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Impact of adhesion molecules of the selectin family on liver microcirculation at reperfusion following cold ischemia

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Abstract We investigated the role of adhesion molecules in the early phase of reperfusion following cold ischemia. Livers of male Lewis rats were preserved for 0 h (group A) or 24 h in University of Wisconsin (UW) solution without additives (group B) or in UW solution with anti-ICAM-1 antibody (group C) or anti-E-selectin-1, SLe^x and SLe^a antibodies (group D). The livers were then reperfused with diluted rat whole blood (DWB; groups A and B), DWB containing anti-ICAM-1 and LFA-1 antibodies (group C) or DWB containing anti-L-selectin, SLe^x and SLe^a antibodies (group D). The reperfusion was performed at 37 °C for 1 h at 5 cm H_2O of perfusion pressure. During reperfusion, hepatic microcirculation was assessed by monitoring portal and peripheral tissue blood flow. Bile production was significantly reduced in group B livers compared with those in group A. Anti-ICAM-1 and LFA-1 antibodies failed to improve hepatic microcirculation, whereas anti-LECAM-1, SLe^x and SLe^a antibodies significantly improved the microcirculation. Bile production in group C and D livers was comparable to that in group B livers. Preservation for 24 h significantly increased the release of TNF-α from 0.207 to 43.7 pg/g per hour during reperfusion. Monoclonal antibodies to the adhesion molecules did not suppress the release of TNF-α in groups C and D. Histological examination demonstrated a lack of leukocyte infiltration or thrombus in hetapic microvessels. The extent of hepatocyte necrosis did not differ among groups B, C, and D. We conclude that the microcirculatory disturbance in the early phase of reperfusion occurs as a result of the tethering of leukocytes through the interaction of the selectin family and their ligands, and that the ICAM-1-LFA-1 pathway is not involved in this step. The lack of improvement in bile production with antibodies to the selectin family and their ligands strongly suggests that other mechanisms participate in the deterioration of hepatic function.

Key words Adhesion molecules, rat, liver transplantation · Liver transplantation, adhesion molecules, rat · Cytokines, liver transplantation, rat

Introduction

Because of the increased incidence of primary nonfunction with prolonged preservation time, the duration of organ preservation is limited to less than 24 h in clinical transplantation [8]. Several studies have examined the mechanisms of tissue injury, termed "cold ischemia-reperfusion injury", which is responsible for primary nonfunction [6, 10, 37]. In the last decade, intensive studies have revealed several important mechanisms of cold is-

chemia-reperfusion injury. Briefly, during cold preservation of the liver with University of Wisconsin (UW) solution [39], sinusoidal lining cells rather than hepatocytes are damaged [7, 13, 24]. Upon normothermic reperfusion following cold preservation, the tissue injury is further exacerbated, even though reperfusion alone is not harmful. The deleterious effects of reperfusion following prolonged cold preservation is characterized by sinusoidal lining cell injury [7, 13, 24], leukocyte adhesion [17], platelet adhesion [19], and increased coagulation [30]. We previously demonstrated that depletion of leukocytes markedly improved hepatic microcirculation after reperfusion following 24-h cold ischemia [12]. It is known that mediators that can alter the endothelial cell surface are released after reperfusion. Among these, cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1, and interleukin-6 (IL-6), are thought to be important for the induction of cold preservation-reperfusion injury [27]. In addition, cell surface receptors, known as adhesion molecules and categorized as belonging to the immunoglobulin superfamily, integrin family, or selectin family, play an important role in the adhesion of leukocytes. Intracellular adhesion molecule-1 (ICAM-1) [1] and vascular cell adhesion molecule-1 (VCAM-1) [25] are the major components of the immunoglobulin superfamily, while the lymphocyte function-associated molecule-1 (LFA-1) [32] and Mac-1 [33] belong to the integrin family. The selectin family includes endothelial leukocyte adhesion molecule-1 (ELAM-1, E-selectin) [23], leukocyte-endothelial cell adhesion molecule (LECAM-1, L-selectin) [9], and granule membrane protein of 140 kD (GMP-140, p-selectin) [14]. Members of the selectin family have high affinity to the polysaccharide chain such as sialyl Lewis x (SLe^x) and sialyl Lewis a (SLe^a) as their ligands [29]. However, it is not clear whether these adhesion molecules are essential for the induction of cold ischemia-reperfusion injury, particularly in the early phase. Nor is the relationship between cytokines and adhesion molecules in this process fully understood.

