
Original Article***Use of a Low-Prime Circuit for Bloodless Heart Transplantation in Xenotransplant of 5–7 Kilogram Primates***

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ABSTRACT

There is a great effort to decrease blood product use during open-heart surgery in pediatrics. We were presented with a research challenge to accomplish heart xenotransplantation from donor cynomologous monkey (*Macaca fascicularis*) to recipient olive baboon (*Papio anubis*) of 5–7 kilograms without benefit of donor or banked blood products. The purpose of this study was to design and implement a practical, low-volume circuit to minimize hemodilution and avoid the use of blood products.

A simple circuit was assembled using a low-volume oxygenator with hardshell venous reservoir, an 1/8-inch arterial line, an 1/4-inch venous line, and gravity drainage. Three xenotransplants were performed and evaluated. The mean recipient weights were 6.3 ± 0.7 kg. Circuit prime volume was 228 ± 5.8 mL, and bypass time was 85 ± 6.7 min. Blood flow rates were 585 ± 113 mL/min with postmembrane arterial line pressures of 344 ± 81 mmHg, and patient mean arterial pressures (MAP) of 51.4 ± 16.7 mmHg. Venous saturations were $63.7 \pm 8.0\%$. The hematocrit prebypass was 37.4 ± 3.2 , bypass 20.7 ± 0.9 , post-MUF 27.8 ± 3.3 , and 7 days postoperative $24.5 \pm 7.5\%$. Platelet count was 289 ± 1.1 K/ μ L, 147 ± 37.1 K/ μ L, and 322 ± 292.7 K/ μ L prebypass, postbypass, and 7 days postoperative, respectively. Plasma-free hemoglobin prebypass was 7.5 ± 4.4 mg/dL and postbypass 22.2 ± 16.5 mg/dL with no noted hematuria during and after the procedure. All patients survived and were successfully weaned from cardiopulmonary bypass (CPB) with same day extubation.

A low-prime circuit for bloodless heart surgery is possible. To achieve low reservoir levels, especially without the use of an arterial line filter (ALF), it is necessary to have a full armament of monitoring and alarm devices.

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INTRODUCTION

A continuous battle in pediatrics is performing open-heart surgery without the use of blood products. The reasons for not using blood are many, including; the increased risk of infection, possible disease transmission, religious beliefs, immunological, increased metabolic load, availability, and cost (1). Our present prime volume, including cardioplegia setup, of 500 mL is normally larger than the patient's circulating blood volume. One major step toward limiting donor exposure is to use low-prime oxygenators, heat exchangers, venous reservoirs, and tubing. Tubing lengths typically contain 40% of the prime volume and, therefore, must be scrutinized (2). The limited hemodilution on CPB preserves hematocrit, oxygen-carrying capacity, and oncotic pressure. Less foreign surface area exposure preserves platelet and plasma protein function. Our modified circuit prime volume of 228 mL is a 54% reduction. The purpose of the study was to perform cardiopulmonary bypass on 5–7 kg nonhuman primates without the use of banked blood products.

MATERIALS AND METHODS

The investigation comprised a heart donor cynomologous monkey (*Macaca fascicularis*) and recipient olive baboon (*Papio anubis*). Animals were selected and matched by weight for compatibility of organs. All animals received humane care in compliance with the *Guide for the Care and Use of Laboratory Animals* of the National Institute of Health (NIH Publication No. 85-23, revised 1985) (3). The cardiopulmonary bypass circuit consisted of a Cobe Micro^a low-prime hollow fiber membrane oxygenator, heart/lung machine, air bubble detector, level alarm, high pressure shut off, and tubing. A Gish^b prebypass filter, Minntech Minifilter Plus^c hemoconcentrator, CDI 100^d saturation/hematocrit in-line monitor and Conducer HX^d cardioplegia single-pass set were employed. The tubing sizes consisted of 3/16-inch arterial pump head, 1/8-inch arterial line, 1/4-inch venous line, and 1/8-inch cardioplegia line. The lengths of the arterial and venous lines were six and four feet, respectively.

Gravity drainage was used, with a 12 fr and 14 fr DLP^e right angle metal tip venous cannulae in the superior and inferior vena cava, respectively. The right atrium was well decompressed. An 8 fr DLP arterial cannula was used in the ascending aorta. A 1/4-inch female perfusion adaptor was used to connect the arterial and venous lines for recirculation. The lines were divided, and the connector was used for the arterial

