Effect of intermittent liver ischemia on outcome in patients with hepatocellular carcinoma on liver cirrhosis

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Abstract: The influence on postoperative liver function of intermittent normothermic hepatic ischemia in cirrhotic patients was studied retrospectively. The mean total ischemia time was 88 (range 30～140) minutes in the hemi-hepatic occlusion group, and 68 (range 10～187) minutes in the total occlusion group. There were no operative deaths due to hepatic failure. Postoperative liver function improved within 1 week of the operation. There was no significant difference in the incidence of postoperative complications between the groups. Thus normothermic hepatic ischemia is tolerated for up to 180 minutes in the cirrhotic liver when an intermittent technique (15 minutes clamped and 5 minutes unclamped) is used. J. Med. Invest. 46 : 205-212, 1999

Key words : *hepatic ischemia, vascular occlusion, liver cirrhosis*

INTRODUCTION

The normal human liver has been shown to tolerate 15 to 20 minutes of normothermic ischemia (1, 2). Recently, tolerance to prolonged normothermic ischemia, periods of 1 hour without interruption has been demonstrated (3). However, in the cirrhotic human liver, the maximum safe ischemia time has not been determined (4). We have used intermittent normothermic ischemia (15 minutes clamped and 5 minutes unclamped) with both hemi-hepatic and total hepatic occlusion (Pringle's maneuver (5)) techniques for hepatic resection. The purpose of this study was to compare the postoperative liver function and clinical course of cirrhotic patients (a no occlusion group, hemi-hepatic occlusion group and total hepatic occlusion group) following hepatectomy to determine the limits of the techniques.

PATIENTS AND METHODS

Between January 1985 and August 1994, 40 patients with histologically proven cirrhosis were entered into this study. These patients were divided into three groups according to the hepatic occlusion method employed. In group A, 10 patients (all men) underwent hepatic resection without vascular occlusion. In group B, 8 patients (all men) underwent hepatic resection with hemi-hepatic vascular occlusion. In group C, 22 patients (14 men and 8 women) underwent hepatic resection with total vascular occlusion. Hepatic vascular occlusion was performed intermittently (15 minutes clamped and 5 minutes unclamped) throughout the procedure.

The average age was 56.0±6.9 years in group A, 61.8±5.8 years in group B, and 62.5±8.5 years in group C (Table 1). Preoperative liver function, intraoperative characteristics, postoperative liver function, and morbidity and mortality were compared between the three groups.

Statistical comparisons were performed using Student's t test and the chi-square test. A p value less than 0.05 was considered statistically significant.

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RESULTS

Preoperative liver function

Preoperative biochemical liver function tests were conducted (Table 1). The serum aspartate amino-

Table 1. Patient background

	group A no occlusion (n=10)	group B hemi occlusion (n=8)	group C total occlusion (n=22)	p
Age (year)	56.0±6.9	61.8±5.8	62.5±8.5	p < .05
Gender (M : F)	10 : 0	8 : 0	14 : 8	.02 < p < .05
Real Risk	2.88±0.63	2.54±0.39	2.82±0.52	ns
AST (IU/L)	86±41	76±46	66±28	ns
ALT (IU/L)	91±62	94±64	64±34	ns
T-Bil (mg/dL)	0.9±0.4	0.8±0.3	1.0±0.3	ns
HPT (%)	74±22	72±12	64±14	ns
$ICGR_{15}$ (%)	25±13	18±6	23±9	ns
KICG (/min)	0.08±0.04	0.11±0.02	0.12±0.06	ns

M : male F : female
ALT : alanine aminotransferase
T-Bil : total bilirubin
HPT : hepa plastin test
$ICGR_{15}$: indocyanine green concentration at 15 minutes
KICG : rate of disappearance of ICG from serum

transferase (AST), alanine aminotransferase (ALT), and total bilirubin (T-Bil) concentrations, and the hepaplastin test (HPT), indocyanine green (ICG) retention at 15 minutes (ICGR 15) and KICG tests were not significantly different between the three groups. The Real Risk , which was the value of the hepatic reserve calculated from several factors such as serum AST, T-Bil, cholinesterase, albumin levels and prothrombin time, HPT, KICG, ICGRmax and the type of oral glucose tolerance test (6), was 2.88 ±0.57 in group A, 2.54±0.39 in group B, and 2.82± 0.52 in group C. This difference was not significant.

