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Nondestructive and real-time evaluation of liver viability in brain dead donor for liver transplantation using near-infrared spectroscopy*

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Abstract A reliable and less-invasive method is currently desired to assess the hemodynamic and functional alteration associated with brain death in the organs of donor candidates. Near-infrared spectroscopy (NIRs) was applied to rat liver in brain-dead donors for assessing tissue oxygenation and intracellular energy metabolism as a means of monitoring the liver viability in the brain-dead donor. Brain-dead rats were divided into 4 according to doses of epinephrine and vasopressin administered. Arterial ketone bodies ratio (AKBR), hyaluronic acid (HA), and NIRs monitoring of a liver graft were performed in the brain-dead phase before the grafts were transplanted into syngeneic rats. NIRs monitoring of oxygenated hemoglobin (Hb) and cytochrome aa3 oxidase (Cytaa3) redox state reflected changes in the hepatic microcirculation and intracellular oxygenation. The administration of high-dose epinephrine proved to be contraindicated due to catecholamine-induced hypoxic stress, while combined administration of adrenaline and vasopressin at an optimal dose rate was beneficial for preservation of the liver viability. The data obtained by NIRs were significantly correlated with the 7-day survival of recipients after liver transplantation. Thus, we conclude that NIRs is a sensitive and nondestructive method for monitoring alterations in the viability of brain-dead liver and can predict liver graft outcome.

Key words Near-infrared spectroscopy (NIR) · Liver viability · Brain dead donor · Transplantation · Oxygenated hemoglobin (Oxy-Hb) · Oxidized cytochrome aa3 oxidase (Oxy-Cyt.aa3) · Arterial ketone bodies ratio (AKBR)

Introduction

It has been well established that brain death significantly alters regional perfusion of the abdominal organs, with possible implications for organ function. Such hemodynamic and functional disturbances are thought to be associated with primary nonfunction. Reliable and real-time estimation of the viability of brain-dead liver will have a significant impact on improving transplantation performance.

In vivo near-infrared (NIR) spectroscopy is a noninvasive optical technique for monitoring oxygen metabolism-related compounds such as hemoglobin (Hb), myoglobin, the redox state of cytochrome oxidase (Cyt.aa3) (a component of the mitochondrial respiratory chain), and other biological compounds in intact tissue [3, 6, 7, 10, 11, 18]. Previously, using NIR spectroscopy, we investigated the level of tissue oxygen saturation and the alteration of Hb in living graft livers after transplantation [16, 17, 26]. The results indicated the possible use of this technique for evaluation of the viability of liver grafts from changes in graft tissue oxygenation. We investigated here the possible use of NIR spectroscopy as a novel method for evaluating the viability of liver in

brain-dead donors using a relatively long-term brain death model in rats. Since the beneficial effects of a vasoconstrictor like catecholamine or vasopressin on improving liver viability in the brain-dead donor is still a controversial point in the management of brain-dead patients, we also investigated the effects of these drugs on brain-dead liver by comparing between the experimental groups with different doses of vasoconstrictor being administered.

Materials and methods

In all, 24 male Lewis inbred rats (RT-1[1]) weighing 250–300 g (Charles River Japan, Yokohama, Japan) maintained on a standard diet were used. After induction of ether anesthesia, the right carotid artery was cannulated with a 3Fr polyethylene tube for monitoring blood pressure and for sampling blood. The left jugular vein was cannulated for continuous drip infusion. A tracheotomy was performed and an endotracheal tube was placed in each animal. Ventilation was performed through a positive-pressure ventilator with room air. After laparotomy, in vivo NIR measurements of control normal livers were performed. Brain death was induced by rapidly inflating the balloon of a Fogarty 4F catheter placed into the epidural space in the right posterior temporal region of the scalp with 0.4 ml of distilled water. Based on the amount of epinephrine administered, the animals were divided into four groups as follows:

- Group A: six brain-dead rats infused with 0.4 ml/h of saline without any drugs in it, which served as controls.
- Group B: six brain-dead rats treated with vasopressin at a rate of 0.1 U/kg/h.
- Group C: six brain-dead rats treated with epinephrine and vasopressin at rates of 0.3 μg/kg/min and 0.1 U/kg/h, respectively.
- Group D: six brain-dead rats treated with epinephrine and vasopressin at rates of 2.0 μg/kg/min and 0.1 U/kg/h, respectively.

