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Therapeutic Effect of Hyperbaric Oxygen in Hepatic Artery Thrombosis and Functional Cholestasis After Orthotopic Liver Transplantation

O. Castro e Silva, A.K. Sankarankutty, A.L.C. Martinelli, F.F. Souza, A.C. Teixeira, O. Feres, E.D. Mente, G.R. Oliveira, R. Akita, V. Muglia, J. Elias Jr., L.N.Z. Ramalho, and S. Zucoloto

ABSTRACT

Among the postoperative complications, hepatic artery thrombosis can occur in up to 10% of adult orthotopic liver transplants and intervention is indicated when this occurs within 30 days by retransplantation. Primary graft dysfunction, which can occur in up to 30% of the cases and is another potential complication, although reversible, has a relatively high mortality rate. Hyperbaric therapy, an efficient mode of tissue oxygenation, is being used in an increasing number of clinical situations. We report here two cases where hyperbaric oxygen therapy greatly benefited patients with complications after orthotopic liver transplantation: one with hepatic artery thrombosis and the other with primary graft dysfunction. Both patients showed rapid clinical recovery with gradual reduction of liver and canalicular enzymes soon after commencing hyperbaric oxygen therapy.

ORTHOTOPIC LIVER TRANSPLANTATION (OLT) has become an accepted therapy for acute and chronic end-stage liver disease, with 1-year survival rates of more than 80% at experienced transplant centers.[1]

However, the postoperative course of liver transplant recipients may be affected by a number of complications.[1–3] Graft dysfunction can be related to the clinical condition of the donor, to cold and warm ischemia, and to ischemia-reperfusion injury (I/R).[3,4] Functional cholestasis is a common manifestation of graft dysfunction after liver transplantation, which usually completely reverses with time. It must be differentiated from primary graft nonfunction, allograft rejection, and biliary tract complications.[1,3,4] Hepatic artery thrombosis (HAT) is a significant complication after liver transplantation, with a reported incidence of 5% in adults and 9% to 18% in children.[3,5] The clinical course is critically dependent on the age of the recipient and the time from the transplant procedure, with survival rates of up to 50%, decreasing to 28% in the absence of retransplantation (re-OLT).[6] Other nonsurgical modalities of treatment range from surveillance or antibiotics to interventional radiological techniques. Because various therapeutic options are available, urgent re-OLT for treatment of HAT has become obsolete. Re-OLT remains an option for deteriorating graft function only after other therapeutic possibilities have been discarded.[2,6]

Experimental evidence suggests that hyperbaric oxygen (HBO) may improve hepatic ischemic-reperfusion injury[7] and increase hepatic regeneration.[8,9] Clinical reports of the use of HBO for treatment of hepatic artery thrombosis after liver transplantation in children[10] led us to determine its effect in two patients after OLT: one with functional cholestasis and the other with hepatic artery thrombosis.

CASE REPORTS

Patient 1

A 53-year-old woman underwent OLT for cryptogenic cirrhosis (Child-Pugh Grade B, MELD 18) in August 2004. On the third postoperative day, the patient was febrile (temperature of 38°C), displaying tremors as well as increased serum levels of alanine

From the Special Liver Transplantation Unit - Departments of Surgery and Anatomy (O.C.S., A.K.S., O.F., E.D.M., G.R.O., R.A.), Internal Medicine (A.L.C.M., F.F.S., A.C.T.) and Pathology (L.N.Z.R., S.Z.), and the Sector of Radiology (V.M., J.E.), Ribeirão Preto School of Medicine, University of São Paulo, São Paulo, Brazil.

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Address reprint requests to Professor Orlando de Castro e Silva, Departamento de Cirurgia e Anatomia, Hospital das Clínicas da FMRPUSP, Campus Universitário, Monte Alegre, Ribeirão Preto, Brasil, Av. Bandeirantes, 3.900, CEP 14049-900, Ribeirão Preto/SP, Brazil. E-mail: orlando@fmrp.usp.br

