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Developing dual hemofiltration plus cardiopulmonary bypass in rodents

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ABSTRACT

Background: Emerging therapies for prolonged cardiac arrest (CA) include advanced circulatory interventions like emergency cardiopulmonary bypass (ECPB) and continuous venovenous hemofiltration (CVVHF). However, preclinical studies are limited because of the absence of a practical method of using CVVHF along with ECPB in rodents.

Methods: We modified a CA model with ECPB resuscitation to include the CVVHF circuit. Adult rats were cannulated via the femoral artery or vein and the jugular vein for the ECPB circuit. A new circuit for CVVHF was added to allow ECPB and CVVHF to be started simultaneously. CVVHF blood flow at 3 mL/min could be controlled with a screw clamp during ECPB. After cessation of ECPB, the CVVHF flow was maintained using a roller pump. The filtration rate was controlled at 40 mL/h/kg in the standard volume of CVVHF and 120 mL/h/kg in the high volume (HV) of CVVHF. The driving force of hemofiltration was evaluated by monitoring transmembrane pressure and filter clearance (FCL).

Results: Transmembrane pressure in both groups was stable for 6 h throughout CVVHF. FCL of blood urea nitrogen and potassium in the standard volume group was significantly less than the HV group ($P < 0.01$). FCL of blood urea nitrogen and potassium was stable throughout the CVVHF operation in both groups.

Conclusions: We developed a method of CVVHF along with ECPB in rodents after CA. We further demonstrated the ability to regulate both standard and HV filtration rates.

1. Introduction

Advanced therapies for the treatment of prolonged cardiac arrest (CA) include circulatory interventions such as emergency cardiopulmonary bypass (ECPB) and continuous venovenous hemofiltration (CVVHF). However, the studies of these advanced technologies are limited because of the absence of a practical method of using CVVHF along with ECPB in small animals.

ECPB, a system that pumps the oxygenated blood through a whole body, is thought to rescue a CA patient [1–3]. This

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system allows an extended window of time to determine the cause of CA and takes the necessary steps to restore adequate organ functions of patients [4].

CVVHF is a therapy for blood purification using a pump to pass the blood over a filter. The driving force of CVVHF is a pressure gradient rather than a concentration gradient. Several studies [5,6] have suggested that the use of CVVHF is associated with improved outcomes in CA. Therefore, CVVHF has been used in CA [5] and cardiac surgeries with cardiopulmonary bypass [7–9].

Although previous studies have shown the method for combination of ECPB with CVVHF, all of surgical sets has been done for the use of large animals [6,10,11]. It is difficult to operate two extracorporeal blood circuits in small animals because of the little blood volume. Therefore, there have been no rodent models to date.

For these reasons, we sought (a) to develop a practical method for dual extracorporeal circuits of CVVHF and ECPB in rats suffering CA, (b) to measure transmembrane pressure (TMP) and filter clearance (FCL) to evaluate the efficacy of CVVHF, and (c) to test the hypothesis that high-volume (HV) CVVHF was feasible in rats.

2. Materials and methods

The study protocol was approved by the Institutional Animal Care and Use Committee of the University of Pennsylvania. Sixteen adult male Sprague–Dawley rats (450–550 g; Charles River Laboratories, Wilmington, MA) were used.

2.1. Procedures

2.1.1. Surgical preparation

All the instrumentation was performed according to the previously described protocol [12,13]. In brief, animals were anesthetized with 4% isoflurane (Isosthesia; Butler-Schein AHS, Dublin, OH)/96% oxygen and intubated with a 14-gauge plastic catheter (Surflo; Terumo Medical Corporation, Somerset, NJ). Animals were mechanically ventilated (Ventilator Model 683; Harvard Apparatus, Holliston, MA), and anesthesia was maintained with isoflurane.

The left femoral artery was cannulated (sterile polyethylene-50 catheter inserted for 2 cm) for the continuous arterial pressure monitoring (MLT844; ADInstruments, Bridge Amplifiers ML221; ADInstruments, Colorado Springs, CO).