EEG. Two small burr holes were made on the left frontoparietal region and a spot 5 mm behind it. Steel screws were driven through these holes to serve as dural leads for electroencephalography. Cortical electroencephalography (EEG) was recorded with a pen-writing polygraph (Nihon Kohden, RM-6200) and an Apple computer.

Definition of brain death. Completion of brain death was determined by the enlargement of bilateral pupils, absence of light reflexes, flattening of EEG, a sudden decrease in arterial blood pressure, no efforts at spontaneous respiration noted during apnea tests, and complete absence of any vasopressor reaction to an increase in the volume of the epidural balloon. As an additional criterion of brain death in our study, the absence of any conscious movement was watched for during the 8 h of the brain-death phase in the absence of anesthesia.

NIR spectroscopy. NIR spectroscopy was performed as previously described [16, 27]. Briefly, NIR reflectance was measured with a multichannel photodetector (MCPD-2000, Otsuka Electronics, Osaka, Japan) connected to a personal computer (PC-9821Xs, NEC, Tokyo, Japan). NIR light from a 300 W halogen lamp (Petite Ace 25; Sanyo Denki, Tokyo, Japan) was directed through a flexible bundle of quartz optical fibers (OD3 mm) into the liver, and the reflected light was conveyed through another bundle to the spectrophotometer. The tips of the two fibers were fixed at a position approximately 3 mm above the brain-dead liver. Throughout the 8 h of the brain death phase, the reflected light was scanned within the range of 500–1100 nm by the continuous wave NIR system, and the sampling time of each scan was 4 s. Multicomponent analysis of the differences in the spectra was performed between pre- and post-brain death by a curve-fitting technique based on the least-square method using standard spectra of purified oxy-Hb, deoxy-Hb, oxidized Cyt.aa3, reduced Cyt.aa3, water, and rat bile with the affiliated computer. Each component was fitted into the equation following the Beer-Lambert law:

$$OD(\lambda) = L(\lambda)(e1(\lambda)\Delta[\text{oxy} - \text{Hb}] + e2(\lambda)\Delta[\text{deoxy} - \text{Hb}] + e3(\lambda)\Delta[\text{oxidized-Cyt.aa3}] + e4(\lambda)\Delta[\text{reduced-Cyt.aa3}] + e5(\lambda)\Delta[\text{water}]) + e6(\lambda)\Delta[\text{rat bile}])$$

where OD (λ), L (λ), e1–5 (λ) are optical density, mean path length, and extinct coefficients, respectively, of each component at a wavelength of λ. The relative changes in each component were detected using this multicomponent analysis calculated on the basis of singular value decomposition [19].

Biochemical parameters. Blood samples were taken at 4-h intervals for the determination of alanine transaminase (ALT), aspartate transaminase (AST), lactate dehydrogenase (LDH), and blood glucose. Serum hyaluronic acid (HA), whose uptake is an endothelial cell damage marker [23], was measured by a radioimmunoassay. The arterial ketone bodies ratio (AKBR) was measured enzymatically by using an AKBR measuring system (KETO-340, Sanwa Kagaku Kenkyusho, Nagoya, Japan).

Histological findings. Before liver harvesting for syngenic liver transplantation, specimens from liver biopsies were fixed in 10% buffered formalin and processed routinely for paraffin embedding. Sections were cut at 3–5 μm thickness, and stained with hematoxylin and eosin (H&E) for examination by light microscopy

Liver transplantation. Orthotopic liver transplantation (OLT) without rearterialization was performed using the cuff technique described previously by Kamada and Calne [12]. The donor liver was perfused immediately after completion of NIR monitoring in the brain-dead phase (8 h) and was preserved at 4°C in 0.9% saline solution until transplantation (less than 1 h). In the recipient, the liver graft was implanted syngeneically after removal of the native liver. Implantation surgery required less than 50 min, during which time the portal vein was clamped for 11–15 min.

