

Hepatic Venous Hemoglobin Oxygen Saturation Predicts Liver Dysfunction after Hepatectomy

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A fiberoptic flow-directed catheter inserted into the hepatic vein continuously measures hepatic venous oxygen hemoglobin saturation (Shv_{O_2}). This study determined whether intraoperatively measured Shv_{O_2} could predict postoperative serum activities of aminotransferases and patient outcome in 83 patients undergoing hepatectomy. The duration of intraoperative $Shv_{O_2} \leq 10, 20, 30, 40$, and 50% was calculated in each case. Significant increases in postoperative serum aminotransferases were associated with more than 1, 11, 31, 51, and 181 min of duration of $Shv_{O_2} \leq 10, 20, 30, 40$, and 50%, respectively. The incidence of postoperative liver failure significantly increased when the duration of $Shv_{O_2} \leq 20, 30$, and 40% exceeded 11, 31, and 51 min, respectively. The mortality from liver failure was significantly higher when the duration of $Shv_{O_2} \leq 30$ and 40% exceeded 31 and 51 min, respectively. Therefore, intraoperative monitoring of Shv_{O_2} may predict not only the increase in postoperative serum aminotransferases but also patient outcome in terms of postoperative liver failure after hepatectomy. (Key words: Equipment: oximeter pulmonary artery catheter. Liver: aminotransferase; liver failure; oxygenation. Monitoring: hepatic venous oxygen saturation. Surgery: hepatic.)

ANESTHETICS AND SURGERY affect both hepatic blood flow and oxygen uptake.¹ Although several techniques have been described to determine hepatic blood flow and splanchnic oxygen consumption,^{2,3} the information derived is neither in real-time nor continuous. Fiberoptic balloon-tipped flow-directed catheters, if placed in the hepatic vein, can be used to measure hepatic venous hemoglobin oxygen saturation (Shv_{O_2}) continuously and provide minute-to-minute information of the hepatic oxygen supply-demand relationship.⁴ We previously described the feasibility and safety of hepatic venous catheterization through the right internal jugular vein.⁵ Thus it remains to be investigated whether Shv_{O_2} monitoring can improve quality of anesthetic management in terms of liver protection and patient outcome. Although early

postoperative deaths after hepatectomy are attributable largely to liver failure,⁶⁻⁸ there has been no adequate monitoring that can predict the risk of postoperative liver failure. Therefore, in this study, we prospectively investigated whether perioperative Shv_{O_2} was related to postoperative liver function and patient outcome.

Materials and Methods

SUBJECTS AND PROTOCOL

Eighty-three consecutive patients (58 men and 25 women) who underwent elective hepatic lobectomy for either hepatocellular or biliary tract tumor from July 1988 to January 1990 were studied. Their average age was 57 yr (range 33-76 yr), height 161 cm (range 145-179 cm), and weight 56 kg (range 32-78 kg). The study was approved by the institutional human research committee, and informed consent was obtained. Thirty-one patients had liver cirrhosis confirmed by postoperative microscopic examination. Abdominal angiography, including selective hepatic venography, was performed for preoperative evaluation of the liver tumor in all patients. Preoperative laboratory tests included complete blood cell count, serum electrolytes, liver function studies, urinalysis, electrocardiogram, and chest x-ray.

Patients received 0.5 mg atropine sulfate and 50 mg hydroxyzine hydrochloride intramuscularly prior to transport to the operating room. A cannula was inserted into the radial artery for monitoring systemic arterial blood pressure, and 50-100 μ g of fentanyl was administered intravenously. An 8-Fr dilator-sheath unit (Arrow, Inc., Reading, PA) was inserted into the right internal jugular vein by the Seldinger guide-wire technique. Under fluoroscopic guidance, a 7-Fr fiberoptic flow directed catheter (Opticath Model P7110-EH, Oximetrix Corp., Mountain View, CA) was inserted through the sheath and placed in the hepatic vein. Two milliliters 30% Iopamidol was infused through the catheter to confirm its positioning by referring to preoperative selective hepatic venography. The catheter was withdrawn 1.5 cm from the wedged position and fixed to the skin. Another dilator-sheath unit was then placed for pulmonary artery catheterization with the same type of the catheter as for hepatic venous catheterization. Fluoroscopy was repeated to confirm the proper placement of both catheters and the absence of coiling.

