VENO-VENOUS BYPASS WITHOUT SYSTEMIC ANTICOAGULATION IN CANINE AND HUMAN LIVER TRANSPLANTATION

Scot W. Denmark, MD, Byers W. Shaw, Jr., MD, Thomas E. Starzl, MD, FACS, and Bartley P. Griffith, MD

PREVIOUS ATTEMPTS TO PERFORM liver transplantation during veno-venous bypass with systemic anticoagulation (heparin) in 12 patients at this medical center resulted in excessive blood loss in six and at least one fatality. The purpose of this study was to test the plausibility and consequences of using a veno-venous circuit without systemic anticoagulation during liver transplantation.

MATERIALS AND METHODS

Orthotopic liver transplantation was performed in ten mongrel dogs (20 to 25 kg) while using the bypass circuit without systemic heparin. Results of hematologic profiles, hemodynamic measurements, and postmortem examination were compared with those in three dogs in which no bypass was used. These three control transplants employed the "cuff" technique described by Cooperman et al (1). Bypass was initiated with drainage from the divided portal vein and proximally occluded infrahepatic vena cava with return to an external jugular vein. The circuit consisted of a centrifugal pump and flow probe with 3/8-inch Tygon tubing coated with 5% albumin and primed with a physiologic electrolyte solution. Appropriately sized Bahnson caval cannulas were used for the jugular vein and cava, while a fenestrated stainless-steel ventricular vent with 1/4-inch Silastic tubing drained the portal vein. Bypass continued for two to four hours at rates of flow between 400 and 1,500 mL/min. In the clinical trial, caval drainage was obtained through 7-mm Gott tubing introduced via the right common femoral vein advanced to the iliac vein; the same size was used for the portal vein, and a 9-mm piece provided venous return to the patient's left axillary vein. The remainder of the circuit was unchanged.

RESULTS

The use of bypass avoided low cardiac output and portal venous congestion usually associated with caval and portal vein occlusion. Hematologic profiles were not significantly different between groups and indicated a slight decrease in RBCs (5.67 to 5.16 $\times$ 10^6/mm^3), WBCs (13.8 to 9.8 $\times$ 10^3/mm^3), platelets (145 to 117.5 $\times$ 10^3/mm^3), and fibrinogen (145 to 80 mg%/dL) associated with the bypass. Fibrin split products and mon-

From the Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh.

omers were moderately elevated (staph cl to 4+). Fibrin threads were seen on the su in two studies in which the flow rate decre and microscopic examination of the lun thrombus. In the clinical trial, PT, PTT, slightly during bypass, whereas fibrin spl and fibrinogen levels decreased. The pat pneumonia during the first postoperative tion, no intravascular thrombus was fou the lung.

DISCUSSI

The use of a bypass circuit in liver advantages by avoiding severe cardiova hypotension, often associated with cava At completion of the infrahepatic vena ca rich in potassium and hydrogen ions is r from the previously stagnant capillary be nic circulations. A bypass circuit that the cava below the liver could prevent t acid which might cause cardiac arrhyth different shunts (without a pump) durin Partial cardiopulmonary bypass provic human liver transplantations performe investigators used heparin systemically bypass without systemic anticoagulati during liver transplantation without im thromboembolism and served to stimu cannulas were heparin bonded. The us associated with normal cardiac output. nificant change in coagulation factors, and monomers, or thromboelastogram feasibility of veno-venous bypass wit experimental and early clinical succe clinical use in human liver transplant

REFERI

1. Cooperman AM, Woods JE, McIlrath hepatic transplantation. Am J Surg 122:797–8

2. Azpeitia D, De Miguel E, Juffe A, et stage of transplantation of the liver (author's t

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omers were moderately elevated (staph clumping 1 to 128, ethanol gel 1 to 4+). Fibrin threads were seen on the support struts of the pump housing in two studies in which the flow rate decreased below 800 mL/min. Gross and microscopic examination of the lungs failed to show intravascular thrombus. In the clinical trial, PT, PTT, and fibrin monomers increased slightly during bypass, whereas fibrin split products remained unchanged and fibrinogen levels decreased. The patient developed a fatal aspiration pneumonia during the first postoperative week. At postmortem examination, no intravascular thrombus was found at the cannulation sites or in the lung.