In the present study, we examined the role of the immunoglobulin superfamily and of the integrin and selectin families on microcirculatory disturbances in the early phase of reperfusion following cold preservation using the isolated liver perfusion model. We also studied the effect of their monoclonal antibodies on TNF-α.

Materials and methods

Liver procurement

Male Lewis rats weighing 200–350 g were purchased from Charles River Japan (Yokohama, Japan) and used for this study. The experimental protocol was approved by the Ethics Review Committee for Animal Experimentation at our institution. The rats were anesthetized by inhalation of 1 % halothane (Takeda Pharmaceutical, Osaka, Japan) and 99 % oxygen at a flow rate of 0.2 l/min. The abdominal cavity was opened and an Intramedic PE-50 polyethylene catheter (Clay Adams, Parsippany, NJ, USA) was inserted into the common bile duct. Heparin (1000 U/kg body weight) was injected into the penile vein. A 14-G angiocatheter was inserted into the portal vein and fixed with a 4-0 silk suture. The liver was then perfused with 50 ml of chilled preservation solution at 15 cm H_2O perfusion pressure. During perfusion, the connective tissues and vessels around the liver were dissected, and the liver was removed and soaked in chilled preservation solution. The liver was reperfused within a short period or 24 h after procurement.

Reperfusion

Pressure-dependent perfusion was performed according to the method described by Hamamoto et al. [11] with a slight modification, as shown in Fig. 1. Briefly, the circuit was placed in a thermo-insulated chamber (Shimizu Rikagaku Kiki, Tokyo, Japan). The liver was perfused by recirculating the perfusate through the portal vein to a Hamilton lung oxygenated with 95 % O_2 + 5 % CO_2. The volume of the perfusate was 20 ml. The portal pressure was continuously measured with a disposable pressure monitoring kit (Viggo-Spectramed, Singapore). The analog signal of the amplified pressure was digitized using an analog/digital (A/D) converter [ADI12-8C(98), Contec, Osaka, Japan] and stored on a personal computer (Model PC9801VX; NEC, Tokyo, Japan). The portal pressure was used as a feedback signal to control the revolution of a peristaltic rotary pump (Model Miniplus 3, Gilson Electronics, Villiers le Bel, France) and to maintain a constant perfusion pressure of 5 cm H_2O. The peripheral tissue blood flow of the liver was continuously measured with a laser-Doppler tissue flow meter (Advance, Tokyo, Japan). The output signal was A/D converted and stored on the hard disk for later analysis. The temperature of the liver was monitored continuously with an electric thermometer using a zener diode (model LM335, National Semiconductor, USA) constructed in our laboratory. The temperature signal was also acquired and stored on the computer through the A/D converter board. The computer-controlled heating pad maintained the perfusion temperature at 37 °C. The portal flow was calculated from the rotation of the rotary pump.

Preparation of the perfusate

For reperfusion of the liver, approximately 10 ml of whole blood was withdrawn from the abdominal aorta of an anesthetized and heparinized Lewis rat using a surgical procedure similar to that described above for the donor rats. The blood was diluted to 6 g/dl of hemoglobin with Krebs-Henseleit solution and used as diluted whole blood (DWB). For the perfusate used in Groups c and d, respective monoclonal antibodies were dissolved and left for 30 min at 4 °C before use.