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Anesthetic induction and tracheal intubation were accomplished by administering 5 mg/kg thiamylal sodium followed by either 1 mg/kg succinylcholine or 0.1 mg/kg vecuronium bromide intravenously, supplemented with 4 μ g/kg fentanyl. Anesthesia was maintained with 67% nitrous oxide and oxygen with 1–2% enflurane. Respiratory and anesthetic gas concentrations were continuously monitored with an infrared spectrometer (Capnomac, Datex, Helsinki, Finland). Ventilation was adjusted to maintain P_{aCO_2} between 35 and 40 mmHg. Radial arterial, central venous, and pulmonary arterial pressures were continuously monitored. In addition, hepatic venous pressure was continuously monitored to detect inadvertent wedging of the hepatic venous catheter during surgery. Cardiac output was intermittently measured by the thermodilution technique. Perioperative fluid loss was replaced mainly by lactated Ringer's solution. Estimated blood loss was replaced mainly by citrate-phosphate-dextrose blood, and transfusion volume was adjusted to maintain hemoglobin concentration between 9 and 10 g/dl. Fresh frozen plasma was used in cases with altered coagulation parameters during surgery. Anesthetic management was supervised by the same anesthesiologist, and the surgery was performed by one of three surgeons.

DATA MEASUREMENTS

The values of mixed venous hemoglobin oxygen saturation (Sv_{O_2}) and Shv_{O_2} were calibrated by the oxygen saturation values of venous blood samples measured with a Co-oximeter (OSM-3, Radiometer, Copenhagen, Denmark), at 2- or 3-h intervals. These values were continuously shown on graphical and numerical display of Oximetrix 3 SO_2 computer (Abbott Laboratories, North Chicago, Illinois). Sv_{O_2} and Shv_{O_2} monitoring was continued to the first postoperative day (POD) in the intensive care unit. Peri- and postoperative values of Sv_{O_2} and Shv_{O_2} were stored and printed out on the recording charts with their graphical display on a scale of 12 cm/h by the printer (Oximetrix 3 printer, Abbott Laboratories).

The activity of serum aminotransferases was measured spectrophotometrically, using an automated analyzer (Hitachi type-736, Tokyo, Japan). Reagents used were obtained from Wako Junyaku Co. Ltd, (Osaka, Japan). According to the study in our institute, the coefficient of variation is less than 2% in both aspartate aminotransferase (AST) and alanine aminotransferase (ALT). The normal range of AST and ALT are 0–41 and 0–45 IU/l, respectively.

In each patient, we calculated the duration while the absolute Shv_{O_2} value was less than 50, 40, 30, 20, and 10%, respectively, from the intraoperative recordings. Then patients were classified by the duration of the re-

spective Shv_{O_2} threshold values as mentioned above. Serum aminotransferases on the first to third PODs in each group were compared with those of cases whose Shv_{O_2} was never less than the respective Shv_{O_2} threshold value. Patients' outcome was also investigated in terms of the intraoperative Shv_{O_2} values. Liver failure was diagnosed by the following criteria: serum total bilirubin of greater than 10 mg/dl and grade III or IV hepatic coma. The incidence of liver failure and mortality due to liver failure were investigated in terms of intraoperative Shv_{O_2} . In addition, serum aminotransferases and patients' outcome were compared in terms of types of operation, intraoperative estimated blood loss, and the operating time.

DATA ANALYSIS

Values were expressed as mean \pm SEM. First, one-way analysis of variance was used for the comparison of postoperative values of serum aminotransferases in each group of patients with a different duration of respective Shv_{O_2} threshold values. Dunnett's test was subsequently applied for multiple comparison. Secondly, chi-square analysis was used to investigate patients' outcome in terms of the duration of respective Shv_{O_2} threshold values. Lastly, simple linear regression analysis with the least-squares method was used to examine the relationships among several parameters, including pre- and postoperative values of serum aminotransferases, estimated blood loss, operating time, incidence of liver failure, and the mortality. A *P* value of 0.05 or less was considered significant.

