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INCREASED PORTAL ENDOTHELIN-1 LEVEL IS ASSOCIATED WITH THE LIVER FUNCTION AFTER CARDIOPULMONARY BYPASS IN RABBITS : INFLUENCE OF HYPOTHERMIA ON THE DAMAGE

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INDEXING WORDS

endothelin-1; cardiopulmonary bypass; splanchnic-hepato circulation; hepatocellular function; hypothermia

SYNOPSIS

The purpose of this study was to prove the hypothesis that ET-1 production is increased in the splanchnic-hepato circulation during cardiopulmonary bypass (CPB) with or without hypothermia and this greatly affects hepatocellular function after surgery. Twelve Japanese white rabbits were used. In group I (n=6), the rectal temperature was kept at 37.0 °C during CPB (90 min). In group II (n=6), the rectal temperature was lowered to 26 °C during the first 30 minutes and then increased to 37 °C for the following 60 minutes. In group I, surface liver tissue blood flow (LBF) remained stable during CPB. While, in group II, LBF was significantly reduced to 66.9% of baseline values during hypothermic CPB, but it increased during the rewarming phase to 84.3% of the baseline value (p=0.0070). At the end of CPB, portal ET-1 levels were increased in both groups, but they were significantly higher in group II (7.32 ± 0.50 pg/ml and 9.29 ± 0.61 pg/ml, respectively). Serum GOT, GPT, LDH and arterial ammonia levels were also higher in group II. Portal ET-1 levels had a significant positive correlation with those liver enzymes. Histopathological examination after CPB showed severe damage of the hepatic parenchyma in zone 3 associated with microvesicular fatty infiltration in group II.

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These results demonstrated that ET-1 production in the splanchnic-hepato circulation increased during CPB and that high portal ET-1 levels were associated with postbypass hepatocellular damage. Furthermore, these findings appeared to be related to steep changes of the rectal temperature during CPB.

INTRODUCTION

Despite advances in the management of patients undergoing cardiopulmonary bypass (CPB), those patients continue to be at risk of developing postperfusion systemic response syndrome.[30] Intraabdominal complications are serious sequelae of CPB, with a mortality of up to 67%.[1,19,22,25,29] Hepatic dysfunction is a relatively frequent finding,[4] and jaundice occurring after CPB is associated with an increased mortality rate. Reduced liver blood flow accompanied by redistribution of circulating blood, vasoactive substances,[13,33] microembolism and O_2 free radicals[5] et al released during CPB may contribute to hepatocellular damage.[26] The damage may be particularly important in patients with preoperative hepatic disorders, preexisting congestive cardiac failure and prolonged bypass time.[26] The integrity of the liver is therefore seriously jeopardized in these cases by CPB procedures.[8]

Endothelin-1 (ET-1) is a strongly vasoconstrictive peptide that may play an important role in controlling systemic blood pressure and/or local blood flow.[31] Various studies have recently focused on ET-1-induced hepatic microcirculatory disturbance and its adverse effects on the metabolism in the liver.[2,20,36] And circulating ET-1 levels have been documented to increase during cardiopulmonary bypass in some clinical studies.[17,18,31] Regarding generation of ET-1 at local level, Kirshbom et al[15] reported that CPB with deep hypothermia stimulated production of ET-1 by the pulmonary vascular endothelium and expression of ET-1 receptors in the pulmonary parenchyma. However, the behavior of portal ET-1 released from splanchnic organs during CPB and its effects on the liver remain unknown.

The purpose of this study is to test the hypothesis that ET-1 production is increased in splanchnic-hepato circulation during CPB and to assess its effects on hepatocellular function under hypo and normothermic conditions.

MATERIALS AND METHODS

Animals

Twelve male Japanese white rabbits weighing 3.0-3.6 kg (3.24 ± 0.19 kg) were used in this study. Before use, all animals were kept in clean cages under a constant temperature of 20 °C for 2 weeks during which they were fed a regular feed and allowed to drink sterile water *ad libitum*. During the 15 hr prior to the operation, the animals were allowed to drink water only. They received humane care in compliance with "Principles of Laboratory Animal Care" formulated by the

Institute of Laboratory Animal Resources and the "Guide for the Care and Use of Laboratory Animals" published by the National Institute of Health. The study protocol was approved by Experimental Animals Committee of Kobe University School of Medicine.

