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Tissue oxygen saturation of human hepatic grafts after reperfusion: paradoxical elevation in poor graft function

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Abstract The present study investigated the pathophysiology of primary nonfunction (PNF) of grafted livers with regard to hepatic tissue oxygenation. Hemoglobin oxygen saturation in hepatic tissue ($H\text{-}So_2$) after reperfusion was determined using near-infrared spectroscopy. Graft tissue oxygen consumption was also estimated according to Fick's principle. Six grafts with PNF were compared with 40 functioning grafts. One PNF graft with extremely low and heterogenous $H\text{-}So_2$ after reperfusion was found to contain multiple intrahepatic portal thrombi. However, five other PNF grafts showed no lower and, on the contrary, more homogeneous $H\text{-}So_2$ at the end of the operation. As a whole, mean $H\text{-}So_2$ was negatively correlated and the coefficient of variation (CV) of $H\text{-}So_2$ was positively correlated with graft tissue oxygen consumption at the end of the operation; grafts whose $H\text{-}So_2$ showed a secondary decrease had better initial function. In later relaparotomy, the $H\text{-}So_2$ of the five PNF grafts was significantly higher and more homogeneous than that of the functioning grafts. These results suggest that the $H\text{-}So_2$ level reflects tissue oxygen consumption as well as oxygenation, and that the dissociation of both factors can occur in hepatic graft reperfusion. Not only low and heterogeneous $H\text{-}So_2$ but also high and homogenous $H\text{-}So_2$, suggesting some shunt mechanism, can be signs of poor graft function.

Key words Liver transplantation, primary nonfunction, tissue oxygen saturation, near-infrared spectroscopy · Tissue oxygen consumption, sinusoidal shunt

Introduction

Despite remarkable progress that has been made in organ harvesting techniques [7], preservation solutions [8, 29], and grafting procedures, the occurrence of primary nonfunction (PNF) remains a stumbling block in clinical liver transplantation. The reported frequency of PNF varies from 2% to 20% in adult cases [3, 6, 11, 18, 22]. Several factors that are suspected to play a role in PNF include donor age, latent liver disease, length of donor hospitalization, use of catecholamines, and prolonged cold and warm ischemia times [3, 18, 20, 22]. However, except in extreme cases, their decisive role as a single factor is still controversial, and it is difficult to find a clear cutoff point for each factor. Furthermore, given the scarcity of donor organs, not only is the prevention of PNF but also its differential diagnosis from initial poor function or delayed function, i.e., the timing of regrafting, a clinical matter of discussion.

Thanks to numerous reports on animal models, the possible mechanisms of preservation and reperfusion injury in hepatic grafts are now being clarified [4]. However, mainly due to the lack of a safe and exact method to evaluate these phenomena in clinical settings, knowledge of their clinical relevance is still limited. The rather homogeneous quality of animal organs and possible differences among species also make it difficult to apply knowledge gained from animal models to the clinical setting.

One of the most important prerequisites for primary graft function is a sufficient oxygen supply to the tissue and subsequent oxygenation of extracellular space and intracellular components. We have recently introduced a novel near-infrared spectroscopy in which a multicomponent curve-fitting analysis is used for the detection of oxygen saturation of hemoglobin in hepatic tissue (H-So_2) [14]. In the context of the accumulated data on reperfusion injury in animal and in vitro models, it would be quite interesting to know whether the signs of PNF, if any, can be detected by changes in tissue oxygenation in the early stage of reperfusion. In this study we analyzed H-So_2 in grafts with PNF in comparison with functioning grafts. As an index of graft oxygen consumption, changes in whole body oxygen consumption were also determined according to Fick's principle and discussed in relationship to graft tissue oxygen saturation.

Patients and methods

Patients and grafts

The study involved 46 patients – 19 males and 27 females – who had undergone orthotopic hepatic transplantation. PNF necessitated replacement of six grafts within 1 week of the operation. The indication for regrafting was determined synthetically on the basis of clinical parameters, i.e., transaminase and glutamate dehydrogenase levels, bilirubin, coagulation factors, bile production and quality, circulatory and mental status, donor and harvesting data, macroscopic reperfusion quality and, if applicable, histological findings. Forty functioning grafts that survived for more than 1 week were used as controls. Pretransplant diagnoses of the recipients and other profiles are shown in Tables 1 and 2. Eighteen recipients were managed in the ICU preoperatively.