Results

Shv_{O_2} before anesthetic induction was $70 \pm 1\%$. Shv_{O_2} decreased in varying degrees following surgical procedures such as skin incision, mobilization of the liver, dissection of the hepatic hilus, and temporary cross-clamping of hepatic inflow. Preoperative AST and ALT were 55 ± 3 and 58 ± 5 IU/l, respectively. Figure 1 shows the relationship between AST and ALT values and the duration of $Shv_{O_2} \leq 10\%$. One minute or longer of $Shv_{O_2} \leq 10\%$ resulted in significant increases in serum aminotransferase activities, except for AST on the third POD. When the threshold value was set at Shv_{O_2} of 20%, more than 11 min was associated with significant increases in serum aminotransferase activities except for AST on the second POD (fig. 2). When the threshold value was set at Shv_{O_2} of 30%, more than 31, 41, and 51 min were associated with significant increases in serum aminotransferase activities on the first, second, and third POD, respectively (fig. 3). When the threshold Shv_{O_2} value was 40%, more than 51 min was associated with significant increases in serum aminotransferase activities on the first

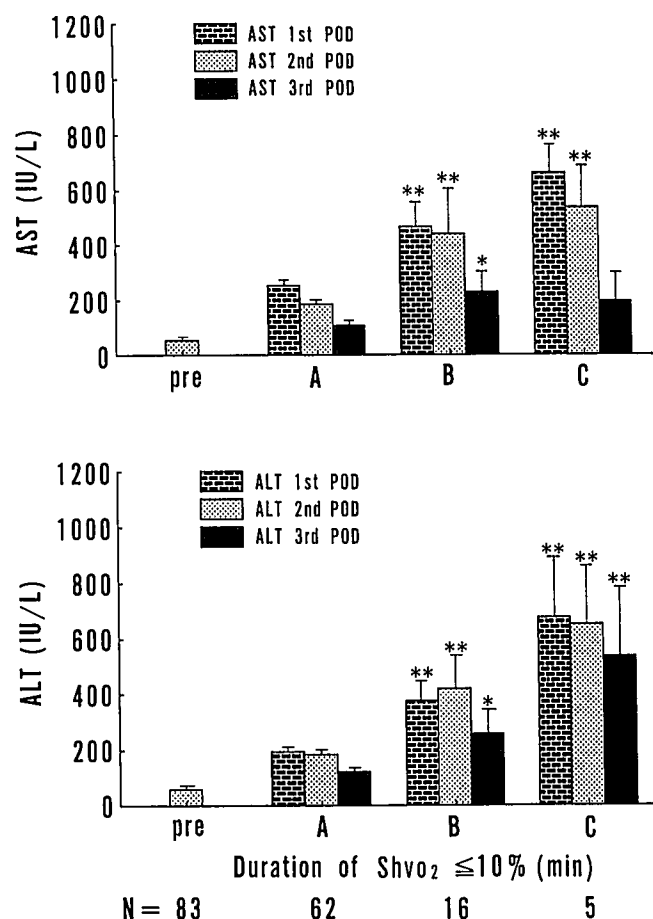


FIG. 1. Serum aminotransferases on pre- and postoperative days when cases were classified according to duration of Shvo₂ ≤ 10%. Data are mean ± SEM. **P* < 0.05, ***P* < 0.01 versus 0 min. A = 0 min; B = 1–10 min; C = >11 min; AST = aspartate aminotransferase; ALT = alanine aminotransferase; POD = postoperative day; N = the number of patients; pre = preoperative value.

POD (fig. 4). When the threshold Shvo₂ was 50%, more than 181 min was associated with significant increases in serum aminotransferase activities (fig. 5). Figure 6 shows the relationship between the duration required to produce significant increases in serum aminotransferase activities and the threshold Shvo₂ value. Tables 1–5 show the relationship between the patients' outcome and the duration of respective threshold Shvo₂ values. The incidence of postoperative liver failure was significantly related to more than 11, 31, and 51 min of threshold Shvo₂ at 20, 30, and 40%, respectively. The mortality due to liver failure was significantly related to more than 31 and 51 min of threshold Shvo₂ at 30 and 40%, respectively.

Preoperative values of serum aminotransferases, the presence of liver cirrhosis, and the type of operation were not related to postoperative values of aminotransferases, incidence of postoperative liver failure, or mortality from

liver failure. Estimated blood loss and operating time were not related to postoperative values of serum aminotransferases. However, estimated blood loss was significantly greater in patients with liver failure ($4,522 \pm 790$ ml) and patients who died of liver failure ($4,561 \pm 881$ ml) than in patients without liver failure ($2,444 \pm 267$ ml) and patients who survived ($2,467 \pm 264$ ml), respectively. Operating time was significantly longer in patients with liver failure (573 ± 115 min) and patients who died of liver failure (574 ± 129 min) than in patients without liver failure (414 ± 20 min) and patients who survived (416 ± 19 min), respectively.