Monoclonal antibodies

Monoclonal antibodies to rat ICAM-1 and α Kogyo and β chains (CD18) of LFA-1 were purchased from Seikagaku (Tokyo, Japan). Monoclonal antibodies to rat L-selectin, human E-selectin, and SLe^a and SLe^x were also purchased from Seikagaku.

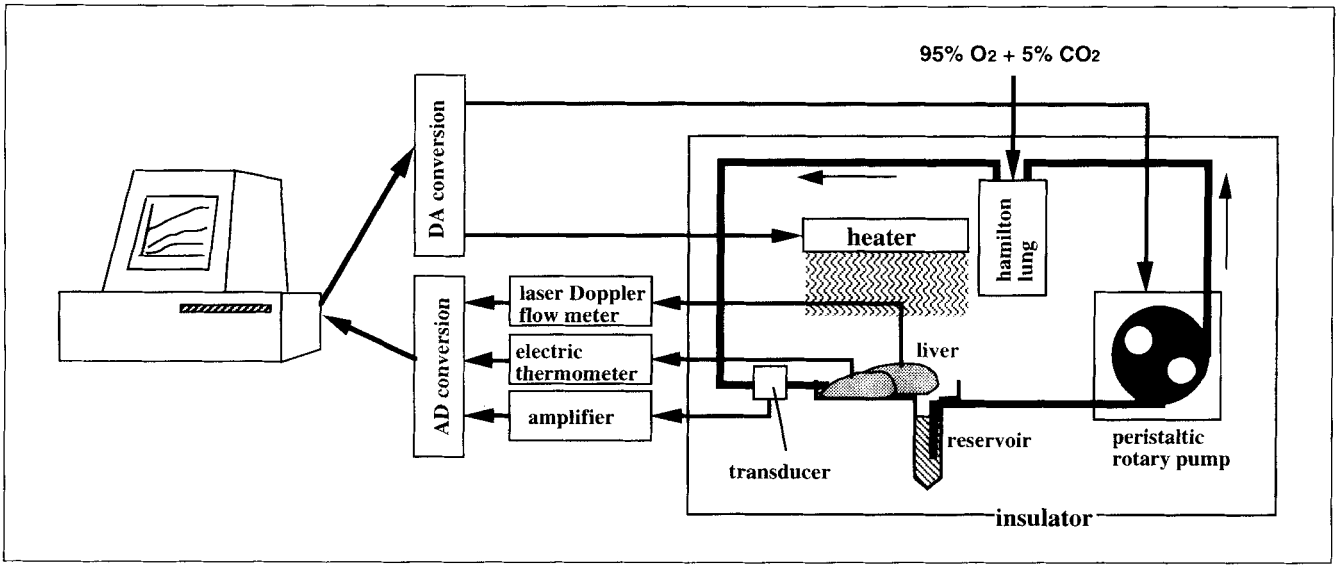

Fig. 1 Schematic illustration of the pressure-dependent liver perfusion system. The perfusate in the reservoir is delivered to the liver through a Hamilton lung for oxygenation. During perfusion, the perfusion pressure, peripheral tissue blood flow, and liver temperature are continuously monitored and entered into a personal computer. The revolution of the peristaltic rotary pump is determined by the computer through feedback from the portal pressure. The heater output is controlled by the computer at 37 °C

Table 1 Experimental groups (*UW,* University of Wisconsin solution, *DWB,* diluted rat whole blood with Krebs-Henseleit solution, *Anti-ICAM-1,* anti ICAM-1 antibody, *Anti-LFA,* anti-LFA-1α antibody and anti-LFA-1β antibody)

Group	Preservation time (hours)	*n*	Preservation solution	Perfusate
A	0	10	UW	DWB
B	24	23	UW	DWB
C	24	6	UW + anti-ICAM-1	DWB + anti-ICAM-1 + anti-CD18
D	24	6	UW + anti-E-selectin + anti-SLe^a and SLe^x	DWB + anti-L-selectin + anti-SLe^a and SLe^x

