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).**

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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

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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].