Intraoperative characteristics

There were no significant differences with respect to the tumor location, approach method and mobilization of the right lobe of the liver (Table 2). However in group A, 4 of 10 tumors were located in the lateral segment, and the rate of thoracoabdominal approach and mobilization of the right lobe was lower than in groups B and C (Table 2).

There were no significant differences with respect to the operative procedure, blood loss, transfusion requirement or weight of the resected specimen between the groups (Table 3). The operative time was 367±66 minutes in group A, 540±132 minutes in group B, and 496±145 minutes in group C. These differences between groups A and B, and groups A and C were significant (p<.01). The duration of ischemia was 88±36 (range : 30 to 140) minutes in group B, and 68±48 (range : 10 to 187) minutes in group C. This difference was not significant.

Operative procedure and hepatic Real Risk

The relationship between the type of hepatic resection and hepatic Real Risk was studied. A wide line separated the safety and danger zones for postoperative hepatic failure. All patients were operated on within the safety zone (Fig.1). In group A (no occlusion ; n=10), partial resection was carried out for 6 patients, subsegmentectomy for 2 patients, and 1 segmentectomy for 2 patients. In group B (hemi-hepatic occlusion ; n=8), partial resection was carried out for 3 patients, subsegmentectomy for 4 patients, and 1 segmentectomy for one patient. In group C (total occlusion ; n=22), partial resection was carried out for 19 patients, subsegmentectomy for 2 patients, and 1 segmentectomy for one patient. There was no postoperative liver failure or operative death except for one patient who had intraoperative cerebral infarction.

Postoperative liver function

In all three groups, the serum AST and ALT concentrations peaked on postperative day 1. These levels had decreased to the preoperative levels by postperative day 7. The total bilirubin concentrations increased more slowly than the AST and ALT levels, and a significant difference (p<.05) was observed between groups A and C on postperative day 1, decreasing gradually over one week in the three groups (Fig. 2).

Table 2. Intraoperative characteristics (1)

	group A no occlusion (n=10)	group B hemi-occlusion (n=8)	group C total occlusion (n=22)	p
Tumor location (Lo)				
L (%)	4 (40.0)	0 (0)	2 (9.1)	
M (%)	0 (0)	0 (0)	2 (9.1)	
A (%)	2 (20.0)	4 (50.0)	8 (36.5)	
P (%)	2 (20.0)	1 (12.5)	3 (13.6)	ns
C (%)	0 (0)	0 (0)	0 (0)	
LM (%)	0 (0)	0 (0)	1 (4.5)	
MA (%)	0 (0)	0 (0)	1 (4.5)	
AP (%)	0 (0)	1 (12.5)	5 (22.7)	
others (%)	2 (20.0)	2 (25.0)	0 (0)	
Approach				
1. abdominal (%)	8 (80.0)	2 (25.0)	10 (45.5)	ns
2.thoracoabdominal (%)	2 (20.0)	6 (75.0)	12 (54.5)	(p=0.056)
Mobilization of the right lobe				
1. no (%)	4 (40.0)	0 (0)	4 (18.2)	ns
2. done (%)	6 (60.0)	8 (100)	18 (81.8)	(p=0.103)

L : lateral segment M : medial segment A : anterior segment P : posterior segment C : caudate lobe

Table 3. Intraoperative characteristics (2)

	group A no occlusion (n=10)	group B hemi-occlusion (n=8)	group C total occlusion (n=22)	p
Procedures (Hr)				
0 (%)	6 (60.0)	3 (37.5)	16 (72.8)	
S (%)	2 (20.0)	4 (50.0)	4 (18.2)	ns
1 (%)	2 (20.0)	1 (12.5)	1 (4.5)	
2 (%)	0 (0)	0 (0)	1 (4.5)	
Operative time (min)	367±66	540±132	496±145	※※ p< .01
	※※		※※	
Bleeding (g)	840±660	1350±890	1140±970	ns
Blood transfusion (ml)	480±460	520±480	480±580	ns
Ischemic time (min)	0	88±36 (30～140)	ns 68±48 (10～187)	
Weight of resected specimens (g)	211±285	161±58	109±69	ns

