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Off-pump coronary artery bypass grafting does not reduce lymphocyte activation

C. Blacher[a,b,*], J. Neumann[a], L.A Jung[a], F.A. Lucchese[a], J.P. Ribeiro[b]

[a]*Cardiology Disivion, Santa Casa de Misericórdia de Porto Alegre, rua Annes Dias, 285, 90020-090, Porto Alegre, RS, Brazil*
[b]*Department of Medicine, School of Medicine, Federal University of Rio Grande do Sul, rua Ramiro Barcelos, 235, 90035-007, Porto Alegre, RS, Brazil*

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Abstract

Objective: In this study, we test the hypothesis that off-pump coronary bypass surgery might result in less lymphocyte activation than on-pump coronary surgery. We also study the behavior of lymphocyte activation markers during and after surgery.
Background: Coronary artery bypass surgery is known to be associated with changes of inflammatory mediators, immune function, and early phase lymphocyte activation, which could cause postoperative lymphopenia and lymphocyte unresponsiveness.
Methods: We studied lymphocyte activation response in 28 patients randomized to off-pump (n=13) or on-pump (n=15) coronary artery bypass surgery. Expression of CD25, CD26, CD69, and DR on T (CD3+) and B (CD19+) lymphocytes on peripheral blood was assessed through flow cytometry.
Results: The response of T lymphocytes and their activation markers, as well as B lymphocytes and their activation markers, was similar after on- and off-pump surgery. Overall, T lymphocytes decreased to the lowest level 9 h after surgery and tended to increase later. For B lymphocytes, there was early reduction with increase on the 1st postoperative day. There was early activation of CD69+ and late activation of CD25+ on T lymphocytes. For B lymphocytes, there was early activation of CD69+ and late activation of DR+.
Conclusions: (1) Compared to on-pump cardiopulmonary bypass, off-pump surgery does not reduce lymphocyte activation. (2) Coronary bypass surgery causes the early activation of lymphocytes, as evidenced by the increased expression of lymphocyte activation markers.

Keywords: Cardiac surgery; Myocardial revascularization; Cardiopulmonary bypass; T lymphocytes; B lymphocytes

1. Introduction

The morbidity and mortality that are still associated with coronary artery bypass surgery may be partially attributed to the use of cardiopulmonary bypass [1]. Therefore, since the 1990s, off-pump coronary artery bypass surgery has been used as an alternative to improve treatment effectiveness and decrease cost. Several investigators have reported better clinical results in patients operated without cardiopulmonary bypass [2–8], but we still have controversies, mainly related to low-risk patients and long-term outcome after surgery [1,9,10].

One effect of cardiopulmonary bypass is the activation of the complement cascade, causing activation of neutrophils and production of cytokines [11]. Cytokines enhance the neutrophil activation process, promoting neutrophil adhesion to vessel walls and migration into the tissues, and making parenchymatous cells, including myocytes, more susceptible to neutrophil-derived products [12].

Lymphocytes are also involved in inflammatory alterations during myocardial revascularization procedures [13]. In the 1980s, Petri et al. [14] reported a decrease in lymphocyte activation in patients submitted to cardiac surgery. The study included patients submitted to closed

* Corresponding author. Serviço de Cardiologia, Santa Casa de Misericórdia de Porto Alegre, rua Annes Dias, 285, 90020-090, Porto Alegre, RS, Brazil. Tel./fax: +55 51 3225 3019.
E-mail address: blacher@via-rs.net (C. Blacher).

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heart (off-pump) valve surgery and concluded that the effects of cardiac surgery on lymphocytes could be associated with cardiopulmonary bypass. Other investigators also studied the possibility that a reduction in lymphocyte activation after cardiac surgery could increase the risk for infection [15,16].

A study employing new flow cytometry techniques showed an elevation of the total number of lymphocytes in the early phase of cardiopulmonary bypass followed by a significant decrease, mainly due to B and cytotoxic T lymphocytes. In contrast, lymphopenia, observed 8 h after the inactivation of heparin, was predominantly related to a drop of helper T lymphocytes. The authors considered that cardiopulmonary bypass was the main cause of these phenomena [17].

