Controlled reoxygenation during cardiopulmonary bypass decreases markers of organ damage, inflammation, and oxidative stress in single-ventricle patients undergoing pediatric heart surgery

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Objective: Single-ventricle patients undergoing pediatric heart surgery are a high-risk group owing to reoxygenation injury during cardiopulmonary bypass (CPB). The present study investigated the effects of controlled reoxygenation CPB on biomarkers of organ damage, inflammation, stress, and long-term functional outcomes in cyanotic patients with either a single or double ventricle during open heart surgery.

Methods: Cyanotic patients with either a single (n = 32) or double (n = 47) ventricle undergoing surgical correction were randomized to receive CPB using either standard oxygen levels or controlled reoxygenation. The markers of cardiac injury, inflammation, stress, and cerebral and hepatic injury were measured preoperatively, at 10 and 30 minutes after starting CPB, and at 10 minutes and 4 and 24 hours after CPB. The data were analyzed using a mixed regression model.

Results: No difference was found in the pre- or intraoperative characteristics between the standard and controlled reoxygenation CPB groups for single- or double-ventricle patients. In the single-ventricle patients, controlled reoxygenation CPB significantly ($P < .05$) decreased the markers of organ damage, inflammation, stress, and oxidative stress. In contrast, the markers of inflammation and cardiac injury were not altered by controlled reoxygenation CPB in the double-ventricle patients.

Conclusions: Controlled reoxygenation CPB decreased the markers of organ damage, stress, inflammation, and oxidative stress in single-ventricle patients undergoing cardiac surgery. (J Thorac Cardiovasc Surg 2014;148:792-801)

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A functional single ventricle describes an array of heart malformations with a single ventricular pumping chamber.[1] Although a variety of diverse anatomies exist (eg, hypoplastic left heart syndrome, tricuspid atresia, and double-inlet left ventricle), children with these malformations are exposed to very similar pathophysiologic states. The functional single-ventricle palliation often includes 3 operations. The first stage of palliation is performed at birth. The second stage is a bidirectional Glenn operation, usually undertaken at 6 to 8 months of age. The third, and final, stage is the Fontan operation, which can be performed between 18 months and 4 years of age. These infants and children are at a very high risk of developing perioperative and long-term complications that could affect their quality of life.[1,2] Additionally, a single ventricle has been considered a risk factor for operative mortality,[3] although this remains debatable.[4]

Reintroduction of high oxygen levels to cyanotic patients when starting cardiopulmonary bypass (CPB) leads to reoxygenation injury with significant organ damage, including the myocardium and triggering of a systemic inflammatory response.[5-7] One of the strategies proposed to avoid reoxygenation injury has been the use of controlled reoxygenation using a partial pressure of oxygen in arterial blood (PaO_2) similar to the patient's preoperative oxygen saturation when starting CPB. This has been shown to ameliorate reoxygenation injury in experimental models,[8,9] in adult patients,[10] and, more recently, in cyanotic pediatric patients with mixed

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Abbreviations and Acronyms

C3α = complement activation
CI = confidence interval
CPB = cardiopulmonary bypass
IL = interleukin
MIF = microphage migration inhibitor factor
PaO_2 = partial pressure of oxygen in arterial blood
TnI = troponin I

pathologic features who are undergoing cardiac surgery.[11] However, the degree and nature of cyanosis will vary depending on the individual pathologic features, with no studies comparing the efficacy of this intervention in cyanotic patients with different pathologic features and different risk stratification. Of particular interest are patients with a single ventricle who are at a greater risk of developing reoxygenation injury and its deleterious effects on multiple organ function. These patients have chronic cyanosis and have a relatively short cardioplegic arrest; thus, it has been easier to identify CPB-induced reoxygenation as the main culprit triggering organ injury and systemic stress. In the present study, we investigated whether controlled reoxygenation when starting CPB would alter the markers of organ damage, stress, inflammation, and oxidative stress in cyanotic patients with a single or double ventricle when undergoing cardiac surgery.

METHODS

The patients in the present study were a part of a large trial (study no. CS/2007/2678, recruitment just completed) investigating the effect of controlled reoxygenation CPB in cyanotic children undergoing surgical correction at the Bristol Royal Hospital for Children. The patients were randomized to receive CPB with either a standard oxygen partial pressure (150-200 mm Hg, hyperoxic to patients) or controlled oxygen partial pressure (matched to patients, normoxic). Data from a group of patients in the initial phase of recruitment have been published without any reference to the specific pathologic features or clinical outcomes.[11] The present study was a subanalysis of the effect of controlled reoxygenation in patients (including those from the first report) with either single (n = 32) or double (n = 47) ventricular pathologic features and included long-term clinical data (eg, cardiac function, New York Heart Association, and survival).

