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ORIGINAL ARTICLE

Prolonged Cardiopulmonary Bypass is a Risk Factor for Intestinal Ischaemic Damage and Endotoxaemia

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Background Intestinal ischaemia–reperfusion, a frequent occurrence during cardiac surgery with cardiopulmonary bypass (CPB) induces a systemic inflammatory reaction. We hypothesised that ischaemia–reperfusion following prolonged CPB could increase intestinal permeability and thus, lead to endotoxin translocation from the intestine to the bloodstream.

Material and Methods Patients subjected to coronary artery bypass grafting with CPB were included: Group 1 (CPB ≥ 90 minutes) or Group 2 (CPB < 90 minutes). Intestinal Fatty Acid Binding Protein (I-FABP), TNF alpha, IL6, IL8, and endotoxin levels were measured before the induction of general anaesthesia (T1), at 6 (T2), and 24 hours (T3) after surgery.

Results The low level of I-FABP at T1 increased for every patient in Group 1 at T2 (1015.5 pg/mL–2608.5 pg/mL, $p = 0.02$) and in Group 2 (1123.5 pg/ml–2284.0 pg/ml, $p < 0.001$). Furthermore, at T3, the I-FABP level was over three times higher in Group 1 than in Group 2 (2178 pg/mL vs 615 pg/mL; $p < 0.001$). I-FABP correlated with CPB time ($R = 0.6$, $p < 0.001$) at T3. After surgery, endotoxins were elevated in 73% of patients in Group 1 and in 32% in Group 2 and correlated with CPB time (at T2, $R = 0.5$, $p = 0.002$; at T3, $R = 0.4$, $p = 0.016$).

Conclusions The duration of CPB is linked to the release of biomarkers that indicate ischaemic-reperfusion damage to the gastrointestinal mucosa and endotoxaemia. I-FABP assay may help to identify patients presenting with intestinal damage, who are at risk of bacterial translocation.

Keywords Cardiopulmonary bypass • Intestinal ischaemia-reperfusion • Intestinal fatty acid binding protein • Endotoxin

Introduction

Intestinal ischaemia–reperfusion, a common occurrence during cardiac surgery with cardiopulmonary bypass (CPB), induces a systemic inflammatory reaction [1–3]. The inflammatory stimulus is mostly related to the exposure of blood to artificial materials used in the circuit and to the altered blood flow and temperature. This can lead to ischaemic damage in sensitive organs like the intestines, and consequently, there can be a possible translocation of bacteria and endotoxins across the intestinal mucosa to the bloodstream. The presence of endotoxins in the circulation can exacerbate a systemic inflammatory response that had already been induced by the surgery [4]. The mechanisms that contribute to the induction of an inflammatory response include activation of the cellular components of inflammation stimulated by an oxygen deficiency, subsequent alterations of coagulation and complement pathways, and the production of reactive oxygen species

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during the reperfusion phase [5]. Different inflammatory mediators are elevated in patients exposed to extracorporeal membrane oxygenation, including interleukins IL-1, IL-6, IL-8, TNF-a [6].

There is no standard, easy procedure or routine laboratory test available to detect and monitor ischaemic damage in the intestines or the increased permeability of gastrointestinal mucosa during cardiac surgery. Some research relies on endoscopic methods to study the induction of intestinal alterations and gastric tonometry has been used to measure gastric intramucosal pH and gastric partial pressure of carbon dioxide [7–9]. A significant increase in the partial pressure of the carbon dioxide gradient between the gastric mucosa and arterial blood and the reduction of gastric intramucosal pH after CPB indicates ischaemic damage of the gastric mucosa. Another way to assess alterations in the intestinal mucosa is to use a test of intestinal permeability with orally administered radioisotopes and a double sugar intestinal absorption test. Using a chromium-labelled test, enhanced intestinal permeability was shown to have increased during CPB and it reached a peak at the sixth and twelfth hour after termination of CPB [7,10].