Statistical analysis. All results were expressed as mean ± SEM, and the non-parametric Mann-Whitney U-test was used to calculate P values. P values of < 0.01 were considered to indicate statistical significance.

Results

Clinical status

The time course of the mean arterial blood pressure (MABP) during the 8 h of the brain-dead period is shown in Fig. 1. In all groups, acute elevation of the intracranial pressure resulted in a violent increase in

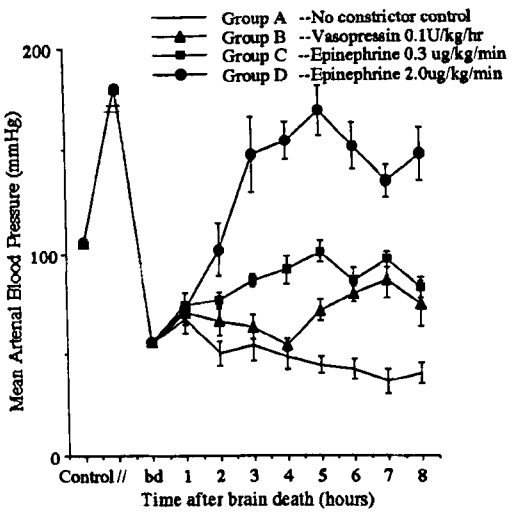

Fig.1 Mean arterial blood pressure was monitored in donor rats during the brain death phase. Values are expressed as mean blood pressure ± SEM

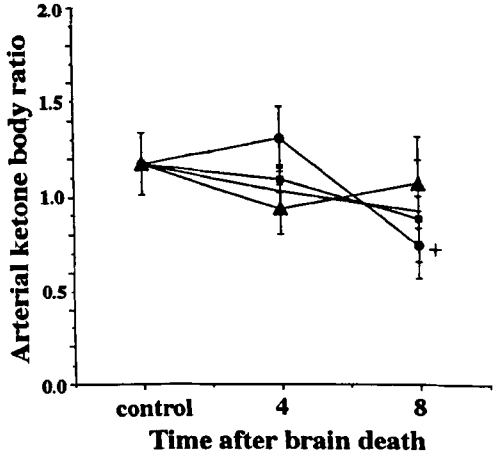

Fig.2 Arterial ketone body ratios (AKBR) were measured in donor rats after induction of brain death at an interval of 4 h. Although little decrease in AKBR can be observed in all the brain-dead groups, there were no significant changes in AKBR values between each group with the differing designed brain death conditions. In group A, saline was used as the nonvasoconstrictor control (*no symbol*); group B, 0.1 U/kg/h of vasopressin were administered (▲); group C, 0.3 μg/kg/min of epinephrine + 0.1 U/kg/h of vasopressin (■); group D, 2.0 μg/kg/min of epinephrine + 0.1 U/kg/h of vasopressin (●). (+) $P < 0.05$ compared with control data from naive rats

MABP from about 100 mmHg to 180 mmHg, with a peak of 240 mmHg within 1 min, which then declined to a mean of 50 ± 10 mmHg within 10 min. After the definition of brain death, in the nonconstrictor group A, blood pressure remained at the decreased level. In group B, MABP gradually increased to 74 ± 11 mmHg following 8 h administration of vasopressin only. In group C, MABP gradually recovered to a near-normal level, while in the high-dose epinephrine group D, blood pressure increased acutely above 150 mmHg.

