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Delayed oxidation of intramitochondrial pyridine nucleotide oxido reduction state as compared with tissue oxygenation in human liver transplantation

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Abstract Intra- and post-operative oxygenation of graft liver and subsequent oxidation of the intramitochondrial redox state of pyridine nucleotide were studied in liver transplantation from living related donors with the arterial ketone body ratio (AKBR), the ratio of oxidized flavoprotein to reduced pyridine nucleotide (FP/PN ratio), and oxygen saturation of hemoglobin in liver tissue (hepatic SO_2). The subjects involved in this study consisted of 20 pediatric patients. Hepatic SO_2 was measured by near-infrared tissue spectroscopy. FP/PN ratio was measured by two-dimensional fluorometric scanning. Tissue oxygenation was normalized at the end of the operation. By contrast, AKBR remained at a low value at the end of the operation. At 24 and 48 h after the operation, the AKBR values increased to near the control value, indicating that it took 24 h for the intramitochondrial redox state to be normalized. The FP/PN ratio also remained at a low value at the end of the operation as compared with the control value. In conclusion, the observed delay in oxidation of the intramitochondrial redox state as compared with tissue oxygenation indicated the transition of the redox state associated with the changes in the metabolic state, and suggested the important role of microcirculation in the normalization of the redox state.

Key words Living related liver transplantation · Near-infrared spectroscopy · Oxidized flavoprotein/reduced pyridine nucleotide (FP/PN) ratio · Arterial ketone body ratio

Introduction

Tissue oxygenation and subsequent oxidation of intracellular components play a key role in successful organ transplantation, since cold preservation shifts the cellular components towards reduction and since an aerobic metabolism supports cellular integrity and functions after reperfusion. The presence of an oxygen gradient from the extracellular space, where hemoglobin is available as an oxygen carrier, to the mitochondria, to which oxygen is transported only by diffusion and where it is consumed for ATP synthesis, has been the subject of debate. Furthermore, an oxygen gradient exists in the hepatic lobule along the sinusoid from the periportal to the pericentral area, independent of the gradient from the extracellular to the mitochondrial compartment [1].

Table 1 Partial liver transplantation from living related donor between September 1991 and October 1992. (20 Pediatric patients: 6 male and 14 female, 3.8±0.9 years old)

Biliary atresia	14
Intrahepatic cholestasis	2
Wilson's disease	1
Tyrosinemia	1
Liver cirrhosis	1
Fluminant hepatitis	1

In the present study, intra- and post-operative oxygenation of graft liver and subsequent oxidation of the intramitochondrial redox state of pyridine nucleotide were studied in liver transplantation from living related donors with the arterial ketone body ratio (AKBR), the ratio of oxidized flavoprotein to reduced pyridine nucleotide (FP/PN), and oxygen saturation of hemoglobin in liver tissue (hepatic SO_2).

Patients and methods

The subjects involved in this study consisted of 20 pediatric patients on whom we performed living related liver transplantation from September 1991 to October 1992. The average age was 3.8 years. Of the children, 14 had biliary atresia, 2 had intrahepatic cholestasis, 1 had Wilson's disease, 1 had tyrosinemia, 1 had liver cirrhosis, and 1 had fulminant hepatitis (Table 1). All recipients in the present series recovered successfully from their terminal liver diseases, and the postoperative courses of all donors were uneventful.

The parameters we measured in the present study were near-infrared tissue spectroscopy for oxygen saturation, arterial ketone body ratio (acetoacetate/β-hydroxybutyrate) for intramitochondrial oxido-reduction state [2], and the FP/PN ratio for cytosolic and mitochondrial oxido-reduction state. Hepatic SO_2 was measured by near-infrared tissue spectroscopy with multicomponent curve fitting analysis [3]. The FP/PN ratio was measured by two-dimensional fluorometric scanning of freeze-trapped liver tissue [4].