Hr : type of hepatic resection (0 ; partial resection, S ; subsegmentectomy, 1 ; 1 segmentectomy)

Procedure (Hr)	Real Risk				
	1.0	2.0	3.0	4.0	5.0
2+ (P, A, m) (L, M, a)					
2 (P, A) (L, M)		safety zone ⬅	➡ danger zone		
1 (A) (P) (L)		△† ☆	○○		
S		☆ ☆ △ △ △ ○ △ ○			
O		☆ ○ △ ○ ☆ ☆ ☆☆☆ ☆△☆☆☆△ ☆☆ ○ ○☆○☆ ☆☆☆☆☆ ○			
	1.0	2.0	3.0	4.0	5.0

Fig.1. Relationship between operative procedure and Real Risk
In group A (no occlusion), partial resection was carried out for 6 patients, subsegmentectomy for 2 patients, and 1 segmentectomy for 2 patients. In group B (hemi-hepatic occlusion), partial resection was carried out for 3 patients, subsegmentectomy for 4 patients, and 1 segmentectomy for one patient. In group C (total hepatic occlusion), partial resection was carried out for 19 patients, subsegmentectomy for 2 patients, and 1 segmentectomy for one patient. All patients were operated on within the safety zone.
L : lateral segment M (m) : medial segment A (a) : anterior segment P : posterior segment ○ : no occlusion (group A)
△ : hemi-occlusion (group B). ☆ : total occlusion (group C) † : operative death
Hr : type of hepatic resection (2+ ; extended lobectomy, 2 ; 2 segmentectomy, 1 ; 1 segmentectomy, S ; subsegmentectomy, O ; partial resection)