Discussion

Shvo₂ represents a summation of hemoglobin oxygen saturation in the blood at the venous ends of all sinusoids

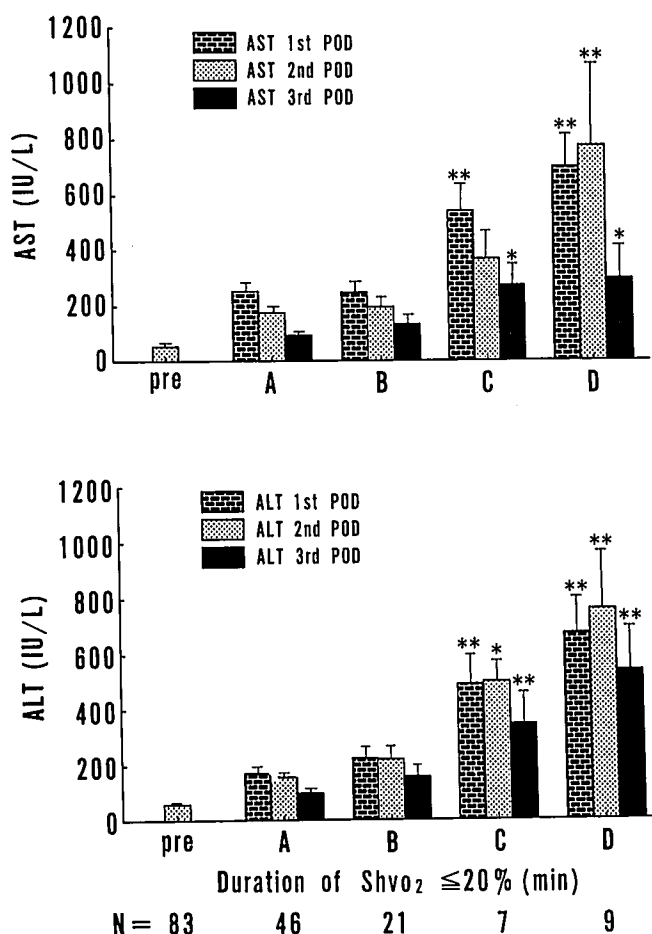


FIG. 2. Serum aminotransferases on pre- and postoperative days when cases were classified according to duration of Shvo₂ ≤ 20%. Data are mean ± SEM. **P* < 0.05, ***P* < 0.01 versus 0 min. A = 0 min; B = 1–10 min; C = 11–20 min; D = >21 min; AST = aspartate aminotransferase; ALT = alanine aminotransferase; POD = postoperative day; N = the number of patients; pre = preoperative value.