The causes of brain death in the donors were: brain trauma ($n = 21$), cerebrovascular accident ($n = 21$), brain abscess ($n = 2$), brain tumor ($n = 1$), and hypoglycemia ($n = 1$). The preservation solutions used were histidine-tryptophan-ketoglutarate (HTK) solution for 25 grafts and University of Wisconsin (UW) solution for 21 grafts. All but two ABO-compatible and two ABO-incompatible grafts were ABO-identical.

The study was approved by the local committee on medical ethics and was performed in accordance with the ethical standards set down in the 1964 Declaration of Helsinki. All participants gave their informed consent prior to their inclusion in the study.

Table 1 Indications for transplantation

	Controls	Failed grafts
Alcoholic cirrhosis	1	
Amyloidosis	1	
Autoimmune hepatitis	2	2
Budd-Chiari syndrome	3	
Chronic graft dysfunction	1[a]	
Cystic liver	1	
Fulminant hepatic failure	8	1
Liver tumor	2	2
Oxalosis	1	
Postnecrotic cirrhosis	6	
Primary biliary cirrhosis	2	1
Primary nonfunction	5[a]	
Primary sclerosing cholangitis	5	
Rejection	2[a]	
Total	40	6

[a] Cases of secondary grafts

Table 2 Profiles of donors, grafts, and recipients

	Controls	Failed grafts	*P*
Donors			
Age (years)	34.9 ± 14.7	41.2 ± 12.5	NS
Body weight (kg)	69.8 ± 14.7	67.3 ± 11.7	NS
ICU stay (days)	3.2 ± 2.8	5.3 ± 5.0	NS
Recipients			
Age (years)	40.4 ± 14.7	46.3 ± 17.4	NS
Body weight (kg)	64.7 ± 12.4	64.2 ± 13.0	NS
Anhepatic time (h)[a]	2.35 ± 4.17	4.36 ± 6.57	NS
Grafts			
Graft/recipient weight ratio (g/kg)	23.2 ± 8.4	23.5 ± 4.6	NS
Cold ischemia time (h)[b]	10.05 ± 3.46	10.28 ± 2.84	NS
Warm ischemia time (h)[c]	0.97 ± 0.32	1.17 ± 0.28	NS

[a] From clamping to declamping of portal vein. Total hepatectomy with portocaval shunting was done in advance in two controls (18.4 and 22.0 h) and in one patient with a failed graft (19.0 h). The incidence of these cases and anhepatic time in the other cases did not differ between the two groups

[b] From start of graft cold perfusion in donor to graft insertion into recipient

[c] From graft insertion into recipient to the institution of portal venous inflow

Operation and patient management

The grafting procedure and intraoperative management were performed as described elsewhere [21]. Anesthesia was maintained with fentanyl and midazolam, supplemented with isoflurane. Partial grafts (two left and one right lobes, all derived from different donors) were used in three cases. Femoro-porto-axillary veno-venous bypass during the anhepatic phase was carried out in 23 cases. At reperfusion, the first blood (300 ml) to come through the graft was discarded to wash out the preservation solution. Other rinsing procedures or agents that could potentially modify reperfusion injury, e.g., Carolina rinse solution or prostaglandins, were not used.

Postoperative immunosuppression consisted of prednisolone and cyclosporin A ($n = 20$) or FK 506 ($n = 26$). All patient management was performed independently with H-So_2 results.

Measurements of hepatic tissue oxygen saturation

A continuous tissue absorbance spectrum in the near-infrared region (every 2 nm from 700 to 1000 nm) was obtained via a multichannel photodiode scanner MCPD1000 (Otsuka Electronics, Osaka, Japan) as described elsewhere [14]. In brief, two quartz fibers, for light emission and detection, were brought into gentle right-angle contact with the graft surface. The distance between the two fibers was approximately 1 cm. The sampling time for each scan was 2 s. A 10% lipid emulsion was used as a reference spectrum. After correcting for scattering effects in the absorption spectrum, a multicomponent curve-fitting analysis was applied following the Beer-Lambert law [14]: absorbance $(\lambda) = L(\lambda) \cdot \{e_1(\lambda) \cdot [\text{oxyhemoglobin}] + e_2(\lambda) \cdot [\text{deoxyhemoglobin}] + e_3(\lambda) \cdot \Delta [\text{oxidized cytochrome } aa_3] + e_4(\lambda) \cdot \Delta [\text{reduced cytochrome } aa_3] + a_1(\lambda) \cdot [\text{hemoglobin-free liver}] + a_2(\lambda) \cdot [\text{HTK or UW solution}]\}$, where $L(\lambda)$, $e_{1-4}(\lambda)$ and $a_{1-2}(\lambda)$ are mean light pathlength, extinction coefficient, and absorbance at λ nm, respectively. The same cold-preserved liver before implantation was used as a hemoglobin-free liver. H-So_2 was calculated as follows:

H-So_2 = [oxyhemoglobin]/{[oxyhemoglobin] + [deoxyhemoglobin]}.