cannulae connection. Cardioplegia consisted of crystalloid UW solution^f and administered at 5 mL/kg/min with system line pressures kept below 100 mmHg. The cardioplegia solution was aspirated via wall suction from the coronary sinus. The dose calculated was 15 mL/kg. No autotransfusion system was used. During initiation of CPB, 10–15% of the patient's circulating blood volume was removed via a stopcock on the venous drainage line. This fresh, heparinized, autologous whole blood was administered postbypass. The prime constituents were Plasmalyte A^g, porcine mucosal sodium heparin (2 USP/mL of prime), sodium bicarbonate (2 meq/kg), and mannitol (0.5 g/kg). A target cardiac index of 2.2 L/min/m² with venous saturations greater than 60%, at 37°C was our goal. No minimum hematocrit was targeted. Alpha-stat blood gas management was used. The MAP was maintained above 30 mmHg throughout CPB using phenylephrine hydrochloride. Isoflurane was used for MAP greater than 60 mmHg and/or venous saturations less than 60%. The Hemochron 401^h was used to monitor activated clotting times (ACT). ACTs were maintained above 480 s. The oxygenator was ventilated with 100% oxygen. Post CPB, modified ultrafiltration (MUF) was initiated at 10–20 mL/kg. Microsoft Excel was used to calculate the mean and standard deviation of the measured values.

RESULTS

All patients survived ($N = 3$) and were successfully weaned from bypass with same day extubation. No donor or banked blood products were transfused. All animals were sacrificed at postoperative day 7.

The hematocrit level pre-bypass was 37.4 ± 3.2 , bypass 20.7 ± 0.9 , post MUF 27.8 ± 3.3 , and 7 days post-operative 24.5 ± 7.5 percent (fig 1). Total protein levels were 6.2 ± 0.1 mg/dL, 3.1 ± 0.5 mg/dL, and 4.9 ± 0.3 mg/dL pre-bypass, post bypass, and 7 days post-operative respectively (fig 2). Platelet counts were 289 ± 1.1 K/uL, 147 ± 37.1 K/uL, and 322 ± 292.7 K/uL pre-bypass, post bypass, and 7 days postoperative respectively (fig 3). Blood flow rates were 585 ± 113 ml/min with cardiac indices of 1.7 ± 0.3 . Venous saturations were $63.7 \pm 8.0\%$. The post membrane arterial line pressures were 344 ± 81 mmHg. Plasma free hemoglobin was 7.5 ± 4.4 mg/dL pre-bypass and 22.2 ± 16.5 mg/dL post bypass with no hematuria observed (fig 4).

DISCUSSION

This study suggests that bloodless open-heart surgery for patients in the 5–7 kg weight range is possible. Bloodless surgery offers the following major advantages: no risk of trans-

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^b Gish Biomedical Inc., Irvine, CA

^c Minntech Corp., Minneapolis, MN

^d Terumo/Sams, Ann Arbor, MI

^e Medtronic-DLP, Inc., Grand Rapids, MI

^f University of Wisconsin solution, Madison, WI

^g Baxter Healthcare Inc., Chicago, IL

^h International Technidyne Inc., Edison, NJ

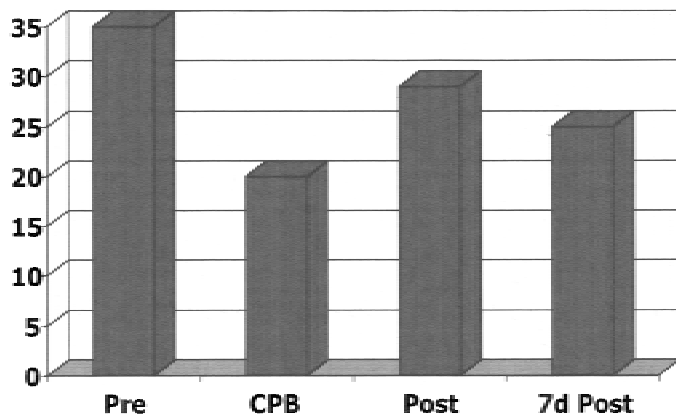


Figure 1: Mean hematocrit preoperatively, during cardiopulmonary bypass, postmodified ultrafiltration, and 7 days postoperatively ($N = 3$).

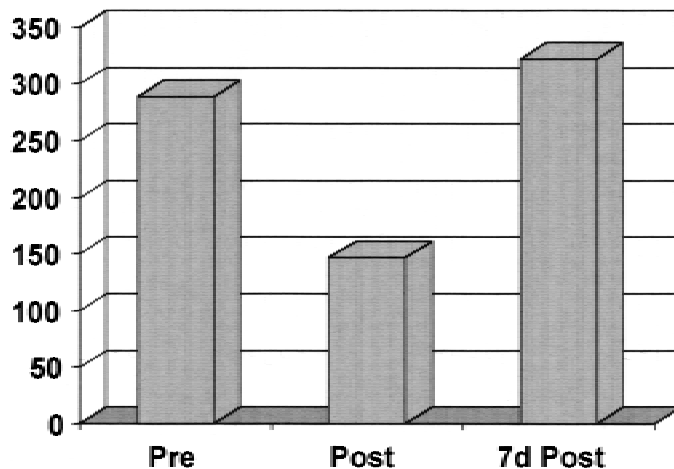


Figure 3: Mean total protein preoperatively, postoperatively, and 7 days postoperatively ($N = 3$).