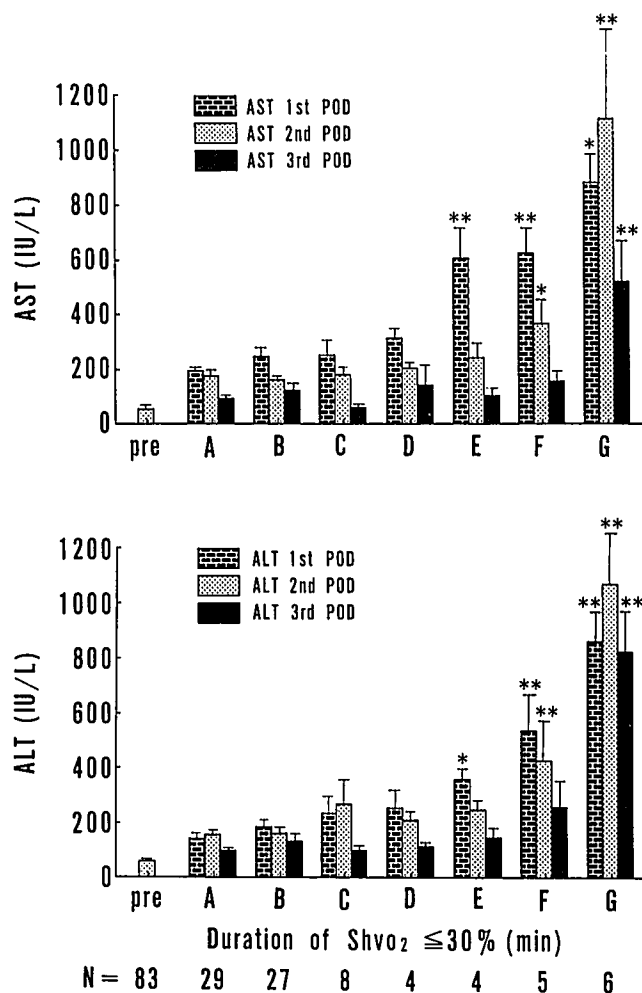


FIG. 3. Serum aminotransferases on pre- and postoperative days when cases were classified according to duration $ShvO_2 \leq 30\%$. Data are mean \pm SEM. * $P < 0.05$, ** $P < 0.01$ versus 0 min. A = 0 min; B = 1–10 min; C = 11–20 min; D = 21–30 min; E = 31–40 min; F = 41–50 min; G = >51 min; AST = aspartate aminotransferase; ALT = alanine aminotransferase; POD = postoperative day; N = the number of patients; pre = preoperative value.

in the liver.⁹ Factors producing an imbalance between hepatic oxygen supply and demand should cause a corresponding deviation in $ShvO_2$, and low $ShvO_2$ implies the presence of areas with very low oxygen tension within the liver.⁹ Decreases in $ShvO_2$ in this study were presumed to be due largely to temporary deterioration of hepatic blood supply, since surgical maneuvers such as dissection in the hepatic hilus and temporary interruption of hepatic inflow were frequently accompanied by a drop of $ShvO_2$ that was subsequently mitigated only by minor modification of these surgical procedures.⁵

Serum activities of aminotransferases reportedly undergo a rapid increase to 300–400 IU/l in the first 48–

72 h and return to normal within 7–10 days after hepatectomy.¹⁰ Frederiks *et al.*¹¹ described a stepwise increase in serum aminotransferases after 15-, 30-, and 90-min interruptions of hepatic blood flow in rats. The early stage of increases in serum aminotransferases following ischemia was associated with a formation of bleblike protrusions from parenchymal cells in the liver, whereas the late stage of ischemia was associated with damage to cytoplasmic structures, including ribosomes and mitochondria. Both types of histologic findings reflect increased permeability of the plasma membrane of hepatocytes for proteins, leading to actual enzyme leakage into the blood stream.^{11,12}

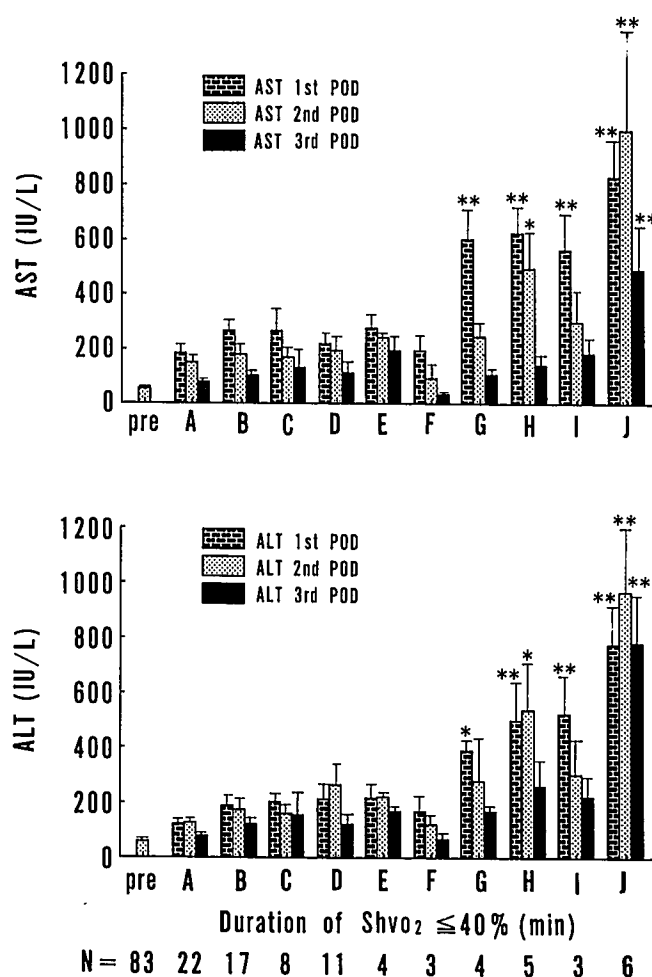


FIG. 4. Serum aminotransferases on pre- and postoperative days when cases were classified according to duration of $ShvO_2 \leq 40\%$. Data are mean \pm SEM. * $P < 0.05$, ** $P < 0.01$ versus 0 min. A = 0 min; B = 1–10 min; C = 11–20 min; D = 21–30 min; E = 31–40 min; F = 41–50 min; G = 51–60 min; H = 61–70 min; I = 71–80 min; J = >81 min; AST = aspartate aminotransferase; ALT = alanine aminotransferase; POD = postoperative day; N = the number of patients; pre = preoperative value.

