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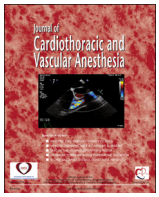

Pulmonary and Systemic Vascular Resistances After Cardiopulmonary Bypass: Role of Hemolysis

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Objectives: Prolonged cardiopulmonary bypass (CPB) is associated with hemolysis, resulting in increased plasma oxyhemoglobin and vascular nitric oxide depletion. The authors hypothesized that hemolysis associated with CPB would reduce nitric oxide bioavailability, resulting in high pulmonary and systemic vascular resistances that after CPB would normalize gradually over time, due to clearance of plasma oxyhemoglobin. The authors also investigated whether prolonged CPB ($\geq$ 140 min) produced increased levels of hemolysis and greater pulmonary and systemic vasoconstriction.

Design: Prospective cohort study.

Setting: Single-center university hospital.

Patients: The study comprised 50 patients undergoing elective cardiac surgery requiring CPB.

Interventions: Plasma hemoglobin and plasma nitric oxide consumption were measured before surgery and after CPB. Pulmonary and systemic hemodynamics were measured after CPB. The effects of short ($<$ 140 min) and prolonged ($\geq$ 140 min) CPB on these parameters were considered.

Measurements and Main Results: Pulmonary and systemic vascular resistances and plasma hemoglobin and nitric oxide consumption were highest at 15 minutes after CPB and then decreased over time. Pulmonary and systemic vascular resistances and plasma hemoglobin and plasma nitric oxide consumption were higher in patients requiring prolonged CPB. The reduction in plasma nitric oxide consumption from 15 minutes to 4 hours after CPB was correlated independently with the reductions in pulmonary and systemic vascular resistances.

Conclusions: Prolonged CPB was associated with increased plasma hemoglobin and plasma nitric oxide consumption and pulmonary and systemic vascular resistances. The reduction in plasma nitric oxide consumption at 4 hours after CPB was an independent predictor of the concomitant reductions in pulmonary and systemic vascular resistances.

Key Words: cardiopulmonary bypass; hemolysis; plasma hemoglobin; nitric oxide; pulmonary vascular resistance; systemic vascular resistance

IN THE UNITED STATES, cardiopulmonary bypass (CPB) is a common procedure used during cardiac surgery with cardio-circulatory arrest. CPB,[1–4] together with the transfusion

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of damaged autologous red blood cells (RBCs) recovered by intraoperative cell salvage devices[1,5-8] and the transfusion of stored RBCs,[1,9–11] are major sources of plasma hemoglobin (Hb) during and after cardiac surgery. Longer cardiopulmonary bypass is associated with increased hemolysis and higher levels of circulating plasma Hb.[1,7]

Plasma oxyhemoglobin (oxyHb) scavenges and depletes nitric oxide (NO).[12,13] The healthy vascular endothelium produces NO, which induces vascular smooth muscle relaxation.[14,15] Previous studies have demonstrated that the decreased bioavailability of NO, caused by increased plasma oxyHb, was associated with both systemic[16] and pulmonary[16-18] vasoconstriction. Prior hemodynamic studies focused on the effects of CPB on the pulmonary vascular resistance (PVR)[19–21] and systemic vascular resistance (SVR).[22,23] Recently, Toikkanen et al[21] highlighted the gradual decrease of PVR in patients undergoing CPB for coronary artery bypass grafting (CABG) during the first postoperative day. Kristof and Magder[22] studied patients undergoing CPB for CABG and heart valve procedures and observed that SVR was higher during the first hours after the discontinuation of CPB compared with the subsequent hours and that SVR continued to decrease for up to 18 hours after CPB.