One set of measurements, which takes about 2 min, consisted of twelve points on the graft surface. In so far as the condition of the patients permitted, two sets of measurements were taken after graft reperfusion, one after bleeding had come under control and circulation was stabilized (early reperfusion phase) and one before the closure of the abdominal wall (late reperfusion phase). All of the measurements were taken with a double supply of blood, from both the portal vein and the hepatic artery. Rotation or manipulation of the graft was strictly avoided for at least several minutes before taking measurements. At occasional later relaparotomy for suspected bleeding or for regrafting, H-So_2 measurements were done in the same way.

Estimation of graft tissue oxygen consumption

Based on Fick's principle, whole body oxygen consumption (Vo_2) was calculated as follows [16]:

$Vo_2(\text{ml/min}) = \{(SaO_2 - SvO_2)/100 \times 1.39 \times Hb + (PaO_2 - PvO_2) \times 0.0031\} \times CO \times 10$, where SaO_2/PaO_2 and SvO_2/PvO_2 are the oxygen saturation of hemoglobin (%) or oxygen tension (mm Hg), respectively, in peripheral arterial and mixed venous blood, Hb is hemoglobin concentration in peripheral blood (g/dl), and CO is cardiac output (l/min) determined by the thermodilution method in duplicate. Only the values of Vo_2 based on the simultaneous measurements of all parameters were adopted. Vo_2 values during the anhepatic phase were averaged in the interval of more than 30 min after stabilization of the systemic circulation. As far as the clinical situation permitted, Vo_2 was determined synchronously with H-So_2 measurements after reperfusion. To offset the influences of body and graft sizes, estimated graft tissue oxygen consumption was calculated as follows:

graft tissue oxygen consumption = [% increase of Vo_2 after graft reperfusion]/[graft/recipient weight ratio (g/kg)].

If not otherwise shown, values represent the mean ± SD. Statistical analyses were performed using a one-way analysis of variance and a modified *t*-test for continuous data, and with a chi-squared test for categorical data. *P* values less than 0.05 were regarded as significant.

Table 3 Postoperative parameters

	Controls	Failed grafts	*P*
Peak GOT (U/l)	847 ± 652	3444 ± 1894	< 0.001
(Day)	0.4 ± 0.7	1.5 ± 0.5	< 0.001
Peak GPT (U/l)	699 ± 472	4084 ± 2271	< 0.001
(Day)	0.7 ± 0.8	1.7 ± 0.5	< 0.01
Bile flow (average for 3 days; ml/day)[a]	170 ± 166 (n = 29)	20 ± 17 (n = 5)	NS
Factor V (average of daily bottom for 3 days; %)	51.0 ±17.6	22.0 ± 5.9	< 0.001
Factor V (average of daily peak for 3 days; %)	66.6 ± 21.2	31.0 ± 5.0	< 0.001
Fresh-frozen plasma administered (total for 3 days; units)	5.5 ± 7.2	22.0 ± 7.5	< 0.001
Day of regrafting	–	3.7 ± 1.4	–

[a] Only cases with T-tube drainage

Results

Clinical parameters

There were no differences in any of the donor, recipient, or graft parameters described earlier between grafts that failed and control grafts. Two of the three partial grafts survived. In the other partial graft (split right lobe), reperfusion was macroscopically very poor. In this case, despite catecholamine treatment, postreperfusion hypotension (around 70 mm Hg) lasted for about 20 min. Similar but shorter mild hypotension was also observed in five controls. In the other grafts that subsequently failed (all whole grafts), reperfusion was macroscopically smooth and homogeneous, except for two cases with mild and transient heterogeneity.

Postoperative parameters are shown in Table 3. Peak transaminases in grafts that failed were significantly higher and delayed. Coagulating factor V level was also much lower, despite more fresh-frozen plasma (FFP). The decision to retransplant was made 1–5 days, and performed 2–6 days, after the initial operation. The histology of all the explanted grafts was characterized by extended dystrophy and necrosis consistent with ischemia. In one graft with persistent hypotension, multiple fresh thrombi were also observed in small to medium intrahepatic portal veins. None of the failed grafts showed histological evidence of either vascular occlusion at the anastomotic site or hyperacute rejection, e.g. intralobular hemorrhagic necrosis.