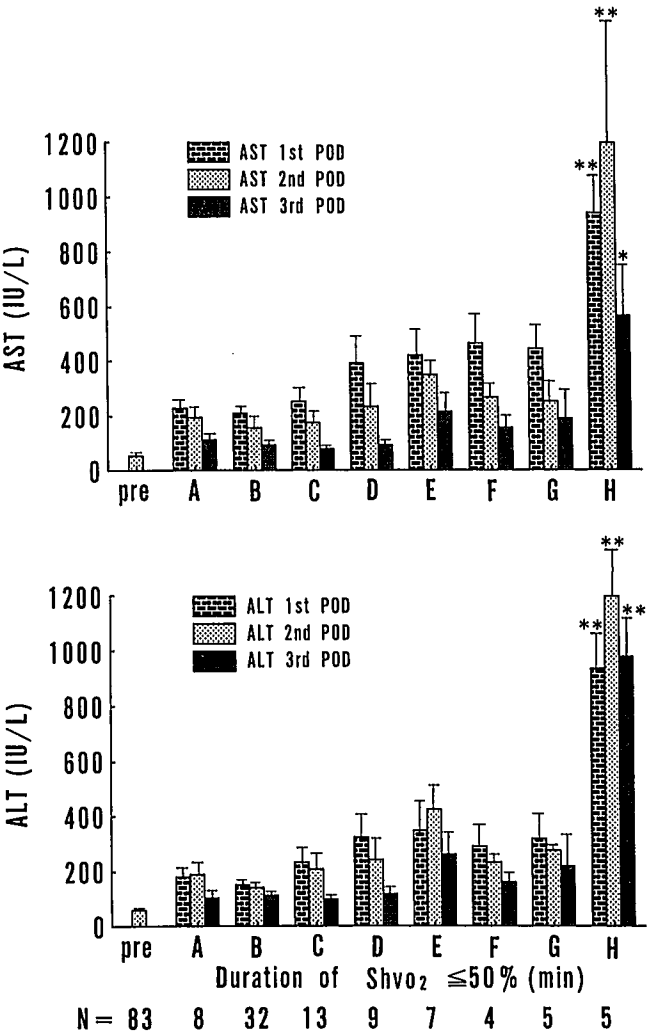


FIG. 5. Serum aminotransferases on pre- and postoperative days when cases were classified according to duration of $ShvO_2 \leq 50\%$. Data are mean \pm SEM. * $P < 0.05$, ** $P < 0.01$ versus 0 min. A = 0 min; B = 1–30 min; C = 31–60 min; D = 61–90 min; E = 91–120 min; F = 121–150 min; G = 151–180 min; H = >181 min; AST = aspartate aminotransferase; ALT = alanine aminotransferase; POD = postoperative day; N = the number of patients; pre = preoperative value.

Lee *et al.*¹³ found significantly greater values of postoperative serum aminotransferases in patients with an episode of intraoperative hypotension than in patients without hypotension. Their observation might well be related to our results of increased serum aminotransferases in patients with a greater duration of low $ShvO_2$, although the duration of hypotension was not detailed in their study. Nagano *et al.*¹⁴ observed in miniature pigs that hepatic oxygen uptake starts to decrease and becomes oxygen-delivery-dependent when oxygen tension in hepatic venous blood reaches 25–28 mmHg, and that the liver stops metabolizing and starts to release lactate when ox-