Experimental groups

Livers of 45 rats were assigned to four separate groups A, B, C, and D as shown in Table 1. Group A livers were procured with chilled UW solution (Du Pont Pharmaceuticals, Wilmington, Del., USA) and reperfused immediately for 1 h at 37 °C. Group B livers were flushed with chilled UW solution and preserved for 24 h at 4 °C with UW solution. The livers were then reperfused with DWB for 1 h. The livers in group C were procured and preserved for 24 h at 4 °C with UW solution containing 0.67 μg/ml of anti-rat ICAM-1 monoclonal antibody. The livers were then reperfused at 37 °C for 1 h using 5 cm H_2O of perfusion pressure with DWB containing 2.5 μg/ml of monoclonal antibody to anti-rat ICAM-1 and 2.5 μg/ml of monoclonal antibodies to α and β chains of rat LFA-1. Group D livers were harvested and preserved for 24 h at 4 °C with UW solution containing 0.67 μg/ml of monoclonal antibodies to human E-selectin and human SLe^x and SLe^a. The livers were perfused at 37 °C for 1 h at 5 cm H_2O perfusion pressure with DWB containing 2.5 μg/ml of monoclonal antibodies to rat L-selectin and human SLe^x and SLe^a.

Biochemical measurements

Following reperfusion, the perfusate was centrifuged at 3000 rpm for 3 min and the supernatant was frozen and stored at – 80 °C until measurement. The period of storage did not exceed 2 months.

Hepatic enyzmes

The concentration of lactate dehydrogenase (LDH) in the perfusate was measured using an automatic analyzer (model 7050; Hitachi, Tokyo, Japan).

TNF-α

The concentration of TNF-α in the perfusate was measured using an enzyme-linked immunosorbent assay (ELISA) kit (Otsuka Pharmaceutical, Osaka, Japan) for human TNF-α and an ELISA kit for rat TNF-α (Cytoscreen; Biosource International, Camarillo, Calif., USA). Five, five and six samples from groups A, B, and C, respectively, were measured with the former kit and six samples each from groups B and D were measured using the latter kit. The values obtained by the former method were calibrated with a calibration factor. The calibration factor was calculated by dividing the mean TNF-α values of group-B livers measured with the latter kit by those measured with the former kit.

Table 2 Portal and tissue blood flow during the last 10 min of reperfusion following cold preservation. Sixty values taken 50–60 min after reperfusion of each experiment were averaged. Data represent the averages and SEM of these means

Group	Portal blood flow (ml/g tissue/min)	Tissue blood flow (arbitrary unit)
A	1.37 ± 0.189 (10)	16.2 ± 1.11 (10)
B	0.325 ± 0.042[a] (23)	4.43 ± 0.514[a] (23)
C	0.244 ± 0.061[a] (6)	3.89 ± 0.701[a] (6)
D	0.680 ± 0.133[a,b,c] (6)	9.45 ± 1.57[a,b,c] (6)

[a] $P < 0.05$ compared with group A; [b] $P < 0.05$ compared with group B; [c] $P < 0.05$ compared with group C

Histopathological examination

Following reperfusion, the liver tissue was fixed with buffered formaldehyde and prepared by hematoxylin and eosin (H & E) staining for light microscopy. Edema and necrosis of the hepatocytes and tissue infiltration of leukocytes were assessed semiquantitatively by one pathologist (S. M.) blind to the treatment. The severity of these criteria was graded from 0 to 2 in deteriorating order.

Statistical methods

Data were analyzed using a one-way analysis of variance and post-hoc analysis using the Fischer test. Semiquantitative data obtained from histopathological examination were compared with the Kruskal-Wallis test. A P value less than 0.05 denoted statistical significance. All experimental results were expressed as mean ± SEM.