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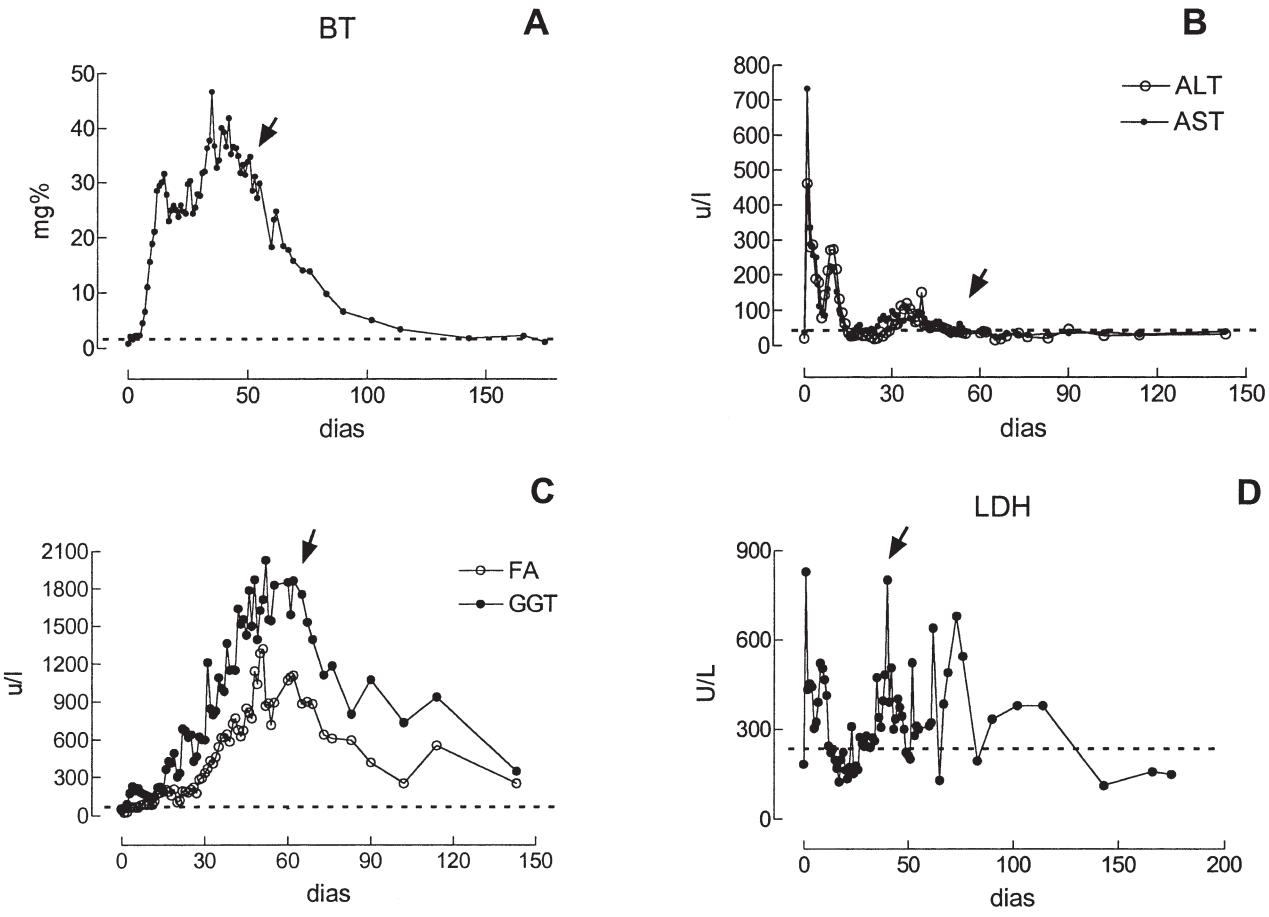

Fig 1. Levels of total bilirubin **(A)**, alanine aminotransferase (ALT and AST) **(B)**, alkaline phosphatase (AP), gamma-glutamyl transferase (GGT) **(C)**, and lactic dehydrogenase (LDH) **(D)** in patient 1 with functional cholestasis before, during, and after 30 sessions of hyperbaric oxygen (starting from the arrow). Dotted line (----) upper normal range.

aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), gamma-glutamyl transpeptidase (gamma-GT), and bilirubin. There were no other clinically significant manifestations and the patient remained stable. On the postoperative day 7 she underwent a percutaneous liver biopsy that suggested acute cellular rejection upon histological analysis requiring treatment with intravenous boluses of methylprednisolone. Aminotransferase levels returned to normal, but the hepatic canalicular enzymes and bilirubin levels increased progressively despite clinical measures (Fig 1A, B, C, D). Doppler ultrasonography showed patency of the hepatic artery as well as the portal and hepatic veins. On the postoperative day 30, a repeat liver biopsy revealed hepatocellular swelling, mild acute cellular rejection, and mild bile duct proliferation. When bilirubin levels reached 40 mg/dL, 30 HBO therapy sessions were commenced on the postoperative day 45. The patient was discharged from the hospital 63 days after liver transplantation with progressively decreasing levels of AP, gamma-GT, and bilirubin. At 1 year after transplantation, the patient remains clinically well with normal AST, ALT, AP, and bilirubin values. The gamma-GT value is still slightly above normal but continues to decline slowly. Magnetic resonance imaging showed a patent hepatic artery and portal vein as well as a normal biliary tree.

Patient 2

A 56-year-old man underwent OLT for alcoholic cirrhosis (Child-Pugh Grade C, MELD 16). On postoperative day 28 the patient had pain in the right upper quadrant and increasing serum bilirubin levels. Arteriography detected HAT. He was wait-listed and underwent re-OLT 7 days later. The immediate postoperative course after retransplantation was uneventful, and the patient was discharged 3 weeks later.

Two months after re-OLT, the patient developed right upper quadrant pain along with increased serum AST, ALT, AP, gamma-GT, and bilirubin. A liver biopsy suggested mild acute cellular rejection without any signs of viral infection. This episode was treated by adjustments in the immunosuppressive scheme. In the postoperative month 4 there was a significant increase in aminotransferases, as well as of bilirubin and gamma-GT (Fig 2). Arteriography again revealed thrombosis of the hepatic artery (Fig 3). Histological examination of the biopsy detected various zones of necrosis (Fig 4A). After 30 sessions of HBO therapy, the patient improved both clinically and in laboratory values (Fig 2). A liver biopsy showed no areas of necrosis (Fig 4B). At 3 years after HBO therapy, the patient remains well, with normal levels of AST, ALT, AP, and bilirubin. Gamma-GT remains stable at 2 to 2.5 times the