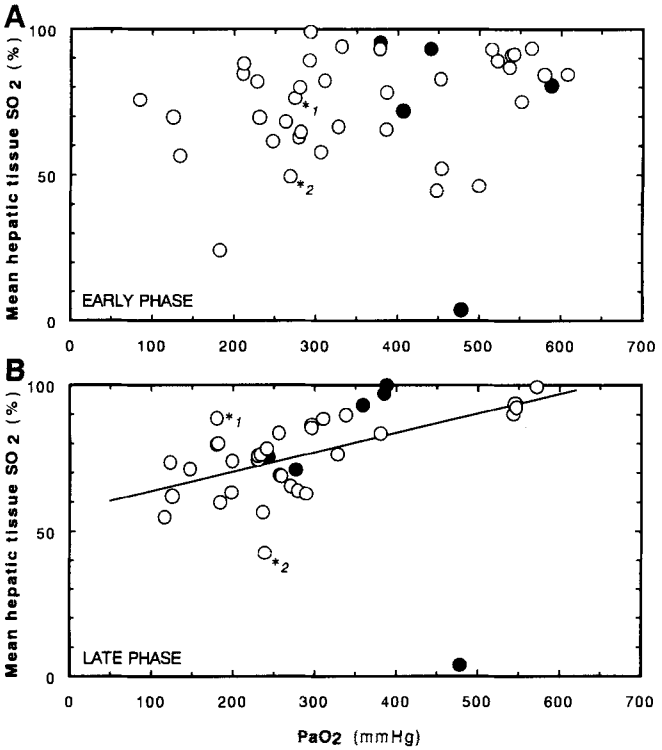

Fig. 1 A, B Mean H-So_2 in relation to PaO_2 in the **A** early phase and **B** late phase of reperfusion. Solid line represents correlation in grafts that survived ($r = 0.628$, $P < 0.001$). (● grafts that failed)

Table 4 Parameters in H-So_2 measurements

	Controls	Failed grafts	*P*
Early reperfusion phase	($n = 37$)	($n = 5$)	
Time after reperfusion (h)	0.54 ± 0.34	0.60 ± 0.27	NS
Systolic blood pressure (mm Hg)	109 ± 20	112 ± 9	NS
Arterial hemoglobin (g/dl)	9.4 ± 1.5	10.2 ± 1.6	NS
PaO_2 (mm Hg)	355 ± 142	458 ± 73	NS
H-So_2 mean (%)	74.5 ± 16.8	69.0 ± 33.7[a]	NS
CV (%)	15.1 ± 10.6	48.7 ± 78.7[c]	< 0.02
Late reperfusion phase	($n = 35$)	($n = 6$)	
Time after reperfusion (h)	1.88 ± 0.68	1.73 ± 0.55	NS
Systolic blood pressure (mm Hg)	113 ± 17	109 ± 9	NS
Arterial hemoglobin (g/dl)	9.9 ± 1.5	9.6 ± 0.9	NS
PaO_2 (mm Hg)	282 ± 121	355 ± 77	NS
H-So_2 mean (%)	75.4 ± 12.8	73.4 ± 32.9[b]	NS
CV (%)	11.1 ± 4.6	38.9 ± 74.9[d]	< 0.05

[a,b] If one graft with an extremely low mean H-So_2 is excluded, the values are 85.5 ± 9.5 (P = NS) and 87.4 ± 11.8 (P = NS), respectively

[c,d] If one graft with an extremely low mean H-So_2 is excluded, the values are 9.4 ± 4.3 (P = NS) and 5.4 ± 4.7 ($P < 0.01$), respectively. The latter value is lower than that of controls

Hepatic tissue oxygen saturation and oxygen consumption

Figure 1 shows the mean H-So_2 after reperfusion. One failed graft, complicated with intrahepatic thrombi, showed an extremely low H-So_2 (3.8 ± 7.9 %; $P < 0.001$ vs other failed grafts). This low H-So_2 persisted in the late reperfusion phase. In other failed grafts, H-So_2 showed no obvious difference from the grafts that survived. Parameters in H-So_2 measurements are shown in Table 4. Systemic circulatory parameters were similar in both groups. If we exclude one failed graft with an extremely low mean and high heterogeneity of H-So_2, the coefficient of variation (CV = SD/mean) being 206 %, H-So_2 in the other failed grafts was significantly more homogeneous than in controls at the end of the operation.