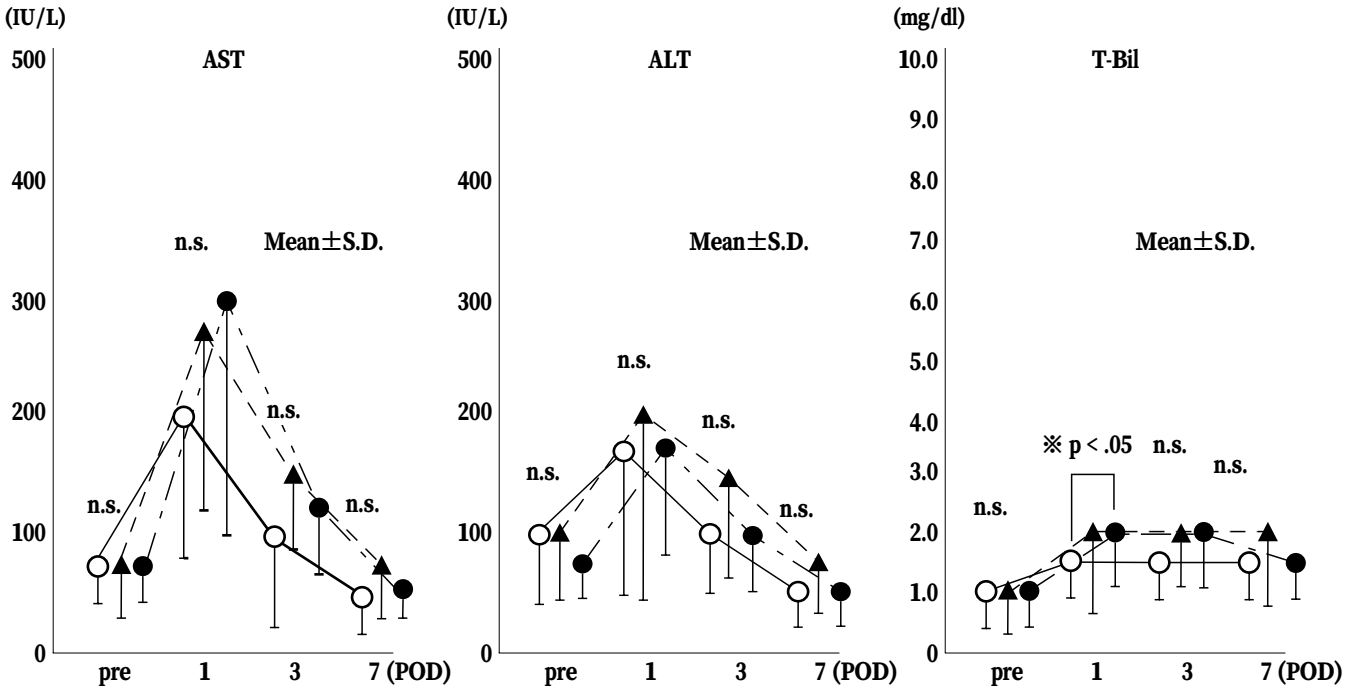

Fig. 2. Postoperative liver function
In all three groups, the serum AST and ALT concentrations reached a peak on postoperative day (POD) 1. These levels had decreased to the preoperative levels by postoperative day 7. The total bilirubin concentration (T-Bil) increased more slowly than the AST and ALT levels, and a significant difference ($p<0.05$) was observed between groups A and C on postoperative day 1, decreasing gradually within one week in the three groups. (○-○ ; Group A (n=10), ▲-▲ ; Group B (n=8), ●-● ; Group C (n=22))

Relationship between ischemic time and serum ALT and total bilirubin level

There was a significant correlation (R=.526, p= .012) between ischemic time and serum ALT levels (postperative day 1) in group C, but not between ischemic time and serum total bilirubin concentrations (postoperative day 3) in group C. In group B, there were no significant correlations between ischemic time and serum ALT levels or total bilirubin concentrations (Fig. 3).

Postoperative complications

Non of the patients suffered from intraabdominal or gastrointestinal bleeding postoperatively. The incidence of hepatic failure occuring postoperatively within three months was 0% in all groups. The incidence of major complications (intraabdominal bleeding or abscess, respiratory failure, severe infection, bile leakage and intractable ascites) was 10.0% in group A, 25.0% in group B and 36.4% in group C. Minor complications (wound infection, mild ascites or pleural effusion et al.) occurred in 30.0%, 37.5%, and 27.3% of patients respectively. The total complication rate was 40.0% in group A, 62.5% in group B, and 63.6% in group C. There was no significant difference between the three groups (Table 4).

Outcome

One patient in group B (12.5%) suffered cerebral infarction during the operation and died on the 14 th postoperarive day. There were no operative deaths in groups A and C. One hospital death on the 118th postoperative day in group B was caused by per-