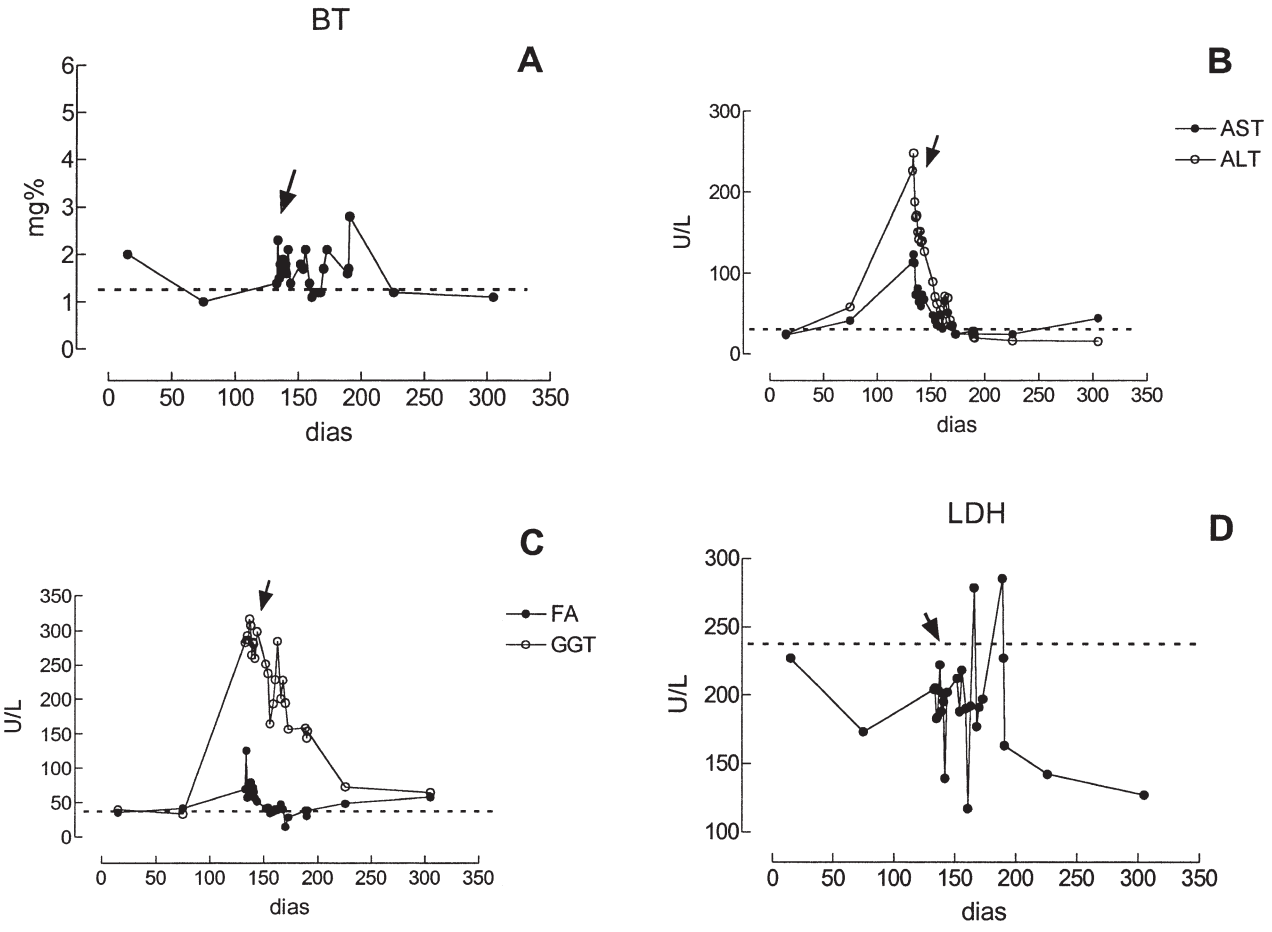

Fig 2. Levels of total bilirubin **(A)**, alanine aminotransferases (ALT and AST) **(B)**, alkaline phosphatase (AP), gamma-glutamyl transferase (GGT) **(C)**, and lactic dehydrogenase (LDH) **(D)** in patient 2 with artery thrombosis before, during, and after 30 sessions of hyperbaric oxygen (starting from the arrow). Dotted line (----) upper normal range.

normal value, and magnetic resonance imaging shows a normal biliary tree.

Hyperbaric Oxygen

Both patients received 30 applications of HBO in a monoplace chamber (Sechrist, model 2500 B) directly pressurized with oxygen. Each daily session lasted 2 hours, with a pressure of 2.5 ATM.

DISCUSSION

Liver transplantation subjects the liver to a wide variety of potential injuries, including hypotension or hypoxia in the donor, cold ischemia during preservation, warm ischemia during and after transplantation, sepsis, viral infection, and immunologically mediated damage. It is not surprising that the majority of livers experience a period of compromised function during the first 30 days after transplantation.[3,5] Graft dysfunction may be due to primary graft nonfunction, a devastating complication that may take place following liver transplantation, or to allograft rejection, viral hepatitis, and functional cholestasis, the last complication being reported in the present study.[4,6,11,12] As shown in Fig 1A,

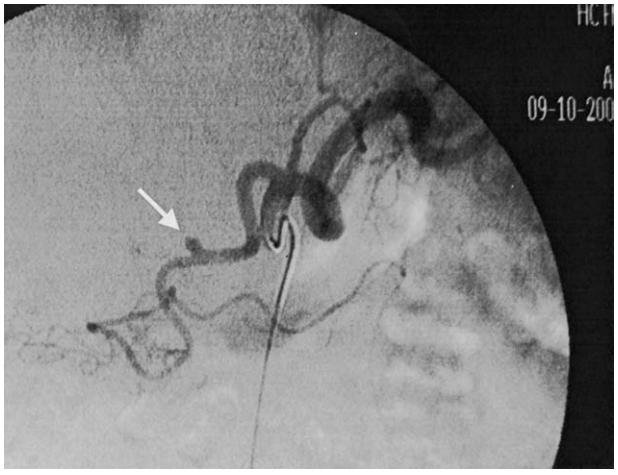

Fig 3. Arteriography showing the occluded hepatic artery (arrow).