Results

Portal and tissue blood flow (Table 2, Figs. 2, 3)

Preservation of the liver in UW solution for 24 h significantly reduced portal and tissue blood flow after reperfusion (group B) compared with 0-h-preserved livers (group A). Anti-ICAM-1 and anti-LFA-1α and β antibodies did not improve portal or peripheral tissue blood flow during reperfusion following 24 h of preservation (group C). Treatment of the liver with anti-E-selectin, SLe^x and SLe^a antibodies and of the perfusate with anti-L-selectin, SLe^x and SLe^a antibodies almost doubled the portal and peripheral tissue blood flow at the end of 1-hour reperfusion compared with those measured under perfusion with DWB (group B).

Bile production (Table 3)

Preservation of the liver for 24 h significantly reduced bile production from 35.5 to 10.8 µl/per hour. However, treatment of the liver and perfusate with various types of monoclonal antibodies to adhesion molecules failed to increase bile production.

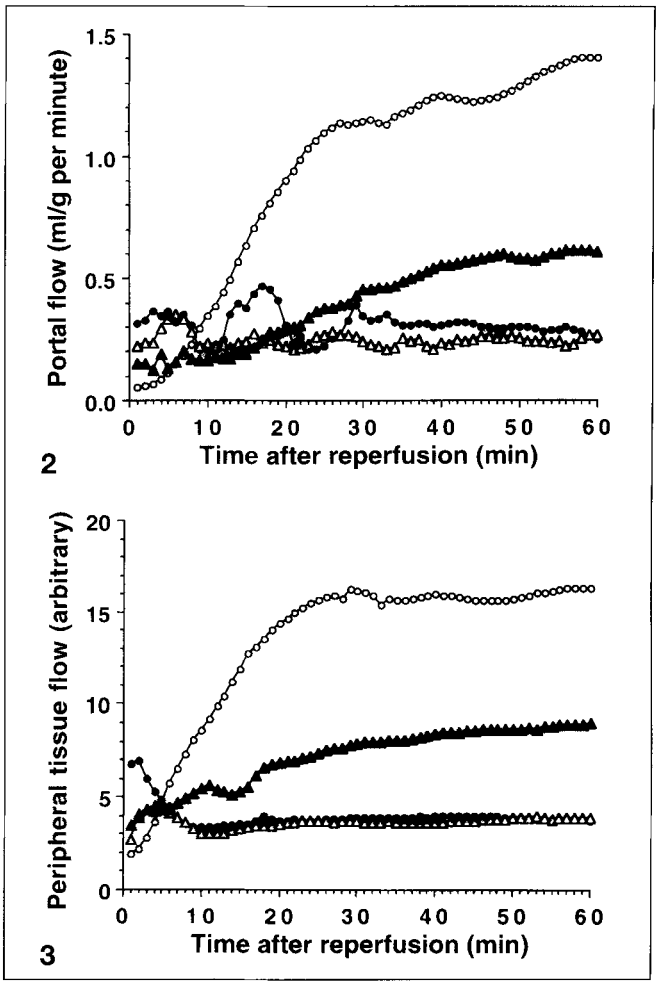

Fig. 2 Portal blood flow of group A, B, C, and D during reperfusion. The flow data were obtained every 10 s. Each point on the respective curve represents the mean of 60 data points for each minute. -○- Group A; -●- group B; -△- group C; -▲- group D

Fig. 3 Peripheral tissue blood flow of groups A, B, C, and D during reperfusion. The flow data were obtained every 10 s. Each point on the respective curve represents the mean of 60 experimental data points for each minute. -○- Group A; -●- group B; -△- group C; -▲- group D

LDH release (Table 3)

Twenty-four-hour preservation followed by normothermic reperfusion caused a significant increase in LDH secretion into the perfusate. No significant difference in LDH secretion among the four groups was detected.