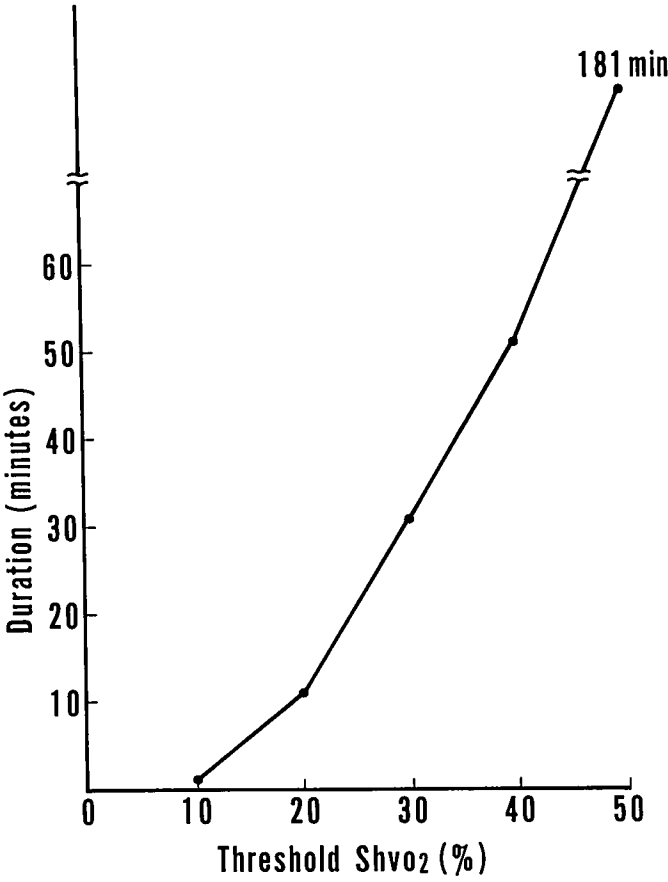


FIG. 6. The relationship between the duration of time required to produce significant increases in serum aminotransferases and threshold $ShvO_2$ value. N = the number of patients.

xygen tension in hepatic venous blood reaches 10–13 mmHg. Although they did not measure serum aminotransferases, such levels of hepatic venous oxygen tension should have a close connection with the critical level of $ShvO_2$ on leakage of serum aminotransferases observed in this study.

TABLE 1. Patients' Outcome When Patients Were Classified into Groups According to Duration of $ShvO_2 \leq 10\%$

	Duration of $ShvO_2 \leq 10\%$ (min)		
	A	B	C
Number of patients	62	16	5
Number of liver failures	7	2	4
Number of deaths due to liver failure	6	1	3
% Patients with liver failure	7/62	6/21	
Mortality due to liver failure	6/62	4/21	

A = 0 min; B = 1–10 min; C = >11 min.

TABLE 2. Patients' Outcome When Patients Were Classified into Groups According to Duration of $\text{Shv}_{\text{O}_2} \leq 20\%$

	Duration of $\text{Shv}_{\text{O}_2} \leq 20\%$ (min)			
	A	B	C	D
Number of patients	46	21	7	9
Number of liver failures	5	2	2	4
Number of deaths due to liver failure	5	1	2	2
% Patients with liver failure	7/67		6/16*	
Mortality due to liver failure	6/67		4/16	

A = 0 min; B = 1–10 min; C = 11–20 min; D = > 21 min.

* $P < 0.01$ versus < 10 min.TABLE 3. Patients' Outcome When Patients Were Classified According to Duration of $\text{Shv}_{\text{O}_2} \leq 30\%$

	Duration of $\text{Shv}_{\text{O}_2} \leq 30\%$ (min)						
	A	B	C	D	E	F	G
Number of patients	29	27	8	4	4	5	6
Number of liver failures	2	2	1	1	1	3	3
Number of deaths due to liver failure	2	2	0	0	2	3	1
% Patients with liver failure	6/68			7/15*			
Mortality due to liver failure	4/68			6/15*			

A = 0 min; B = 1–10 min; C = 11–20 min; D = 21–30 min; E = 31–40 min; F = 41–50 min.

* $P < 0.01$ versus < 30 min.

The recommended tolerance time of normothermic cross-clamping of the hepatic artery and portal vein has recently been increased to 60 min, although it was formerly limited to 15–20 min.^{15–17} In this study, such cross-clamping induced variable degrees of a decrease in Shv_{O_2} , reflecting differences in the extent of intrahepatic venous collateral channels and/or in the degree of spontaneous decreases in intrahepatic temperature during cross-clamping.^{16,17} Therefore, the tolerance time of cross-clamping should be individualized, and the duration of a decrease in Shv_{O_2} should be a better indicator of cross-

clamping to determine how long each patient can tolerate intrahepatic hypoxia.