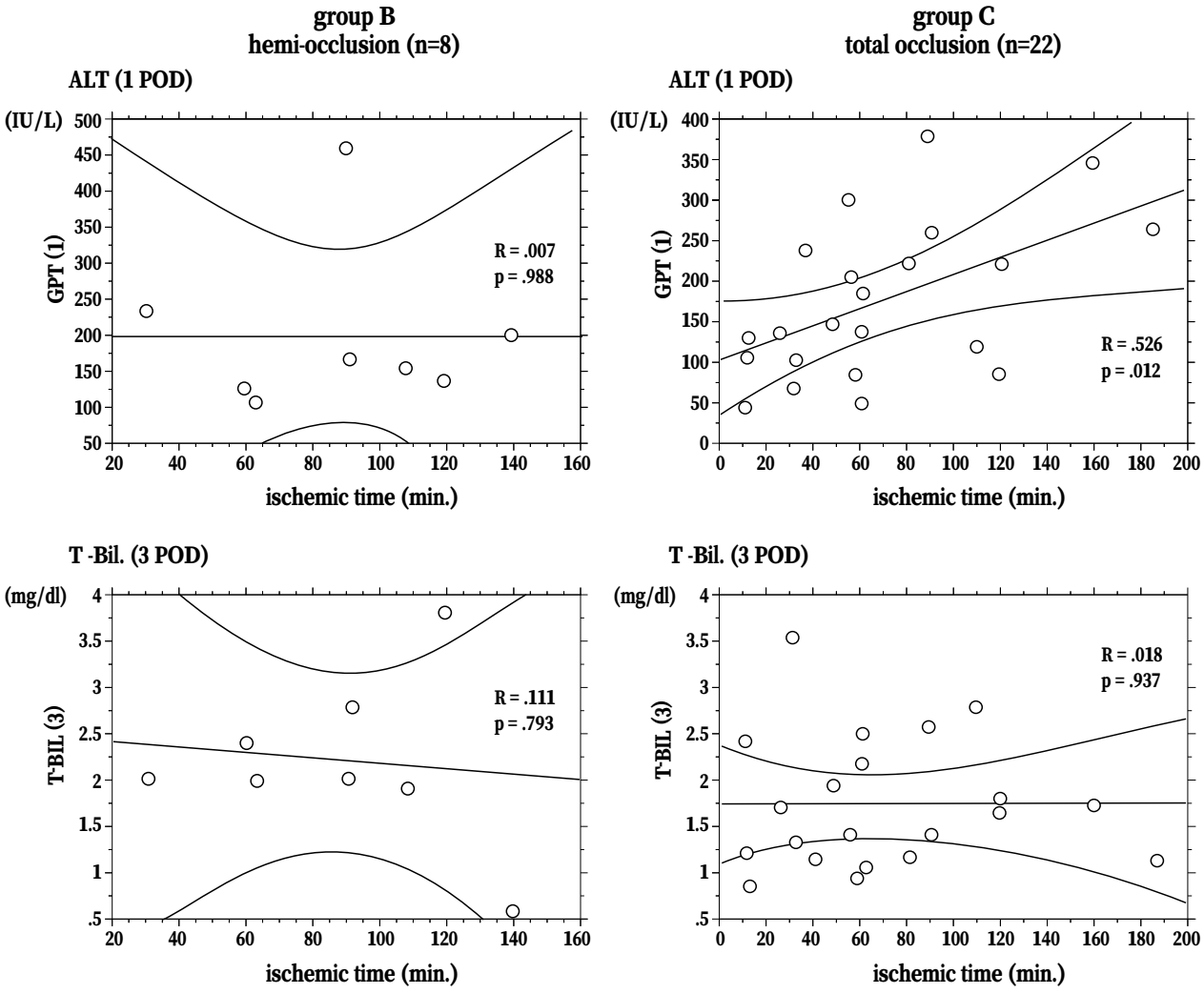

Fig. 3. Relationship between ischemic time and ALT and Total bilirubin level
There was a significant correlation (R=0.526, P=0.012) between ischemic time and serum ALT level (postoperative day 1) in group C, but not between ischemic time and serum total bilirubin concentration (postoperative day 3). In group B, there were no significant correlations between ischemic time and serum ALT level or total bilirubin concentration.

sistent infection following pre and postoperative hepatitis. Another hospital death, in group C, on the 122th postoperarive day, was due to tumor (Table 5).

Relationship between complications and ischemic time

In the hemi-hepatic occlusion group (group B), there was no correlation between the type of complication and the ischemic time. In the total occlusion group (group C), there was no correlation between the minor complications and the ischemic time. However major complications tended to occur in the patients in whom the length of ischemia exceeded 90 minutes. In all three groups, the complications did not occur in all the high risk patients (Fig. 4).

DISCUSSION

In patients with a cirrhotic liver the risk of postoperative complications including intraabdominal bleeding and abscess, respiratory failure, hepatic failure, gastrointestional bleeding, and intractable ascites or pleural effusion is higher than in patients with a normal liver. This depends mainly on the relationship between preoperative liver function and intraoperative factors such as the operative procedure, the noncancerous weight of resected specimen, intraoperative bleeding, and the duration of hepatic ischemia. Minimizing intraoperative bleeding reduces the risk of postperative morbidity and mortality after hepatic resection, especially in the cirrhotic liver. The Pringle maneuver has been widely used to control intraoperative bleeding from the cut surface of the liver during hepatic recection (5). A number of authors have reported the tolerance of normothermic ischemia using this method (1, 2, 3). Elias et al have reported that intermittent ischemia (20 minutes clamped and 5 minutes unclamped) was well tolerated for more than 120 minutes (7). However the limit of ischemia has not been accurately determined, especially in the cirrhotic liver.