DISCUSSION

The use of a bypass circuit in liver transplantation provides several advantages by avoiding severe cardiovascular derangements, particularly hypotension, often associated with caval clamping prior to hepatectomy. At completion of the infrahepatic vena caval and portal anastomoses, blood rich in potassium and hydrogen ions is returned to the systemic circulation from the previously stagnant capillary beds of the lower body and splanchnic circulations. A bypass circuit that decompresses the portal vein and the cava below the liver could prevent the accumulation of potassium and acid which might cause cardiac arrhythmias. Azpeitia et al used several different shunts (without a pump) during liver transplantation in dogs (2). Partial cardiopulmonary bypass provided hemodynamic stability during human liver transplantations performed by Calne et al (3). All of these investigators used heparin systemically. In this experiment, veno-venous bypass without systemic anticoagulation preserved the physiologic state during liver transplantation without imposing significant coagulopathy or thromboembolism and served to stimulate a clinical trial in which bypass cannulas were heparin bonded. The use of this system in one patient was associated with normal cardiac output, portal decompression, and no significant change in coagulation factors, platelet count, fibrin split products and monomers, or thromboelastogram. This study has demonstrated the feasibility of veno-venous bypass without systemic anticoagulation. The experimental and early clinical success has prompted plans for routine clinical use in human liver transplantation.

REFERENCES

1. Cooperman AM, Woods JE, McIlrath DC: Simplified method of canine orthotopic hepatic transplantation. Am J Surg 122:797–801, 1971

2. Azpeitia D, De Miguel E, Juffe A, et al: [Bypass techniques during the anhepatic stage of transplantation of the liver (author's transl)]. Ann Chir 29(2):155–160, 1975

3. Calne RY, Smith DP, McMaster P, et al: Use of partial cardiopulmonary bypass during the anhepatic phase of orthotopic liver grafting. Lancet 2(8143):612–614, 1979

CYCLOSPORINE TREATMENT FOR LUNG ALLOGRAFT REJECTION IN MONGREL DOGS: INDUCTION OF UNRESPONSIVENESS AND MIXED LYMPHOCYTE AND CYTOLYTIC T-CELL ACTIVITY

Allen J. Norin, PhD, Eugene E. Emeson, MD, Stephan L. Kamholz, MD, Kenneth L. Pinsker, MD, and Frank J. Veith, MD, FACS

A MAJOR GOAL of transplantation research is the induction of a state of specific unresponsiveness to allografted organs so that immunosuppressive therapy could be terminated without subsequent rejection. We previously reported that single lung allografts in unmatched mongrel dogs survived for more than 95 to 420 days after termination of Cyclosporine (Cys) therapy (1,2). In this report we compared the cytolytic activity of the prospective recipient's T-cells after mixed lymphocyte culture (MLC) with irradiated donor lymphocytes to the cytolytic activity of the recipient's T-cells after transplantation.

MATERIALS AND METHODS

Left lung allotransplantation was performed in male mongrel dogs (Biomedical Associated Inc, Friedensberg, Penn) as previously described (3). Cys (Sandoz Ltd, Basel, Switzerland) was administered at an initial dose of 17 mg/kg/day and tapered as detailed elsewhere (2,4). Lung allografts were evaluated by chest roentgenograms, radionuclide ventilation-perfusion lung scans, analysis of cells in BAL and open lung biopsies or necropsies (2,3). Cytolytic T-cell activity was measured in a lectin-dependent ^{51}Cr-labeled Raji target cell assay as published previously (5,6). The percentage of cytotoxicity was calculated by the formula (cpm ^{51}Cr experimental − cpm ^{51}Cr spontaneous ÷ ^{51}Cr maximum − cpm ^{51}Cr spontaneous). One-way MLC were initiated as previously reported (7).

From the Departments of Microbiology and Immunology, Surgery, Pathology and Medicine, Montefiore Medical Center-Albert Einstein College of Medicine, New York. *Supported in part by NIH grant HL17417 and the Manning Foundation.*

RESU

The cytolytic activity of recipient T
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DISCUS

We have previously shown that spe
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REFER

1. Norin AJ, Emeson EE, Veith FJ: Unres
after cessation of cyclosporin A therapy. Tra
2. Norin AJ, Emeson EE, Kamholz SL,
pressive agent for canine lung transplantation
phenomena. Transplantation 34:372–375, 198
3. Veith FJ, Norin AJ, Montefusco CM
transplantation. Transplantation 32:474–481,
4. Norin AJ, Veith FJ, Emeson EE, et
mongrel dogs treated with cyclosporin A. Tr
5. Emeson EE, Norin AJ, Veith FJ: Lect
and simple method to quantitative cytotoxic
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