Biochemical parameters

Table 1 shows the biochemical examination in each group. Group D had an elevation of serum transaminases (ALT, AST, LDH) and HA, while a mild tendency to increase was observed in group C. There was no significant change between each group statistically for these biochemical parameters, since the standard deviation of these indications was too large. Glucose was markedly increased in groups C and D, which probably reflects the adverse effects of catecholamine. Figure 2 showed the time course changes of AKBR in the brain-dead phase. Similar to some previous reports by other authors [8, 15], our experiment showed that AKBR, which is considered to be an indicator of the mitochondrial energy charge level, showed little decrease within a near-normal range in all the brain-dead groups. There were no significant changes in these values among the experimental groups.

NIR spectroscopic data

The kinetics of oxy-Hb and oxidized Cyt.aa3 levels are shown in Fig. 3. Under the various hemodynamic conditions, the time course of changes in oxidized Cyt.aa3 level was well preserved only in group C, with a statistically significant difference when compared with control group A. The levels of oxidized Cyt.aa3 in group B showed a similar decline to those in group A. In the high-dose epinephrine group D, those levels declined

Table 1 Changes in biochemical parameters at 8 hours after brain death (± SE)[a]

Group	Epinephrine (μg/kg/min)	Vasopressin (U/kg/h)	GOT (IU/l)	GPT (IU/l)	LDH (IU/l)	HA (ng/ml)	GLU (mg/ml)
A	–	–	172 ± 41	48 ± 18	1548 ± 1503	103 ± 44	152 ± 17
B	–	0.1	174 ± 96	56 ± 21	955 ± 449	191 ± 184	249 ± 83[b]
C	0.3	0.1	152 ± 52	55 ± 35	607 ± 165	91 ± 29	320 ± 165[b]
D	2.0	0.1	287 ± 234	105 ± 90	2430 ± 1613	314 ± 211	346 ± 144[b]

[a] $n = 6$ in each group [b] $p < 0.01$ vs Group A

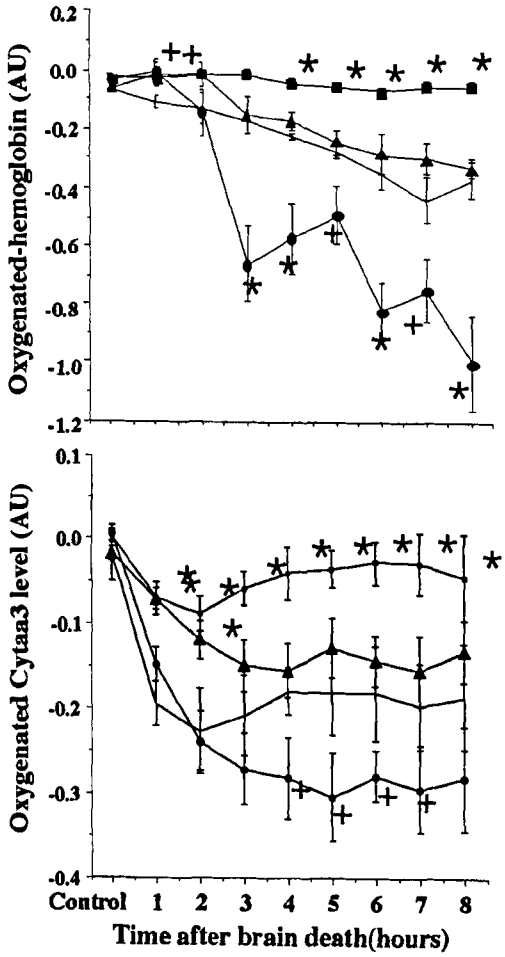

Fig.3 Changes in levels of oxygenated hemoglobin (oxy-Hb) and oxidized cytochrome oxidase (Cyt. aa3) in donor liver measured by NIR spectroscopy: group A (*no symbol*); group B (▲); group C (■); group D (●). Results are expressed as mean ± SEM in arbitrary units (+) $P < 0.05$; (*) $P < 0.01$ compared with group A