The hemi-hepatic occlusion method was described by Makuuchi et al in 1987 (8). They reported a mean ischemic time of 45±4 (range : 15 to 112) minutes in patients with cirrhosis. This technique using intermittent ischemia (30 minutes clamped and 10 minutes unclamped) significantly reduces the intraoperative blood loss and the postperative hyperbilirubinemia. We have used intermittent ischemia (15 minutes clamped and 5 minutes unclamped) since 1985 with both hemi-hepatic and total hepatic occlusion. There was no significant difference in the amount of bleeding among the three groups in our study. The incidence of tumor in the lateral segment was higher in group A than the other groups, therefore in group A the thoracoabdominal approach and the technique of mobilization of the right lobe were used less offen than in groups B and C. These factors seemed to induce the shorter operative time (P<.01) and lower blood loss in spite of no hepatic occlusion in group A than groups B and C. In this study, we retrospectively examined

Table 4. Complications after liver resection

	group A no occlusion (n=10)	group B hemi-occlusion (n=8)	group C total occlusion (n=22)	p
Major	1 (10.0%)	2 (25.0%)	8 (36.4%)	n.s.
Minor	3 (30.0%)	3 (37.5%)	6 (27.3%)	
Total	4 (40.0%)	5 (62.5%)	14 (63.6%)	

Table 5. Outcome after liver resection

	group A no occlusion (n=10)	group B hemi-occlusion (n=8)	group C total occlusion (n=22)	p
Operative death	0 (0 %)	1 (12.5%)	0 (0 %)	n.s.
Hospital death	0 (0 %)	2 (25.0%)	1 (4.8%)	