TNF-α release (Table 3)

Zero-hour-preserved livers (group A) released a small amount of TNF-α after reperfusion. However, 24-h

Table 3 Bile production and release of LDH and TNF-α. Numbers in parentheses represent the sample number

Group	Bile (μl/g per hour)	LDH (U/g per hour)	TNF-α (pg/g per hour)
A	35.5 ± 4.79 (10)	3.90 ± 0.335 (10)	0.207 ± 0.0419 (5)
B	10.8 ± 1.11[a] (23)	4.77 ± 0.441 (23)	43.7 ± 8.03[a] (11)
C	8.52 ± 4.50[a] (6)	4.99 ± 0.610 (6)	38.6 ± 5.61[a] (6)
D	10.6 ± 1.20[a] (6)	5.13 ± 0.778 (6)	38.4 ± 16.9[a] (6)

[a] $P < 0.05$ compared with group A

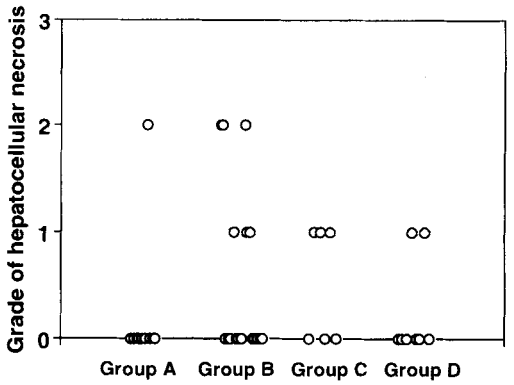

Fig. 4 Histopathological examination of the reperfused liver. The severity of the hepatocellular necrosis was graded from 0 to 4 in deteriorating

preservation with UW solution significantly increased the release of TNF-α into the perfusate from 0.207 to 43.7 pg/ml per gram tissue after reperfusion. Treatment of the liver with monoclonal antibodies to ICAM-1 and LFA-1 or selectin family and its ligands caused a reduction, albeit insignificant, of TNF-α release during reperfusion compared with group B.

Histopathological examination (Fig. 4)

Histopathological examination demonstrated a lack of intravascular coagulation in the hepatic tissue. Furthermore, semiquantitative histopathological analysis revealed absence of edema of the hepatocytes and of leukocyte infiltration into the liver tissue during reperfusion in all groups. In contrast, hepatocyte necrosis was observed in all groups. The severity of the latter was minimal in group A compared with the other groups, although no significant differences were observed between the groups.

Discussion

In the present study, we examined the effect of cold preservation of the liver on hepatic microcirculation and cytokine release in the early phase of reperfusion with a pressure-dependent perfusion system. Our results demonstrated that cold preservation for 24 h produced a significant reduction in portal and peripheral tissue blood flow after reperfusion. This deterioration occurred even though the perfusate contained a considerable amount of heparin to prevent coagulation. In fact, we could not detect intravascular coagulation by histopathological examination (Fig. 4). Recently, the role of leukocytes in ischemia-reperfusion injury has been noted [17], particularly in relation to the interaction between intracellular adhesion molecules [2] that are regulated by a variety of cytokines [27]. In our previous study, elimination of leukocytes from whole blood improved portal and peripheral blood flow upon reperfusion and was associated with a low secretion of TNF-α [37], suggesting that leukocytes are responsible for the reduction in portal and peripheral blood flow of the cold-preserved liver on normothermic reperfusion.