More recently, a study including patients submitted to esophageal carcinoma surgery and cardiac surgery assessed the expression of CD69, an early activation marker [18]. The activation of lymphocytes in the transoperative and postoperative period showed no difference between the two types of surgery. The authors concluded that the lymphopenia observed after the surgery was caused by a process related to the activation of lymphocytes, probably apoptosis. In a nonrandomized study, Akbas et al. [19] found greater reduction in immunologic response for on-pump coronary artery bypass surgery when compared to off-pump coronary artery bypass surgery. However, until the present moment, no randomized studies have compared the activation of lymphocytes in patients submitted to coronary surgery with and without cardiopulmonary bypass. Therefore, the objectives of this study were (1) to test the hypothesis that lymphocyte activation (and thus, the inflammatory process) is less intense in off-pump than in on-pump coronary artery bypass surgery and (2) to study the behavior of lymphocyte activation markers during and after surgery.

2. Methods

2.1. Patients

Twenty-eight consecutive patients with indication for coronary artery bypass surgery and anatomical characteristics that allowed surgery without cardiopulmonary bypass were randomly allocated to two groups: on-pump and off-pump coronary artery bypass surgery. Patients were considered to have favorable anatomical characteristics for off-pump coronary artery bypass surgery if they did not have any of the following findings: severe left main coronary artery disease, intramyocardial left anterior descending coronary artery, severely calcified coronary arteries, and diffuse distal atherosclerotic involvement of coronary arteries. All patients were assessed for lymphocyte activation and were managed following the routine of the service. The study project was approved by the Research Ethics Committee at Santa Casa of Porto Alegre, Brazil, and patients provided written informed consent prior to randomization.

The following characteristics were considered as exclusion criteria for the study: previous history of heart surgery; acute myocardial infarction 3 months before the study; need for concomitant cardiac procedure (valve replacement, correction of congenital defects, or other surgical procedures); renal failure, defined as serum creatinine above 177 μmol/L; immunodeficiency syndrome; chronic or perioperative corticotherapy; ejection fraction lower than 40% on left ventricular angiography; active infection; unstable angina requiring intensive care; and class III or IV heart failure, according to the classification of the New York Heart Association.

After randomization, the patients were excluded from the study in the presence of any of the following events during or after surgery: acute myocardial infarction, characterized by the appearance of new Q waves, reduction of over 25% in R wave amplitude in two or more contiguous leads, levels of creatinephosphate kinase isoenzyme MB≥5% of the creatinephosphate kinase value for over 18 h; shock, characterized by systolic pressure <80 mm Hg, oliguria, and signs of tissue hypoperfusion (nonresponsive to volume infusion); and cardiac arrhythmia requiring electric cardioversion/defibrillation.

2.2. Anesthesia

Patients received 0.02–0.04 mg/kg oral lorazepam on the night before surgery and 90 min before anesthesia induction. Anesthesia was induced with midazolam (50–100 μg/Kg) and 1–2 mg/kg propofol. Muscle relaxation was achieved with pancuronium (0.008 mg/Kg). Mechanical ventilation was carried out with a tidal volume of 10–12 mL/Kg, a respiratory rate of 10–12 c/min (subsequently altered according to blood gas samples), and an inspired fraction of oxygen of 30%. In patients operated with cardiopulmonary bypass, anesthesia was maintained by means of continuous infusion of midazolam (0.5–2 μg/kg min) and fentanyl (0.04–0.16 μg/kg min). In the off-pump group, subarachnoid administration of preservative-free fentanyl (100 μg) and morphine (0.5 mg) was performed prior to anesthesia induction. Anesthesia was maintained with isoflurane (expiratory concentration of 0.5–1.5 vol.%). Midazolam and fentanyl were administered as described for the on-pump group.

In the group operated with cardiopulmonary bypass, 500 IU/Kg of heparin was administered as a loading dose, followed by 100 IU/Kg every hour. The action of heparin was controlled through the activated clotting time, which was kept above 480 s. In the off-pump group, an initial dose of 150 IU/Kg was used, in addition to continuous infusion of heparin at 1000 IU/h. Reversion of heparin action was obtained with protamine at a mg/mg ratio.