Pro- and anti-inflammatory cytokine patterns during and after cardiac surgery in young children

Received: 10 March 1997 / Accepted in revised form: 26 August 1998

Abstract The systemic inflammatory response that occurs after cardiopulmonary bypass shows many changes similar to those seen in sepsis. The mechanisms for these changes have been attributed to cellular and humoral activation, such as increased secretion of cytokines and complement. The aim of our study was to investigate the cytokine pattern of pro- and anti-inflammatory cytokines in young children during and after bypass surgery. Nineteen children undergoing either septal defect correction ($n=12$), or more complex surgery ($n=7$), were prospectively included in this study. There were significant higher pre-operative levels of circulating cytokines in the latter group. Cardiopulmonary bypass surgery induced in both groups a rise in circulating cytokine levels and a sharp decline in the capacity of the leucocytes to secrete interleukines-6 and -8 in response to ex vivo stimulation with lipopolysaccharide. Ex vivo production of interleukine-1 receptor antagonist was slightly attenuated by the procedure.

Conclusions The downregulation of ex vivo pro- and, to some extent, anti-inflammatory cytokine production may be a reflection of a cellular stress response, induced by anaesthesia, cardiopulmonary bypass and surgery.

Key words Cytokines · Cardiopulmonary bypass

Abbreviations A/VSD atrial/ventricular septal defect · CPB cardiopulmonary bypass · ICU intensive care unit · IL-1RA interleukine 1 receptor antagonist · IL-6sr soluble interleukine 6 receptor · LPS lipopolysaccharide · TNF tumor necrosis factor

Introduction

The use of extracorporeal circulation in correcting congenital heart defects has been associated with postoperative clinical sequelae very similar to that observed in septic patients. These include fever, leucocytosis, capillary leakage, respiratory distress, renal and CNS dysfunction. During the last few years, considerable research has focused on identifying mechanisms involved in this systemic inflammatory response syndrome [2, 4, 15, 23]. Cytokines are now believed to be key factors [5, 21]. Among other functions, they serve signal communication between immunological and inflammatory cells. Some cytokines appear to inhibit the inflammatory reaction, thereby constraining the potential deleterious effects of ongo-
The aim of our study was to investigate whether in children below the age of 1 year, cardiopulmonary bypass (CPB) is associated with changes in the levels of circulating pro- and anti-inflammatory cytokines [19, 25]. We measured the levels of circulating IL-1β, IL-6, IL-1 receptor antagonist (IL-1RA) and the soluble IL-6 receptor (IL-6sR) before and after CPB. To measure putative changes in the capacity of leucocytes to produce cytokines, we also determined the ex vivo production of IL-6, IL-8 and IL-1RA during and after CPB.

Methods

Nineteen patients undergoing open heart surgery were prospectively included in this study. Patient characteristics and operative procedures are shown in Table 1. There was a significant difference in age between the group with septal defects (mean age 5.7 months) and the group admitted for more complex surgery (mean age 1.7 months). The duration of CPB was longer in the group undergoing complex surgery. None of the patients had pre-operative signs of infections, both clinically and biochemically. The study was approved by the institutional ethical and research review boards and informed consent was obtained from the parents.

Surgical procedure

Anaesthetic management was uniform in all patients. As part of the anaesthesia protocol, dexamethasone (1 mg/kg) was given during induction. To evaluate the influence of corticosteroids, 6 of the 12 patients with septal defect correction did not receive dexamethasone. The CPB circuit was identical in all patients and included a Cobe VPCML oxygenator, a roller pump and an arterial filter. Nonpulsatile flow was used. Pump priming consisted of crystalloid, human albumin and donor blood. During prolonged bypass, fresh frozen plasma and platelets were given in order to control blood coagulation. The myocardium was protected with Plegisol (30 ml/kg) during bypass. Heparin was administered for 18 h in 96-well flat-bottom microtitre plates (Nunc, Glostrup, Denmark) with 200 pg/ml lipopolysaccharide (LPS; Difco, Detroit, MI). At the end of the culture period, plates were centrifuged for 5 min at 450 × g. Supernatants were collected and stored at −80°C until analysis.

Results

Pre-operative levels of circulating cytokines in septal defect patients

In all pre-operative plasma samples of patients admitted for septal defect correction, IL-1β and IL-6 were below the detection level (Table 2). IL-6sR was detectable in all pre-operative plasma samples of atrial/ventricular septal defect (A/VSD) patients (Table 2). In only 2 out of 12 plasma samples of A/VSD patients, was IL-1RA pre-operatively detectable. One of these patients suffered from pre-operative cyanosis. The plasma IL-1RA levels in the other 12 patients were below 50 pg/ml.

Table 1 Patient characteristics (AVSD atrioventricular septal defect, DILV double inlet left ventricle, HAO hypertrophic aorta obstruction, PS pulmonary stenosis, TGA transposition of the great arteries, Tr. Art. truncus arteriosus)