Figure 2 shows the relationship between the mean or CV of H-So_2 and the estimated graft tissue oxygen consumption in the late reperfusion phase. Since graft H-So_2 apparently reaches a plateau at PaO_2 around 400 mm Hg (Fig. 1), measurements at PaO_2 less than and more than 400 mm Hg are shown separately. Graft oxygen consumption could not be measured in the failed graft with the extremely low H-So_2. Mean H-So_2 was negatively correlated and CV of H-So_2 positively correlated with estimated tissue oxygen consumption at PaO_2 less than 400 mm Hg. These relationships were not observed in the early reperfusion phase.

In the cases where H-So_2 measurement was repeated under constant inhalation oxygen, the changes in mean H-So_2 were compared with initial graft function (Fig. 3). The grafts whose mean H-So_2 decreased in the late reperfusion phase had significantly better synthetic function than those with increased or the same mean H-So_2. PaO_2 at H-So_2 measurements was similar in both groups.

Two cases that are in contrast in Fig. 1 (*1 and *2) will now be described in detail. The ICU stay of the donor was 3 days and 1 day, and the grafts were preserved in UW and HTK solutions, respectively. Cold ischemia time, warm ischemia time, and anhepatic time were 17.4, 1.17, and 1.80 h, respectively in case 1, and 13.0, 0.85, and 1.13 h, respectively, in case 2. The difference in mean H-So_2 was $P < 0.001$ in both phases. The CV of H-So_2 in the early and late phases was 14.0 and 8.1 in case 1, and 25.6 and 24.3 in case 2, respectively. Postoperative peak GOT/GPT was 523/397 U/l in case 1 (graft/recipient weight ratio 15.9 g/kg) and 1190/700 U/l in case 2 (20.0 g/kg). In case 2, the average bile secretion and daily peak of factor V for the first 3 days were 583 ml/day and 76 % (total FFP 2 units) and factor V recovered to 100 % on the 3rd day. In case 1, those were

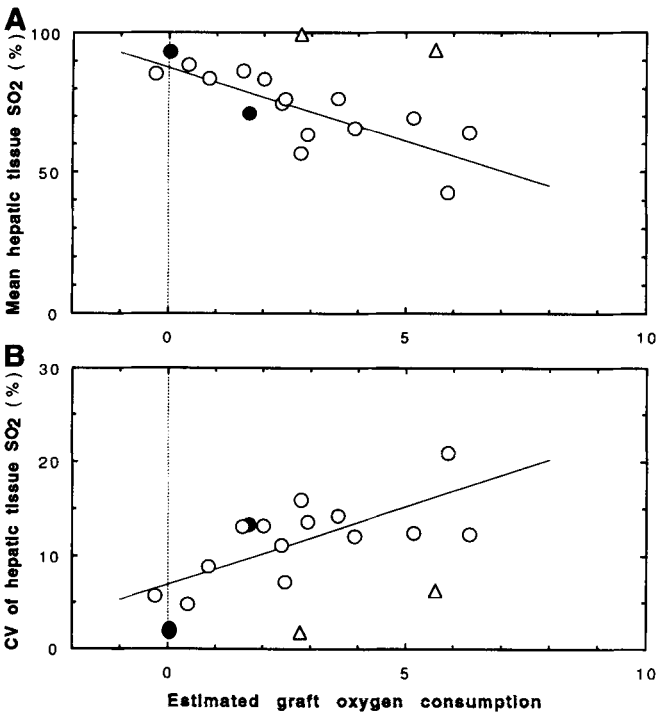

Fig. 2 A, B Relationship between **A** mean H-So_2 or **B** CV of H-So_2 and estimated graft tissue oxygen consumption in the late reperfusion phase. Solid lines represent correlations at $PaO_2 < 400$ mm Hg (**A** $r = -0.795$, $P < 0.001$; **B** $r = 0.708$, $P < 0.01$). (○ H-So_2 measurement at $PaO_2 < 400$ mm Hg, △ H-So_2 measurement at $PaO_2 > 400$ mm Hg, ● grafts that failed)