Here, we assess changes in intestinal fatty acid binding protein (I-FABP), which has been recently used as a blood biomarker to study the occurrence and consequences of intestinal damage in critically ill patients [11,12]. We aimed to establish whether elevated I-FABP levels were associated with the activation of an immune response and endotoxin translocation during cardiopulmonary bypass. Despite the evidence of intestinal barrier dysfunction in patients subjected to cardiac surgery, there is little data on the risk factors and consequences of bacterial antigen translocation. We hypothesised that ischaemia-reperfusion following prolonged CPB could increase intestinal permeability and thus, lead to endotoxin translocation from intestinal flora.

Material And Methods

The study protocol was approved by the Bioethics Committee of Wroclaw Medical University and all patients provided written informed consent. Clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki. All patients were scheduled to undergo elective on-pump coronary artery bypass grafting (CABG) at the Department of Cardiac Surgery, Wroclaw Medical University, Poland. Patients were excluded if they required emergency surgery or a surgical procedure in addition to coronary artery bypass grafting surgery (CABG). Other exclusion criteria were a previous coronary artery bypass graft, a preoperative left ventricular ejection fraction less than 0.40, unstable angina, or other co-morbidities related to diabetes mellitus, or renal or liver failure.

Surgery

The anaesthetic and surgical procedures were previously described in detail [13]. Briefly, patients were anaesthetised with propofol and sufentanyl. Pancuronium was given to facilitate intubation. Anaesthesia was maintained with sevoflurane 1–3 Vol%, associated with sufentanyl infusion 0.2–0.5 μg/kg/h. Surgical techniques were the same for all patients and were performed by either of two cardiac surgeons with uniform myocardial protective techniques. In all patients a standard open bypass circuit was used, composed of uncoated polyvinylchloride tubing, a hard-shell venous reservoir, a hollow fiber membrane oxygenator (Sorin Group, Italy) with an integrated polyester arterial line filter of 40 μm pore size, and a roller pump with a non-pulsatile flow 2.2–2.4 l/minutes/m2 (Stockert S3, Sorin Group, Germany). Heparin (300 IU/kg) was given to maintain an activated clotting time of > 480 seconds during CPB. Perfusion pressure was kept at 60–80 mmHg. After aortic cross-clamping, intermittent warm blood cardioplegia was delivered at a perfusate temperature. Normothermia (37 °C) was maintained during the entire procedure. Postoperatively, patients were cared for in a specialised Intensive Care Unit (ICU). Sedation with propofol 0.5-1.0 mg/kg/h was continued until patients were able to be weaned from the ventilator and extubated.

Bypass Time

In our study, mean CPB time was 90 ± 23 minutes. Based on the duration of CPB and on the recently published data, patients were divided into Group 1 (CPB ≥ 90 minutes, N = 15) or Group 2 (CPB < 90 minutes, N = 19). Results of a recently published large analysis of 1,863 cardiac surgery procedures indicated that bypass time was a significant factor for morbidity, associated with mediastinal blood loss, ICU length of stay, postoperative length of stay, and inhospital mortality; CPB duration ≥ 90 was considered as a prolonged time [14]. In another study of a total of 2,469 CABG operations, CPB time ≥ 90 minutes was a significant predictor of blood transfusion in the operating room [15].

Samples

Arterial blood samples for determining Intestinal Fatty Acid Binding Protein (I-FABP), tumour necrosis factor alpha (TNF-alpha), interleukin 6 (IL-6), interleukin 8 (IL-8), and endotoxin levels were drawn before the induction of general anaesthesia (T1, baseline), at 6 (T2), and 24 hours (T3) after surgery. Serum was obtained by centrifugation of blood at 3000 rpm for 10 minutes. Samples were stored at 70 °C. Serum concentrations of I-FABP, TNF-alpha, IL-6, and IL-8 were measured using quantitative sandwich enzyme immunoassay techniques (R&D Systems, Minneapolis, USA). The endotoxin concentration was measured with a commercially available Limulus Amebocyte assay (Pierce LAL Chromogenic Endotoxin Quantitation Kit, Rockford, USA).

Statistical Analysis

Data were analysed with Statistica 12.0 (StatSoft, Inc. Tulsa, USA). Data are expressed as median and interquartile ranges

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