there is a protracted postoperative activation of the inflammatory pathways after coronary bypass surgery performed both on- and off-pump, and these findings might be of pathophysiological and therapeutic interest in the treatment of patients undergoing coronary bypass surgery, whatever the revascularization strategy (on- or off-pump) is chosen.

The authors wish to express their appreciation for the cooperation of Dr Fabrizio Veglia, PhD, Biostatistical Unit, Centro Cardiologico Monzino, in data analysis, and of Dr Chiara Cavoretto for English editing of the manuscript.

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