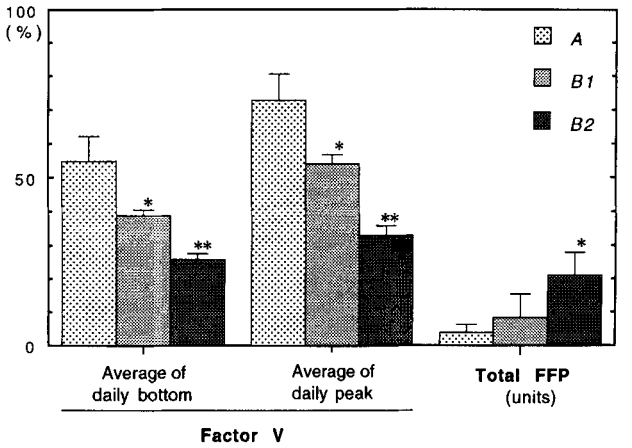

Fig. 3 Postoperative coagulation factor V for the first 3 days in groups classified by intraoperative changes in mean H-So_2. Bars represent standard error. [A grafts whose H-So_2 in the late phase was lower ($n = 6$) than in the early phase under the same oxygen concentration; B grafts whose H-So_2 in the late phase was higher or not changed ($n = 14$) than in the early phase under the same oxygen concentration; B1 grafts that survived ($n = 10$); B2 grafts that failed ($n = 4$)]. * $P < 0.05$, ** $P < 0.01$ compared with group A

60 ml/day and 41 % (FFP 13 units); factor V did not recover to within the normal range until the patient died of sudden variceal bleeding on the 13th day.

Figure 4 shows graft H-So_2 at occasional relaparotomy. All of the patients with functioning grafts and one with a failed graft were reoperated due to suspected bleeding. Other failed grafts were measured at regrafting. One failed graft that showed an extremely low H-So_2 was not measured before regrafting. The time after reperfusion (69.6 ± 21.1 h for failed grafts vs 71.1 ± 51.8 h for functioning grafts) and PaO_2 (243 ± 103 vs 223 ± 96 mm Hg, respectively) were comparable in both groups. H-So_2 in failed grafts was significantly higher and more homogeneous than that in functioning grafts.

Report of a graft split into two

Figure 5 shows the course of one graft that was split and transplanted into two recipients. The graft donor was 36 years old with an ICU stay of 16 days ($P < 0.001$ vs the other failed grafts, 3.2 ± 1.5 days), and the graft was preserved in UW solution. Recipient A was the PNF case with persistent hypotension, shown in Fig. 1. This patient was a 59-year-old female with primary biliary cirrhosis. The graft cold ischemia time, warm ischemia time, anhepatic time, and graft/recipient weight ratio were 13.7, 1.13, and 1.32 h and 24.0 g/kg, respectively. Postoperative peak transaminases were: GOT 3498 U/l and GPT 8195 U/l ($P < 0.01$ vs the other failed grafts, 3198 ± 1077 U/l), and the average daily peak of factor V for the first 3 days was 29 % (FFP 15 units). This graft was replaced 2 days after grafting.

Recipient B was an 18-year-old female with paracetamol-induced fulminant hepatic failure. Because this patient underwent auxiliary transplantation, she was excluded from the abovementioned study group. During the first operation, her native liver had a bright red and homogeneous appearance. H-So_2 averaged more than 90 % and was very homogeneous. After left lobectomy of the native liver, the left lobe of the graft was implanted orthotopically. Graft cold ischemia time, warm ischemia time, and graft/recipient weight ratio were 13.4 and 1.73 h and 11.5 g/kg (no anhepatic phase). After reperfusion, graft H-So_2 was heterogeneous but much higher than in the other part of the graft. Peak GOT and GPT were 1067 and 1628 U/l, respectively, and the average daily peak of factor V for the first 3 days was 34 % (no FFP). Subsequently, factor V recovered to 100 % on the 10th day. A liver scintigram performed on the 7th day showed better function in the remaining native liver than in the graft. After an episode of rejection, the graft was removed on the 39th day. The histology of the removed graft showed subacute dystrophy accompanied by map-like necrosis, in addition to cellular infiltration. In contrast, the native liver

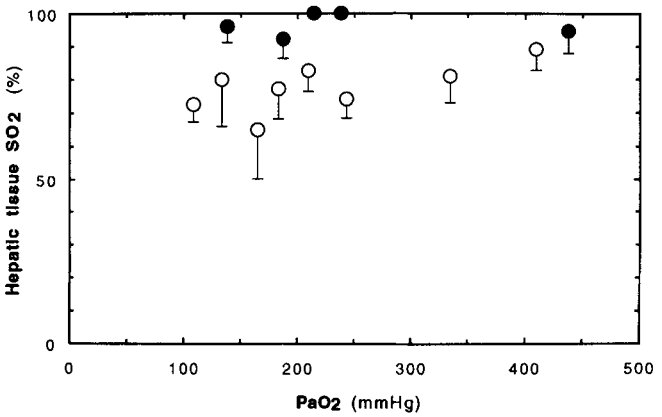

Fig. 4 H-So_2 at relaparotomy. Circle and bar represent mean and SD of one graft. In grafts that failed (●), mean H-So_2 is higher (96.6 % ± 3.0 % vs 77.7 % ± 6.8 %, $P < 0.001$) and CV of H-So_2 is lower (3.7 % ± 3.1 % vs 11.4 % ± 5.4 %, $P < 0.02$) than those in grafts that survived