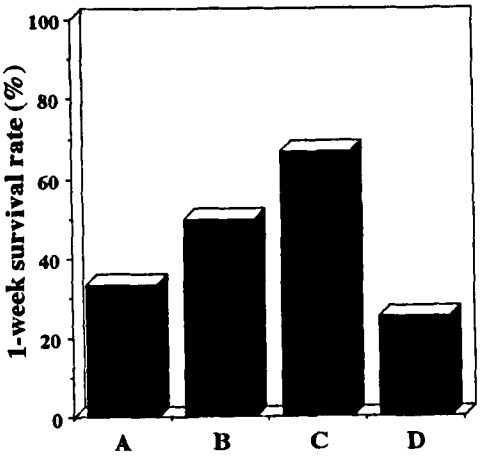

Fig.4 The 7-day survival rate of each group is shown. Group C had the best survival of all the groups (67%). In the high-dose catecholamine group D, only 25% of recipients survived longer than 1 week

further, indicating the state of hypoxic stress. The changes in oxy-Hb showed similar results to oxidized Cyt.aa3. The hemoglobin oxygenation began to decrease following brain death and continued evidently decreasing after 2 to 3 samples. Group D showed a violent decrease of oxy-Hb levels. However, those levels in group C remained relatively constant.

Pathological finding

The liver specimens taken from the 8-h brain-dead donor were microscopically diagnosed. Mild central venous congestion indicated as a dilated central vein, intrasinusoidal congestion, and perisinusoidal hemorrhage in the portal areas were observed indefinitely in each specimen.

Transplantation performance

In Fig.4, the 1-week survival rate of each group is shown. In group C, the survival rate reached 66.6%, which was the best performance in all the brain-dead groups, while in group D, only 25% of recipients survived longer than 1 week. The outcome of the recipients grafted with brain-dead donor liver showed a reasonable result that coincides with NIR data. The severely deteriorated microcirculation and intracellular oxygenation status detected in livers in group D resulted in the worst prognosis for the host.

Discussion

The clinical evaluation of brain-dead donors for liver harvesting has always been a difficult task, due to the lack of reliable decision-making criteria. It is well-known that brain death significantly alters regional perfusion of the abdominal organs, with possible implications for organ function. The hemodynamic and metabolic disturbances resulting from brain death could be associated with primary nonfunction. Schiffner et al. have reported that total hepatic blood flow decreased to 53.9% of the normal value during the state of brain death in dogs and pigs [21]. Therefore, the reliable and real-time estimation of the viability of brain-dead livers is important for improving brain-dead transplantation performance.

AKBR is a traditional method for evaluating hepatic viability, which is calculated as acetoacetate/β-hydroxybutyrate. It is considered to reflect the reduction-oxidation (redox) potential of hepatic mitochondria (NAD + /NADH) and the energy-producing ability of

the liver. However, some previous reports on the assessment of liver viability in the brain-dead donor demonstrated that AKBR levels were altered just within a near-normal range even when the hemodynamic conditions were varied widely. Our experiment also showed similar results. As a biochemical parameter, AKBR might be easily influenced by various metabolic factors like alteration in lipid metabolism or electrolyte maladjustment and acid-base imbalance which often occur in brain-dead donors. In the present experiment, other biochemical parameters, i.e., serum transaminase and HA, also failed to offer precise diagnostic values on donor liver viability. Thus, for monitoring brain-dead liver, an alternative or additional method seems to be desirable.