The relationship between PVRs and SVRs and the level of hemolysis after prolonged CPB in patients undergoing cardiac surgery has not been determined. The authors designed a prospective, observational study in patients undergoing cardiac surgery requiring CPB. The authors hypothesized that these patients would develop hemolysis associated with CPB, which would reduce NO availability, resulting in elevated PVRs and SVRs. PVRs and SVRs decrease over time after CPB as plasma oxyHb is turned into methemoglobin (metHb) and cleared from the circulation; lower levels of plasma oxyHb would be associated with decreased plasma NO consumption. The authors further investigated whether prolonged CPB (≥ 140 min) was associated with increased plasma Hb, decreased NO bioavailability, and increased PVRs and SVRs.

Methods

Institutional Review Board and Study Protocol

This study was carried out in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki). The Partners Institutional Review Board approved all procedures, and the enrolled patients provided written, informed consent. The authors designed a prospective, observational, cohort study in the cardiac operating rooms and in the cardiac intensive care unit (ICU) of the Massachusetts General Hospital. Inclusion criteria were as follows: (1) age > 18 years, (2) a cardiac surgical procedure requiring use of CPB, and (3) admission to the cardiac ICU after surgery. Exclusion criteria were as follows: (1) patients who received 1 or more packed red blood cells (PRBCs) transfusions in the 6 hours before surgery, (2) pre-existing hemolysis of any origin, and (3) a preoperative Hb level < 7 g/dL. Patients were included in the study after entry criteria were met and informed consent was obtained. This study was conducted at the Massachusetts General Hospital from June 2014 to March 2015.

The authors identified patients from preoperative assessment lists, and the proposal of their enrollment was discussed before and then approved consensually with the cardiac surgeons. Demographic, preoperative, intraoperative, and postoperative information were recorded until patient discharge or death. The authors stratified patient surgical risk using the EuroSCORE II model.[24] The study did not influence the patient standard of care, which was managed by anesthesiologists and surgical teams in accordance with Massachusetts General Hospital institutional protocols. Induction of anesthesia was managed with midazolam, propofol, fentanyl, and rocuronium. Anesthesia was maintained with isoflurane. CPB was usually primed with 1,600 mL of saline. Patient temperature was maintained at 34°C (18°C during deep circulatory arrest) during the surgical procedure through a water cooler connected with the CPB machine (Stockert S5; Sorin Group Italia, Mirandola, Modena). In all patients blood was saved, collected, and then reinfused with an intraoperative cell salvage system (XTRA; Sorin Group Italia, Mirandola, Modena) during the entire surgical procedure. Criteria for blood product transfusions followed the Blood Component Utilization Guidelines of Massachusetts General Hospital.[25]

Patients were transferred to the ICU intubated and mechanically ventilated with propofol infusion. Pain was controlled with opioids (hydromorphone or morphine) immediately after surgery and during the postoperative period. Ketorolac and/or acetaminophen were added in the ICU if needed. Perioperative use of vasopressors (norepinephrine, epinephrine, and vasopressin); vasodilators (nitroglycerin and nitroprusside); and inotropic infusion (milrinone and dopamine) was recorded, in accordance to clinical choice.

Blood Samples

Blood was sampled via an arterial line placed in the radial artery and used to monitor invasive arterial pressure. Blood from the arterial line was sampled at the following 4 time points: before surgery (preoperatively) and 15 minutes, 4 hours, and 12 hours after CPB. After collection, the samples were centrifuged at 2,500 rpm for 10 minutes at 4°C and stored at −80°C. Hemolysis and plasma NO bioavailability were measured during the perioperative period by measuring plasma Hb (expressed as heme) and plasma NO consumption, respectively.

Plasma Hb and NO consumption measurements are detailed in the following:

- Plasma Hb measurement: Plasma Hb was measured with a QuantiChrom Hemoglobin Assay Kit (BioAssay Systems, Hayward, CA), which measures the concentration of Hb, including all Hb derivatives.
- Plasma NO consumption: Plasma NO consumption was determined with an NO chemiluminescence analyzer (Sievers 280i; GE, Boulder, CO), with a validated assay as reported by Wang et al.[26] Briefly, a steady-state NO signal (in mV) with a solution of DETA-NONOate (Caymen