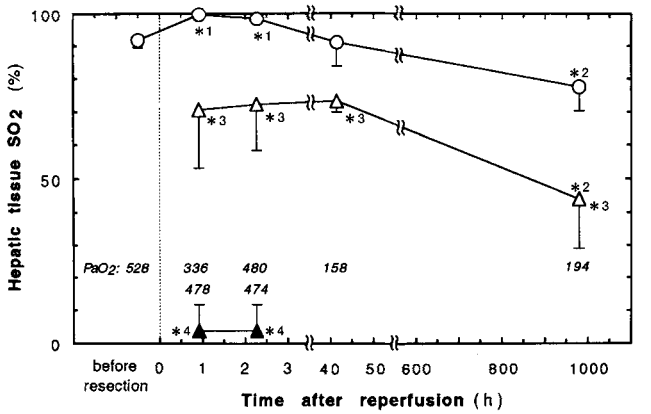

Fig. 5 Time course of H-So_2 in two patients who received split grafts of the same origin. The right lobe was implanted in a non-auxiliary fashion into recipient A. The left lobe was implanted auxiliarily and orthotopically into recipient B after left lobectomy of native liver. Bars represent SD of each set of measurements. (▲ graft in recipient A, △ graft in recipient B, ○ native liver of recipient B) *1 $P < 0.001$ compared with before partial resection, *2 $P < 0.001$ compared with all previous measurements, *3 $P < 0.001$ compared with native liver, *4 $P < 0.001$ compared with counterpart of the same graft

showed a remarkable regeneration, and massive necrosis seen during the first operation disappeared completely. The H-So_2 of the native liver, as well as of the graft, at the time of the last operation was significantly lower than previous measurements despite a higher PaO_2.

Discussion

A rather unexpected finding from this study is that a high and homogeneous tissue So_2 can be a sign of poor function. In contrast to tissue Po_2, which can reflect oxygenation of all compartments of the tissue, tissue So_2 reflects the oxygenation state of blood perfusion space in the tissue. In animal experiments, hepatic tissue So_2 is much closer to hepatic venous So_2 than to hepatic arterial or portal venous So_2 [14]. This is thought to be due to anatomical background that perfusion space in the pericentral area is larger than that in the periportal area [10]. This also suggests that H-So_2 can reflect remaining oxygen after consumption, as well as the oxygen supply to the tissue. This characteristic feature of tissue So_2 is also shown in other organs, e.g., decreased brain oxygen consumption accompanied by a diminished electroencephalogram results in high brain tissue So_2 [17]. In a normal liver with active oxygen consumption, a physiological oxygen gradient exists along with hepatic sinusoids [12, 23]. This produces "physiological" heterogeneity of oxygenation in many organs [17]. H-So_2 heterogeneity observed in functioning grafts may be at least partly attributed to this physiological heterogeneity.

The decrease in H-So_2 in the late reperfusion phase, which is associated with better function, is consistent with these physiological backgrounds. Despite hours of cold preservation, the tissue So_2 of many grafts was restored already in the early phase to nearly the same level as in the late phase. This suggests that the recovery of perfusion is considerably smooth in many cases and that a rapid oxygen consumption, reflected in the decrease in H-So_2, follows. Such a delay in oxygen consumption is consistent with a report in living related liver transplantation (where cold ischemia time is much shorter than in cadaveric transplantation) that the recovery of the intramitochondrial redox state after reperfusion is much delayed, despite the earlier normalization of tissue oxygenation [28]. Our results suggest that H-So_2 in the late reperfusion phase is determined by the balance between the microcirculatory factor of oxygen supply and the metabolic factor of oxygen consumption (Fig. 2). Presumably, in case 1 in Fig. 1, the recovery of oxygen consumption was much delayed compared with the recovery of perfusion, and the former started in the early phase, parallel to the latter in case 2.