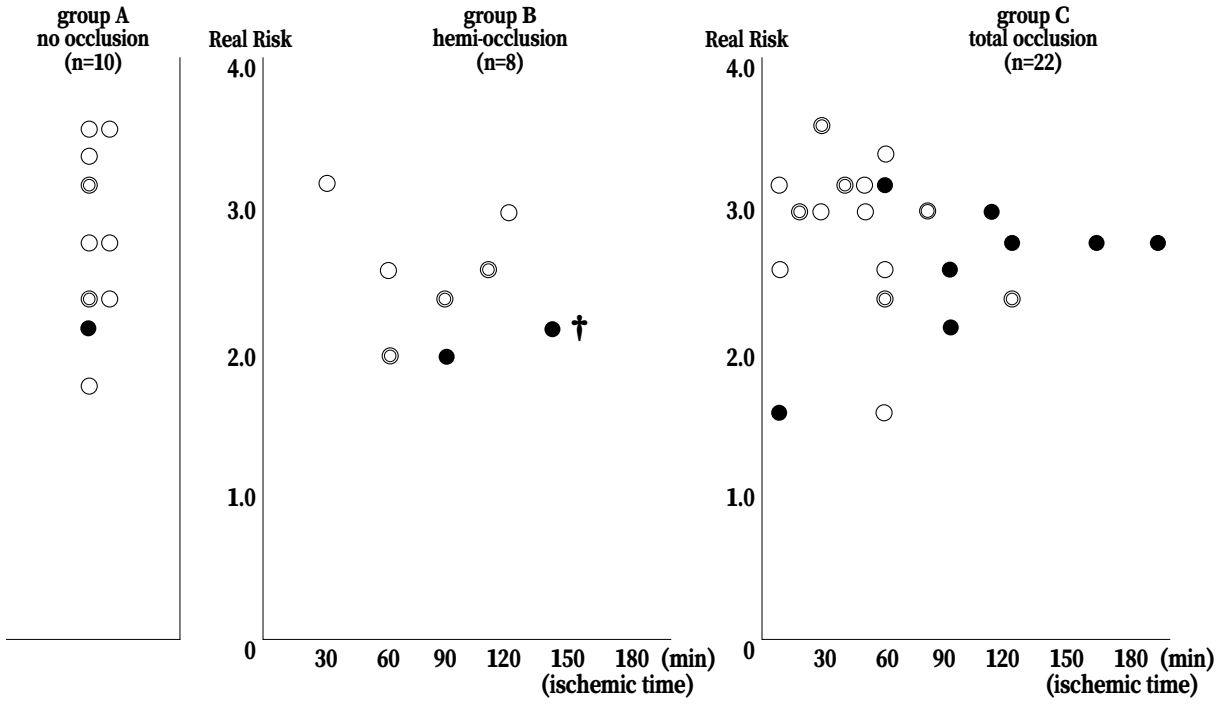

Fig. 4. Complications
In the hemi-hepatic occlusion group(group B), there was no correlation between the type of complication and the ischemic time. In the total occlusion group (group C), there was no correlation between the minor complication and the ischemic time. However major complications tended to occur in the patients in whom the length of ischemia exceeded 90 miniutes. In all three groups, the complication did not always occur in the high risk patients.
(○ ; no complication, ◎ ; minor complication, ● ; major complication, † ; operative death)

the relationship between the type and duration of normothemic hepatic ischemia and postperative liver function, and morbidity and mortality in patients with a cirrhotic liver. In this way, the tolerance limits of these techniques were evaluated.

Huguet et al have reported no significant difference in postperative hepatic function between patients with a normal liver and those with an abnormal liver (9). The duration of ischemia was 68.1±7.5 minutes in the former and 64.7±6.8 minutes in the latter group. Using our intermittent clamping method, there was good recovery of postperative liver function in both the hemi-hepatic and total hepatic occlusion groups.

Delva et all have shown a significant difference in the rate of postoperative hepatic failure between the patients with a normal liver (3% with 32.3±1.2 minutes of ischemia) and those with a cirrhotic liver (33% with 34.1±4.2 minutes of ischemia)(10). They showed no significant difference in the mortality rate between the normal liver (4.7%) and cirrhotic liver (13.3%) groups. Elias et al studied 20 patients (including one with cirrhosis) who underwent intermittent portal triad clamping for more than 90 minutes (mean : 109 minutes) (7). They reported no postoperative mortalities and acceptable morbidity (35%). Nagasue et al have studied cirrhotic patients, and found no significant difference in the incidence of postoperative liver failure between the no occlusion group (11.8%), and the total occlusion group (10.5%) with 23±8 minutes of ischemia time (4). In our study, there were no episodes of postoperative liver failure and no operative deaths in the total occlusion group.

The question remains as to the limit of normothermic hepatic ischemia time in the cirrhotic liver using intermittent total or hemi-hepatic occlusion. There may be a theoretic relationship between preoperative liver function and the tolerance for hepatic resection in the cirrhotic liver. The type of hepatectomy is selected according to tumor location and severity of preoperative liver function using Noguchi's hepatic Real Risk (6). All of our patients were operated on the safety zone. There was a significant correlationship between ischemic time and serum ALT levels (post oprative day 1), but these levels had decreased to the preoperative levels by postoperative day 7, and no significant difference was seen among the three

groups. On the other hand, no significant correlation was seen between ischemic time and total biririubin concentrations in group B and C. There was no significant correlation between the weight of resected specimen and postoperative liver function (data not shown).

Another question is the relationship between the length of ischemia and the type and severity of the postoperative complications. The incidence of major complications was not related to the type of hepatic occlusion. In the hemi-hepatic occlusion group, two major complications occured, postoperative persistent infection in 91 minutes of ischemia, and intraoperative cerebral infarction in 140 minutes of ischemia. The former was followed by preoperative active hepatitis (AST 167, ALT 217 IU/L), and the latter was provoked accidentaly. In the total occlusion group, 6 of 8 major complications (respiratory failure ; 3 cases, pneumonia, intraabdominal abscess and bile leakage from cut surface of the liver ; one case respectively) occured in patients who had long ischemic times (exceeding 90 minutes). However all except one patient (bile leakage) recovered within 1 month of the operation. There were no episodes of postoperative hepatic failure and no operative deaths in this group.

Thus intermittnent normothermic ischemia (15 minutes clamped and 5 minutes unclamped) may be tolerated for up to 180 minutes in cirrhotic patients.

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