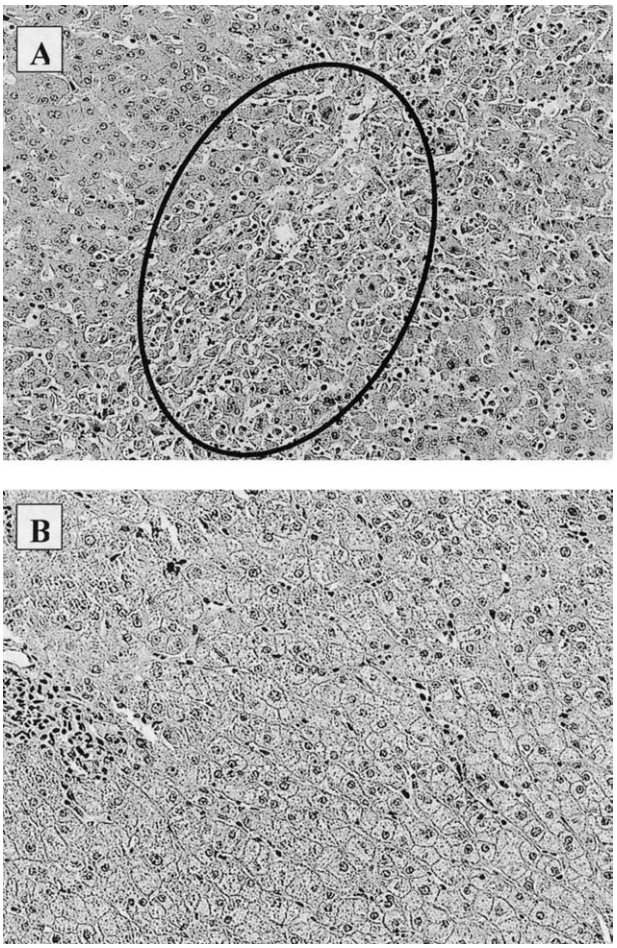

Fig 4. **(A)** Light micrographs (250X,H.E.) showing several zones of hepatocellular necrosis, with the highest concentration shown inside the circle. **(B)** Apparently normal liver tissue.

during the immediate postoperative period there was a progressive increase in serum bilirubin levels up to 46.6 mg/dL, with a return to normal levels after the application of HBO. A similar course occurred with serum AP and gamma-GT levels. It is important to point out that aminotransferase levels did not increase significantly, as also reported in the literature. In this case, the warm ischemia time was longer than that usually reported in the literature. The time for arterial revascularization was also long, possibly explaining the more intense hepatocellular injury due to I/R, which probably accounted for graft dysfunction.

In the patient with arterial thrombosis, the hepatocellular injury was due to a lack or a reduction in arterial blood flow to the liver. Contrary to liver transplantation in rats, arterial perfusion is essential to ensure liver graft success in humans.[13] As shown in Fig 2, in this case there was increased hepatocellular enzymes and gamma-GT, but not AP; it was only slight for bilirubins. Probably, due to the time of approximately 4 months after OLT for HAT stabilization, the effect of the I/R injury was not as intense as in cases of HAT occurring during the first 30 days post-OLT.

Both patients were treated with HBO to improve liver tissue oxygenation because the most important effect of HBO treatment is tissue hyperoxygenation from oxygen dissolved in plasma. The presence of a dual blood flow may explain the effect of hyperbaric oxygenation in liver grafts with HAT. Hyperbaric oxygenation may thus provide a means to obviate the effects of interruption of arterial blood flow by increasing portal blood oxygen content and possibly enhancing the development of hepatic artery collaterals.[10,13,14]

In an experimental study, Uwagawa et al,[9] compared the effect of HBO therapy in rats undergoing ligation of the right branch of the portal vein, simulating the technique of preoperative embolization of the portal vein. The authors observed a significant increase in serum levels of hepatocyte growth factor, increased cell proliferation, and compensatory hypertrophy in the nonligated hepatic segments of the groups that received HBO. Hyperbaric oxygen has been reported to increase the levels of some antioxidant enzymes in hepatic tissue, such as glutathione and superoxide dismutase, and to decrease malondialdehyde levels.

Mazariegos et al[10] compared the clinical courses of children undergoing liver transplantation who developed early hepatic artery thrombosis whether treated or not with HBO. There was no significant difference in survival or in the rate of retransplantation. However, in cases that required retransplantation, the procedure was performed after a longer time and under semi-elective conditions in the HBO-treated group.

In conclusion, HBO therapy was effective in both cases. As shown in Fig 4B, there was a significant improvement in hepatocellular necrosis after the use of HBO. Similarly, the patients clearly improved in both biochemical and clinical terms, without permanent late side-effects due to functional cholestasis or hepatic artery thrombosis.

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