All patients were in a stable condition without preoperative respiratory or inotropic support. Standard CPB referred to a pump prime prepared to the current ''best practice'' protocols, which has an oxygen partial pressure that is relatively hyperoxic for a cyanotic patient. The hospital research ethics committee approved the present study, and parental informed consent was obtained for all patients. Treatment allocations, stratified by age (<6 months vs ≥6 months), were generated by computer in advance of starting the study, using block randomization with varying block sizes. The surgical team, with the exception of the perfusionists, were unaware of the treatment allocation. The preoperative characteristics of the 2 groups for the single- and double-ventricle patients are summarized in Table 1 and Table E1.

All operations were performed with CPB. The intraoperative anesthetic and operative techniques were standardized as previously reported.[12] Cold blood (4°C-6°C) St Thomas' no. I-based blood cardioplegic solution (4:1 dilution blood/St Thomas' no. I crystalloid cardioplegia) was used for myocardial preservation, with the following composition: 16 mM $MgCl_2$, 2 mM $CaCl_2$, 20 mM KCl, 147 mM NaCl, and 1.0 mM procaine HCl. Additional cardioplegia was administered after each 20 minutes of aortic crossclamping. Postoperatively, all the patients were admitted to the pediatric intensive care unit and were treated according to the unit protocols[12,13] by intensivists and pediatric cardiologists who were unaware of the treatment allocation.

CPB and Control of Oxygen Partial Pressure

The reoxygenation strategy when starting CPB was developed in our clinical perfusion science department.

Controlled reoxygenation CPB. The CPB circuit was set up and primed in accordance with the protocol,[5,13] usually with a red blood cell/albumin prime solution or, occasionally, a clear prime solution, depending on the patient's hemoglobin level. Just before the initiation of CPB, medical nitrogen was delivered to the gas exchange device (oxygenator) by way of a bacteriologic filter (0.2 μm) at a rate of 100 to 200 mL/min, and the prime was circulated at approximately 1000 mL/min. An in-line PaO_2 monitor was used to measure the PaO_2 of the prime. Using this technique, we were able to reduce the PaO_2 of the prime fluid to match that of the patient's own PaO_2 levels. Finally, before CPB was established, the prime PaO_2 was confirmed using a point-of-care blood gas analyzer, and the in-line PaO_2 monitor was calibrated. CPB was initiated in this relatively ''normoxic'' manner, and the PaO_2 levels of the arterialized blood were adjusted accordingly during CPB (Table 1).

Standard (hyperoxic) CPB group. Oxygen delivery was run at 100% to maintain the arterial oxygen saturation at >95% and PaO_2 levels of 150 to 200 mm Hg when starting CPB (Table 1 and Table E1).

Biomarkers of Organ Injury and Stress

The primary endpoints were the release of troponin I (TnI) (enzyme-linked immunosorbent assay; Access Immunoassay System, Beckman Instruments Inc, Fullerton, Calif) and 8-isoprostane (enzyme immunoassay; Cayman Chemicals, Ann Arbor, Mich) as measurements of myocardial cell damage and oxidative stress, and the release of markers of the whole body inflammatory response, including complement activation (C3α; BD OptEIA Human C3a ELISA; BD Biosciences, Franklin Lakes, NJ), interleukin (IL)-6, IL-8, IL-10, and microphage migration inhibitor factor (MIF) (enzyme-linked immunosorbent assay; Amersham Biosciences UK, Little Chalfont, United Kingdom), and stress response (cortisol; Access Immunoassay System, Beckman Coulter, Pasadena, Calif). Cerebral injury was assessed by the postoperative release of protein S100 (CanAg S100 EIA; CanAg Diagnostics AB, Goteborg, Sweden), and α-glutathione S-transferase (Biotrin High Sensitivity Alpha GST EIA Assay; Biotrin International, Dublin, Ireland) was used to assess hepatic cell damage.

Blood (2-3 mL) was collected preoperatively, at 10 and 30 minutes after starting CPB, and at 10 minutes and 4 and 24 hours after the cessation of CPB. This was immediately centrifuged at 4°C, at 4000 rpm for 15 minutes. The resulting plasma was then frozen in liquid nitrogen before storage at −80°C. A laboratory technician, who was unaware of the treatment allocation and clinical status of the patient, performed the assays.

The clinical outcomes (inotropic support, renal failure, intubation time, postoperative hospital stay, New York Heart Association class, and survival at follow-up) were also recorded. Myocardial function was assessed preoperatively, immediately postoperatively, and during follow-up for patients with a single ventricle using commercially available instruments (Vivid 7 imaging device, GE Healthcare, Little Chalfont, United Kingdom). All echocardiographic and Doppler data were obtained in digital format and stored on a workstation for offline analysis (EchoPAC; GE Vingmed Ultrasound AS, Horten, Norway). Ventricular function was defined as

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