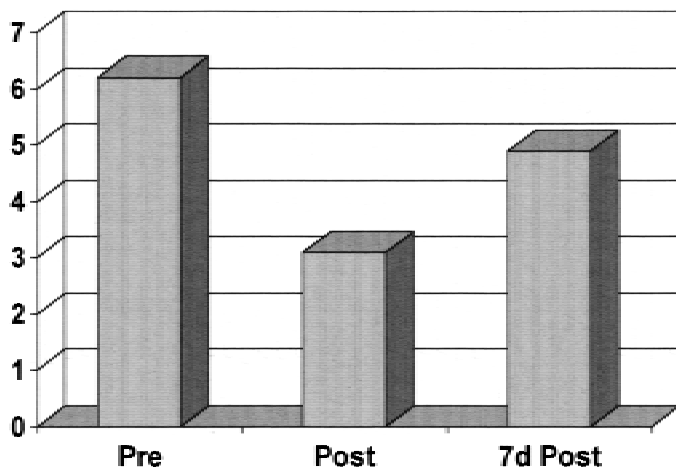


Figure 2: Mean platelet count preoperatively, postoperatively, and 7 days postoperatively ($N = 3$).

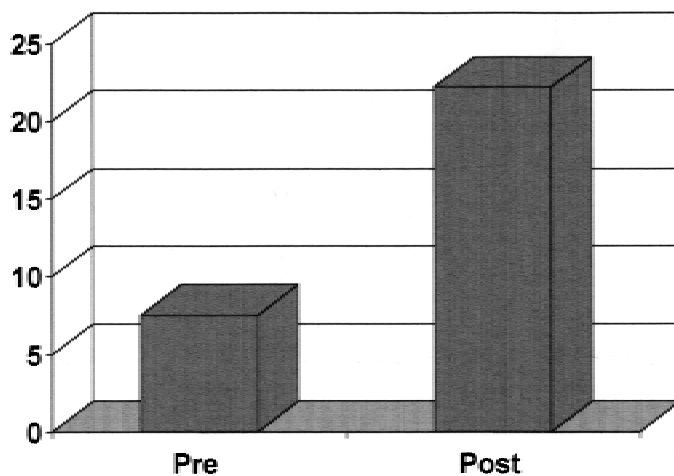


Figure 4: Mean plasma hemoglobin preoperatively and postoperatively ($N = 3$).

fusion-related immune reactions or transfusion-related disease transmission. High serum lactate, potassium, and acid exposure are avoided (1). A consistent, concerted, and committed effort is needed to accomplish this goal, with all disciplines involved.

Safety is of concern without an ALF. Groom et al. (4) surveyed pediatric centers in 1995 and found that 4% were not using ALF routinely. Today, reduction in prime volume has elevated this number (personal discussion). Risk of air emboli can be reduced with the use of an air bubble detector and level detector (5). A high-pressure pump shut-off adds additional safety. High postmembrane pressures were seen while on cardiopulmonary bypass. This was expected, because we were at the limits of the 1/8-inch arterial line and cannulae. Intraoperative and postoperative urine output remained clear, and there was not a clinically significant increase in plasma hemoglobin. A decrease in hematocrit at postoperative day 7 is possibly attributable to a loss of damaged red cells or bleeding (6). Venous saturation, arterial blood gas, hematocrit, and MAP were all within limits to show proficient tissue perfusion

(7, 8). All circuit components were used within the manufacturers' recommended limits. We manually configured every component of the circuit. Gravity drainage was used because of its simplicity and familiarity. Vacuum-assisted venous drainage is another technique that may help reduce circuit size; however, gaseous microemboli are of concern (9, 10).

Retrograde autologous priming and antegrade autologous priming help eliminate hemodilution. Erythropoietin may be a valuable drug, preoperatively, for raising hematocrit. MUF use can concentrate the circulating blood volume, thereby increasing hematocrit, coagulation factors, and platelets (11). The use of antifibrinolytics may preserve coagulation factors and platelets (12). The fresh autologous heparinized whole blood administered postoperatively not only increases hematocrit, but also aids in the reduction of bleeding. This circuit may also be used for Jehovah's witness patients who require cardiac surgery without blood product administration.

CONCLUSION

With circuit miniaturization and priming volume reduction, newborn baboons were supported in a safe and effective manner without the use of donor blood. Based on this laboratory experience, we intend to use this circuit for newborn open-heart surgery patients.

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