The estimation of graft oxygen consumption by Fick's principle is a rather rough parameter because it assumes a constant oxygen consumption by the other parts of the body. Actually, a high Vo_2 value, surpassing the preclamping value, is reported in the early reperfusion phase, which is presumably influenced by increased cardiac output immediately after reperfusion [16, 27]. Despite this, an increase in Vo_2 after liver grafting is often reported as a reliable clinical parameter of graft

function [1, 16]. A good correlation between estimated graft tissue oxygen consumption and mean H-So_2 suggests that the balance between tissue perfusion and consumption becomes nearly stable in the late reperfusion phase.

One failed graft had an extremely low and heterogeneous H-So_2, probably attributable to a perfusion disturbance due to intrahepatic portal thrombi. This heterogeneity is obviously a "pathological" one. On the other hand, in the other failed grafts, a reduction in heterogeneity had already started during the operation and was later accompanied by a higher H-So_2 level. It is interesting that these apparently different oxygenation abnormalities, i.e., higher and lower heterogeneity, both led to greater and prolonged ischemic injury.

The contrast between a partial graft with PNF and its counterpart suggests that extrinsic factors can contribute to the pathogenesis of PNF. One such extrinsic factor is the persistent hypotension after graft reperfusion seen in the failed graft. Taking into consideration the rather poor initial function of the counterpart, these cases suggest that persistent hypotension in a graft recipient can be a relative risk factor of graft failure if combined with intrinsic graft factors. As for H-So_2 in partial grafts, a previous study in living related liver transplantation suggested its heterogeneity in split grafts [15]. The persistent effect of such heterogeneity, potentially attributed to anatomical backgrounds, on graft function remains to be clarified.

A factor contributing to elevated H-So_2 in failed grafts is the loss of oxygen consumption by hepatocytes. The high H-So_2 observed in drug-induced fulminant hepatic failure with massive hepatocyte necrosis and its decrease after regeneration may be at least partly explained by this mechanism. Cold preservation induces several changes in hepatocytes, such as cell swelling, intracellular acidosis, loss of mitochondrial function, and decreased ATP [4, 13]. Also, reactive oxygen intermediates and some cytokines, e.g., tumor necrosis factor [26], released on reperfusion have direct effects on hepatocytes. These factors may lead to decreased oxygen consumption by hepatocytes in failed grafts. Another possible explanation is a breakdown of oxygen transport from the sinusoidal space to hepatocytes. On reperfusion, sinusoidal endothelial cells are injured by oxygen products, protease, and cytokines [2, 30]. Such injured endothelial cells can lose their physiological function and fenestration [19]. In addition, increased procoagulant activity and adhesions of leukocytes and platelets potentially deteriorate transendothelial oxygen transport [4]. Secondary injury of parenchymal cells through these nonparenchymal injuries may also result in decreased oxygen consumption by the tissue.

In a normal liver, there is no direct anastomosis between the portal venous or arterial system and the central venous system [9]. Such an anatomical shunt is limited to congenitial anomalies or to some chronic liver diseases such as congestion, fibrosis, and cirrhosis [9, 24]. On the other hand, it is reported that a paradoxical elevation of hepatic tissue Po_2 occurs after repeated hemorrhagic hypotension [25]. This is explained by a phenomenon called "sinusoidal shunt", i.e., the development of low or no-flow sinusoids and predominantly perfused sinusoids. Such a sinusoidal shunt loses nutritional effects and finally results in hepatic parenchymal necrosis. Sinusoidal shunt formation is consistent with a report that the mechanical obstruction of tissue perfusion does not occur, despite leukocyte trapping in the reperfused liver [5]. Given some analogies between hemorrhagic shock and reperfusion injury, such a phenomenon might also contribute to high H-So_2 in grafts with poor function. Because a light pathlength of 1 cm in our method reflects the sum of many sinusoids, H-So_2 homogeneity among sampling points does not exclude the obstruction of some sinusoids distributed evently in the liver. In other words, our H-So_2 homogeneity represents a macroscopic homogeneity among large areas and not a microscopic homogeneity among sinusoids.

This study shows that there are at least two different types of early graft failure, i.e., an oxygenation- or perfusion-limited type and a consumption-limited type. The latter might be a special form of the former type. The former type is characterized by pathological heterogeneity of tissue oxygenation and the latter by loss of physiological heterogeneity. High and homogeneous H-So_2, as well as low and heterogeneous H-So_2, can be a sign of poor graft function. In other words, a homogeneous, bright red hepatic graft may still be subject to poor reperfusion and oxygenation. Exactly what discriminates these two types of early graft failure is not yet clear, but a histochemical study investigating this is now under way. Further studies are expected to clarify the pathogenesis of different types of primary nonfunction in clinical liver transplantation.

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