The present investigation extended our earlier studies by examining the role of adhesion molecules in the microcirculatory disturbance after cold ischemia and reperfusion. Adhesion molecules play an important role in leukocyte infiltration. Three families of adhesion molecules participate in leukocyte infiltration through the endothelium. These include the immunoglobulin superfamily and the integrin and selectin families [35]. Leukocyte infiltration is achieved in five sequential steps: (1) the release of chemotactic factors, such as cytokines, complements, leukotrienes, and platelet-activating factor, from the endothelial lining cells and Kupffer cells [36, 40]; (2) activation of leukocytes by the release of chemotactic factors and expression of adhesion molecules [18]; (3) rolling of the leukocytes on the sinusoidal lining cells mediated by cell surface receptors that belong to the selectin family, such as L-selectin, E-selectin, and P-selectin [22, 34]; (4) adhesion of leukocytes to the sinusoidal lining cells mediated by activated LFA-1, Mac-1, or ICAM-1 [32]; and (5) emigration of the leukocytes out of the vessel.

Adhesion molecules such as LFA-1, Mac-1, and p150.95, which belong to the integrin family, have a common β subunit [20]. Since we used monoclonal antibodies to α and β chains of LFA-1 in this study, not only LFA-1 but also Mac-1 and p150.95 could be blocked with the antibodies. However, neither blocking of these leukocyte adhesion molecules which these antibodies nor treatment of the liver with anti-ICAM-1 antibodies improved the microcirculatory disturbance on reperfusion. Therefore, it is unlikely that the immunoglobulin superfamily or integrin family are involved in the circulatory disturbance in the early phase of reperfusion following prolonged cold ischemia. Furthermore, the lack of leukocyte infiltration in group B, as demonstrated on histopathological examination, indicated that strong

adhesion or migration of the leukocytes did not occur in the early phase of reperfusion.

In contrast to the immunoglobulin superfamily and integrin family, monoclonal antibodies to the selectin family (E-selectin and L-selectin) and their ligands (SLe^x and SLe^a) significantly increased hepatic blood flow upon reperfusion. The selectin family is comprised of three proteins designated by the prefix E (endothelial), P (platelet), or L (leukocyte) [5, 21]. E-selectin and P-selectin are expressed by endothelial cells and L-selectin is expressed only on leukocytes. These molecules participate in the rolling of leukocytes on endothelial cells in inflammation, a prerequisite for a strong adhesion of leukocytes through the immunoglobulin superfamily-integrin family pathway [22]. It is known that adhesion molecules related to the selectin family bind to sialylated derivatives of the Lewis x oligosaccharide [26]. We treated the L-selectin, E-selectin, and their ligands, SLe^x and SLe^a, with their monoclonal antibodies. However, the recovery of microcirculation was not perfect. Recently, MAdCAM-1, CD34, and GlyCAM-1 have been proposed as the ligands of L-selectin [3, 4, 15] and P-selectin, and glycoprotein ligand as the ligand of P-selectin [31]. It is possible that these unblocked P-selectin and their ligands are still active in leukocyte rolling, which kept the microcirculation from full recovery.

Histological examination demonstrated the presence of necrotic hepatocytes even in group A livers, although the proportion of these cells was less than those in other preserved groups. The flow rate of the portal vein under normal physiological conditions of the rat liver is approximately 1–2 mg/g per minute as measured with a transit time flowmeter (data not shown). Since the rolling of the leukocytes on endothelial cells depends strongly on the shear stress [16, 22], the flow rate selected for the control livers (group A) was adjusted to a level comparable with the phyisological flow rate at the end of reperfusion. However, it took approximately 20–30 min to reach the maximum flow rate, as shown in Figs. 1 and 2, and the livers were exposed to warm ischemia at the beginning of the reperfusion. This may explain the necrosis of hepatocytes even in the control group. Since the maximum flow of other groups was significantly lower, this tendency was more emphasized and resulted in more severe hepatocyte necrosis in groups B, C, and D.

In conclusion, our study confirmed that the selectin family, and not the immunoglobulin superfamily or integrin family, plays an important role in the microcirculatory disturbances of the liver after cold preservation. However, the lack of improvement in bile production following the use of antibodies to the selectin family suggests that other factors, such as nitric oxide or endothelin, which are known to worsen hepatic function after reperfusion subsequent to cold ischemia, may play a role in this phenomenon.

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