It is well-known that mitochondria play a critical role in the mechanism of the cell's energetic metabolism. Oxidative phosphorylation requires an intact mitochondrial electron transport system wherein NADH and $FADH_2$ from the tricarboxylic acid cycle are re-oxidized and oxygen is reduced by four electrons to water, accompanied by the generation of adenosine triphosphate (ATP). Oxidized Cyt.aa3 is the terminal electron acceptor in the electron transport chain that reacts with molecular O_2. Because it rapidly becomes reduced when oxygen is unavailable, monitoring changes in the redox status of Cyt.aa3 can reflect the adequacy of oxidative metabolism in the liver tissue [24]. In this study, NIR spectroscopic monitoring of oxy-Hb and Cyt redox states well represented the changes in metabolic viability of the liver tissue in brain-dead organ donors. By comparing the kinetics between those two parameters (Hb and Cyt.aa3), the details of the pathophysiological status in the livers could be recognized. In our brain-dead model, the decrease of the oxy-Hb level seems to occur more evidently and earlier than that of Cyt.aa3 in high-catecholamine group, indicating that intracellular oxygenation deteriorated after microcirculation imbalance was induced by the high doses of catecholamine. Thus, NIR spectroscopic monitoring of oxy Hb and Cyt.aa3 redox state could show different time courses of changes in each group, and those parameters were significantly correlated with the 7-day survival of recipients after liver transplantation. On the other hand, AKBR levels and other biochemical parameters failed to predict the prognosis or reflect the sensitive changes in liver viability. These findings suggest that monitoring the oxygenation state of brain-dead liver tissue using NIR spectroscopy is useful for evaluating the degree of liver viability to improve brain-dead donor procurement and to facilitate donor organ selection.

Considering that NIRs can measure relative changes in each oxygen metabolism-related components by arbitrary units, future advanced technique that have the capability to measure optical path length at the same time will enable NIR spectroscopy to quantify the concentrations of oxygen-dependent chromophores. Theoretically, since NIR light has a high transparency in biological tissues, NIR spectroscopy should be able to detect the absorbance spectra of liver deeply through the abdominal wall from outside the body. However, the present technique still cannot offer an ideal solution for removing the influence of NIR absorbance by the abdominal wall clearly. So, in this study, we performed laparotomy to obtain a pure spectrum directly from the liver. Although this measurement is nondestructive to the liver tissue, a non- or less invasive system is needed to bring this technique closer to clinical application either by advancing this technique or by combining it with another medical technique. A combined technique of NIR spectroscopy with laparoscopy may contribute to wide clinical application of this technique to monitor liver perfusion and tissue oxygenation levels in the brain-dead donor.

The beneficial effects of the administration of a vasoconstrictor like catecholamine or vasopressin on improving the hemodynamic stability and hepatic viability of the brain-dead donor is still a controversial point in the practice of transplantation [4, 5, 12, 13]. In the management of brain-dead patients as organ donors, hemodynamic stability is a prerequisite to obtain a viable graft since the liver is highly vulnerable to the low flow status caused by hypotension [14]. To sustain the arterial blood pressure until procurement, it often becomes necessary to administer vasoconstrictor agents, such as catecholamine. However, some reports indicated that the administration of these drugs is associated with an increased incidence of primary graft nonfunction in liver transplantation. We confirmed that infusion with high doses of catecholamine is contraindicated for liver donors, but administration of catecholamine at an optimal dose rate was beneficial and necessary for protecting liver viability, instead of inducing hypoxic stress. We assessed that synergistic administration of epinephrine at a rate of 0.3 μg/kg/min and vasopressin at a rate of 0.1 U/kg/h is an optimal protocol for maintaining the hepatic viability and hemodynamic stability in the rat brain-death model in our experiment.

The precise effects of the brain-death phase on organs for transplantation is still unclear. The various metabolic changes in hormones and cytokines during the brain-dead phase are suspected of contributing to the impairment of graft viability along with tissue ischemia in the brain-dead donor [1, 2, 9, 20, 22, 25]. The unclear impairment mechanism as well as hypoperfusion has received considerable attention around the world recently. In our experiment, even in group C, in which the hemodynamics and tissue oxygenation were maintained at normal levels, the 1-week survival rates were not 100%. It is likely that the above-mentioned factors may contribute to an understanding of the reasons for

such a survival outcome in the rat OLT using a brain-dead donor. To elucidate the underlying mechanisms, the key may lie in the discovery of the responsible cytotoxic substance developed from cerebral damage.

In conclusion, NIR spectroscopy is a sensitive and nondestructive method for monitoring the alteration in the viability of brain-dead liver and can predict liver graft outcome. Using this method, we could determine an optimal regimen consisting of the synergistic administration of epinephrine and vasopressin for maintaining the hepatic hemodynamic stability and functional viability in the rat brain-death model.

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