2.1.2. CA and resuscitation with cardiopulmonary bypass

After all the instrumentation, 2 mg/kg of vecuronium bromide (Hospira, Lake Forest, IL) was administered and asphyxia was induced for 12 min. Circulatory arrest was defined as a mean arterial pressure of <20 mm Hg. The ECPB circuit was primed with 10 mL of Plasma-Lyte A (Baxter, Deerfield, IL), 10 mL of 6% Hetastarch (Hospira), 0.8 mL of 0.406 mEq/mL magnesium sulfate (APP Pharmaceuticals, Schaumburg, IL), and 0.3 mL of 3.3 mmol/mL THAM Solution (XVIVO Perfusion AB, Göteborg, Sweden). Additional 8 mL of Plasma-Lyte A and 4 mL of 6% Hetastarch, a total volume of 12 mL, was added to the venous reservoir to maintain a stable circulating volume during ECPB. After 12 min of asphyxia, resuscitation was started with the initiation of the ECPB blood flow. Activated coagulation time (ACT) was maintained with heparin (SAGENT Pharmaceuticals) at >250 s during ECPB. At the end of 30 min ECPB, the remaining blood in the ECPB circuit was collected for a retransfusion into the animal. The rate of the transfusion was 6 mL/kg/h through the postresuscitation care period.

2.1.3. Development of CVVHF during and after cardiopulmonary bypass

The left femoral vein was cannulated with a 20-gauge catheter cannula (Insyte-W; BD, Franklin Lakes, NJ) for blood inflow to the CVVHF circuit. The right femoral artery was cannulated with a 20-gauge catheter cannula for blood inflow to ECPB. The right internal jugular vein was cannulated for the venous outflow of ECPB and CVVHF with a modified 4 hole 14-gauge catheter (Surflo; Terumo Medical Corporation), which was advanced to the vena cava. This catheter was heparin locked with 300 UI of heparin.

CVVHF was started simultaneously with the resuscitation by ECPB. The blood flow of both circuits was supplied from the same roller pump. A flow sensor (TS410; Transonic Systems, Ithaca, NY) was placed on the tube to monitor the rate of blood flow (Fig. 1A), which was controlled at 3 mL/min (5.5–6.5 mL/min/kg). The rate of blood flow was adjusted by a screw clamp placed on a tube (inside diameter 1.4 mm) for the inflow of CVVHF (Fig. 1A). The screw clamp was carefully adjusted according to the flow rate measured by the flow sensor throughout ECPB (Fig. 1A and C).

At the end of 30 min ECPB, the ECPB circuit was removed (Fig. 1B and D). And then, the roller pump in the CVVHF circuit was started at the blood flow rate of 3 mL/min (5.5–6.5 mL/min/kg). CVVHF was operated for 6 h in all animals.

2.1.4. Two settings of hemofiltration volume

The filtration rate was controlled at 20 mL/h (35–45 mL/h/kg) for the standard volume CVVHF and 60 mL/h (110–135 mL/h/kg) for the HV CVVHF. Animals were randomly assigned into each group. The effluent was drawn from a side hole of the hemofilter using a drawing pump (Genie Touch Syringe Pump; Kent Scientific, Torrington, CT). A replacement fluid, added at the same rate as the effluent was drawn, was infused through a pump using a three way stopcock placed between a catheter inserted into the left femoral vein and a tube for the inflow of CVVHF (Fig. 1, post-dilution, zero-balanced filtration). For CVVHF, a hollow-fiber hemofilter, AN69ST (GAMBRO Industries, Meyzieu, France; Table 1), was used. PrismaSATE BGK 4/2.5 (Gambro Renal Products, Daytona Beach, FL) was used as the replacement fluid. Priming volume of the CVVHF circuit was 6.9 mL. A total of 50 UI of heparin was injected between 2 and 3 h after the start of CVVHF, and then ACT was maintained at >180 s during CVVHF.