We have found in our clinical cases that the severity of intraoperative hepatic hypoxia as demonstrated by the degree of a decrease in Shv_{O_2} and its duration was related to the patients' outcome in terms of the frequency of liver failure and its mortality. The liver failure was clinically diagnosed by signs and symptoms with massive hepatocellular necrosis, including jaundice, ascites, and neurologic unresponsiveness. If hepatic dysfunction is suspected on postoperative laboratory tests, persistent elevation of serum bilirubin has been considered as a characteristically unfavorable sign leading to liver failure.^{6,7} Because oxygen consumption and extraction by the liver are high, oxygen deficits are implicated in centrilobular regions farthest from the oxygen supply. Thus, hypoxia on hepatocytes caused by the decreased hepatic oxygen supply should lead to impairment of their ability to excrete bilirubin.^{18,19} Thompson *et al.*⁶ reported that 11 of 138 patients had liver failure with serum bilirubin of greater than 10 mg/dl after hepatectomy. Therefore, we included serum bilirubin of greater than 10 mg/dl in tentative criteria of liver failure in this study.

Tissue hypoxia can be defined by an imbalance between oxygen demand and supply that is characterized by an oxygen uptake–supply dependency.²⁰ The resulting oxygen debt may be followed by an occurrence of anaerobic metabolism and subsequent development of the organ failure. We previously reported in rats that hepatic energy charge abruptly decreased when Shv_{O_2} decreased to less than 30%,²¹ a value that is in good accordance with the critical level of hepatic venous oxygen tension by Nagano *et al.*¹⁴ These animal data could support our clinical result that intraoperative hepatic hypoxia shown by a decrease in Shv_{O_2} was related to the development of postoperative liver failure.

Several substances, such as lactate,²² hypoxanthine,²³ uric acid,²⁴ and ketone bodies²⁵ have been measured to assess the severity of tissue hypoxia in clinical and labo-

TABLE 4. Patients' Outcome When Patients Were Classified According to Duration $\text{Shv}_{\text{O}_2} \leq 40\%$

	Duration of $\text{Shv}_{\text{O}_2} \leq 40\%$ (min)									
	A	B	C	D	E	F	G	H	I	J
Number of patients	22	17	8	11	4	3	4	5	3	6
Number of liver failures	1	1	2	1	0	0	2	2	2	2
Number of deaths due to liver failure	1	1	2	0	0	1	1	1	1	1
% Patients with liver failure	5/65					8/18*				
Mortality due to liver failure	5/65					5/18†				

A = 0 min; B = 1–10 min; C = 11–20 min; D = 21–30 min; E = 31–40 min; F = 41–50 min; G = 51–60 min; H = 61–70 min; I = 71–80 min; J = >81 min.

* $P < 0.01$ versus < 50 min.† $P < 0.05$ versus < 50 min.

TABLE 5. Patients' Outcome When Patients Were Classified According to Duration of $\text{Shv}_{\text{O}_2} \leq 50\%$

	Duration of $\text{Shv}_{\text{O}_2} \leq 50\%$ (min)							
	A	B	C	D	E	F	G	H
Number of patients	8	32	13	9	7	4	5	5
Number of liver failures	0	3	2	3	2	1	0	2
Number of deaths due to liver failure	0	2	2	1	2	1	0	2
% Patients with liver failure				11/78				2/5
Mortality due to liver failure				8/78				2/5*

A = 0 min; B = 1–30 min; C = 31–60 min; D = 61–90 min; E = 91–120 min; F = 121–150 min; G = 151–180 min; H = >181 min.

* $P < 0.05$ versus < 180 min.

ratory settings, although the interpretation of these values in an individual remains difficult.²⁶ Preoperative measurement of retention rate of intravenously administered indocyanine green has also been proposed to estimate the hepatocyte function and predict the risk of liver failure after hepatectomy.²⁷ However, these tests are not able to reflect intraoperative hypoxia directly and therefore cannot be used as monitoring tools during anesthesia for hepatectomy.

Our results of blood loss and prolonged operating time relating to the development of liver failure are in good agreement with previous reports.^{28,29} However, these factors could not be primarily responsible for the complication but the consequence of other causative factors. Nagao *et al.*²⁸ attributed postoperative liver failure to an impairment of hepatic oxygen supply resulting in a disturbance of mitochondrial high-energy phosphate production that was frequently accompanied by major blood loss and prolonged operating time. Therefore, a long duration of hepatic hypoxia, rather than major blood loss or prolonged operating time, could be a predominant factor in inducing postoperative liver failure. In addition, other factors including preoperative aminotransferases, preexistence of liver cirrhosis, and type of operation had no relationship to postoperative increase in aminotransferases and occurrence of liver failure.

In conclusion, the intraoperative decrease in Shv_{O_2} was significantly related not only to postoperative increases in aminotransferases but also to patients' outcome regarding postoperative liver failure. Shv_{O_2} monitoring might help improve surgical outcome in patients undergoing liver surgery.

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