Results

Hepatic SO_2 in the donor graft was significantly decreased from the control value of 82.8±1.7% before harvesting to 55.6±4.2 and 72.9±3.5%. After reflow of the portal vein the hepatic SO_2 reached 77.9±2.4%, indicating that tissue oxygenation was normalized at the end of the operation (Fig. 1). By contrast, AKBR was significantly decreased from the control value of 2.09±0.35 to 0.43±0.05, 0.67±0.06, and 0.78±0.07 after reflow of the portal vein, hepatic artery and at the end of operation, respectively. At 24 and 48 h after the operation, the values were increased to near the control value, indicating that it took 24 h for the intramitochondrial redox state to be normalized (Fig. 1). The

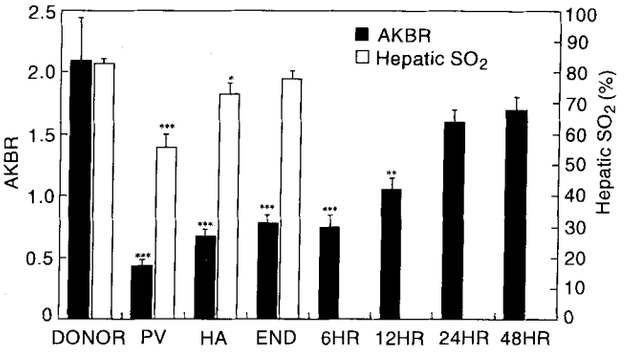

Fig. 1 Changes in arterial ketone body ratio (AKBR) and oxygen saturation of hemoglobin in sinusoid (hepatic SO_2) in 20 cases. Error bars indicate SE, DONOR, before harvesting; PV, after reflow of the portal vein; HA, after reflow of the hepatic artery; END, at the end of the operation; HR, hours after the operation. Significantly different from the value of DONOR (* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

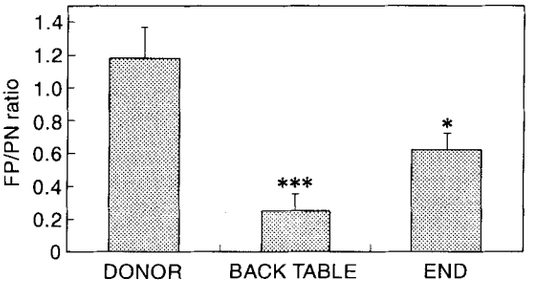

Fig. 2 Changes in the mean value of ratio of oxidized flavoprotein to reduced pyridine nucleotide (FP/PN ratio) in nine cases of partial liver transplantation with living related donor. *.***; significantly different from the value of DONOR ($P < 0.05$, 0.001, respectively)

FP/PN ratio was successfully measured in 9 cases of the 20 cases. The FP/PN ratio also remained at a low value of 0.62±0.10 at the end of operation, as compared with the control value of 1.18±0.19 (Fig. 2).

Discussion

As shown in Figs. 1 and 2, the recovery of the intramitochondrial oxido-reduction state from reperfusion and rewarming in liver transplantation was clearly delayed as compared with early recovery of hepatic oxygenation. It has been reported by our laboratory that the recovery of the AKBR during shock, ischemia, and hypoxia is closely correlated with tissue oxygenation as determined by mean arterial blood pressure or partial pressure in blood [3, 5, 6]. The relationship between tissue oxygenation and

intramitochondrial oxido-reduction state differed after reperfusion. The FP/PN ratio also suggested delayed oxidation of the cytosolic and mitochondrial oxido-reduction state in liver transplantation. These results would imply that the most essential factor determining the oxidative metabolism in liver transplantation is the intramitochondrial oxido-reduction state.

In conclusion, the combined study of tissue oxygenation at sinusoid level and intramitochondrial oxido-reduction state affords essential information with respect to energy transduction and pathophysiology in the transplanted liver.

References

1. Kekonen EM, Jauhonen VP, Hassinen IM (1987) J Cell Physiol 133:119–126
2. Tanaka J, Ozawa K, Tobe T et al (1979) Gastroenterology 76:691–696
3. Kitai T, Tanaka A, Tokuka A et al (1993) Hepatology (in press)
4. Ozawa K, Chance B, Tanaka A, Iwata S, Kitai T, Ikai I (1992) Biochem Biophys Acta 1138:350–352
5. Ikai I, Ozaki N, Shimahara Y et al (1989) Circ Shock 27:63–72
6. Wakashiro S, Shimahara Y, Ikai I et al (1988) Surg Res Commun 5:193–198