Anesthesia

Anesthesia was induced by a single intramuscular injection of ketamine (33 mg/kg) and xylazine (3 mg/kg).

Surgical intervention

The rabbits were intubated and placed on mechanical ventilation (ventilator model SN-480-5; Shinano Industries, Inc., Tokyo, Japan). Respiratory rate was set to maintain an arterial Pco_2 of 35 to 45 mm Hg. Sodium bicarbonate (7%) was used to maintain a base excess between -5 and 5 mmol/L.

A small midline laparotomy was performed, and a thin wall polyethylene catheter (3Fr.) was inserted via the ileocecal vein up to the portal trunk to sample portal venous blood. And a laser Doppler probe (PeriFlux PF3; Laser Doppler Perfusion Monitor; PERIMED, Sweden) was applied to the surface of the anterior right lobe of the liver. Laser Doppler hepatic blood flow was measured after calibration of the probe. Continuous serial laser Doppler flow readings were displayed on a color-memory scope (model VM-185G, Nihon Koden, Tokyo, Japan) and were recorded using a thermal-array recorder (model RTA-1200, Nihon Koden). After the procedure, the abdominal wall was closed to limit heat and fluid losses.

Establishment of cardiopulmonary bypass in rabbits

After systemic heparinization (500 IU/kg), the cardiopulmonary bypass was instituted from the right atrium via the jugular vein to the right carotid artery. The CPB circuit consisted of a hollow-fiber membrane oxygenator (MENOX AL-2000; Kurare, Tokyo, Japan) and a roller pump (PA-21A; Cole Parmer Masterflex, Chicago, Illinois). The pump was primed with 110 ml of a solution containing 16.7 mEq sodium bicarbonate, 2 mEq KCL and 1000 IU heparin in 500 ml lactate Ringer's solution. Once on bypass, fresh homologous blood was added to the circuit to maintain a hematocrit of 18% to 22%. Blood flow was maintained at 90 ml/kg/min to keep the mixed venous oxygen saturation (Svo2) at 70% during the bypass, and alpha-stat pH methodology was employed.

Experimental protocol

The rabbits were divided into two groups. Group I (n=6): cardiopulmonary bypass with nonpulsatile flow was performed under normothermic conditions (rectal temperature of 37 °C) for 90 minutes. Group II (n=6): CPB was performed under hypothermic conditions with core cooling of the rectal temperature to 26 °C for 30 minutes followed by rewarming to 37 °C for 60 minutes. Portal venous and mixed venous blood were sampled before and at the end of CPB to measure the

plasma concentration of ET-1. As parameters of liver function, serum glutamic-oxaloacetic transaminase (GOT)(IU/L), glutamic pyruvic transaminase (GPT)(IU/L), lactic dehydrogenase (LDH)(IU/L) and arterial ammonia concentration were measured. As to know the gut metabolic condition during CPB, the difference in base excess (ΔBE) between mixed venous blood (BE_{RA}) and portal vein blood (BE_{PV}) was calculated using the following formula: $\Delta BE=BE_{PV}-BE_{RA}$.

After the end of CPB the water content of liver tissue (tWC: [(wet weight - dry weight/ wet weight)] X 100) was measured by means of desiccation at 80 °C for 48 hours. Both liver tissue and intestines were frozen in liquid nitrogen, immersed in formalin, and embedded in paraffin. Four-micrometer-thick sections were stained with hematoxylin and eosin and examined under a light microscope. All microscopic sections were examined in a blind fashion by a pathologist.

Plasma ET-1 concentration

Mixed venous and portal blood were collected before and after CPB, and plasma ET-1 levels were measured. Each blood sample was placed in a chilled tube containing EDTA and aprotinin; after centrifugation the plasma was stored at -80 °C until assayed. After ET-1 was extracted through a C18 cartridge (Waters Associates, Milford, MA), the concentration was measured by radioimmunoassay using an antibody to ET-1 (Peninsula Laboratories, Belmont, CA) and ^{125}I-labeled ET-1 (Amersham International plc., Bucks, UK). This assay is specific for ET-1 and cross-reacts with ET-3 or big ET-1 at < 0.1% efficacy.

Statistical analysis

Results were expressed as the mean ± SEM. For blood parameters, the statistical significance of differences between groups or between time points was determined by repeated measure ANOVA. When differences between groups were found by ANOVA, statistical significance was evaluated by Scheffe's F multiple comparison test. For hepatic tissue parameters, results were compared using one factor ANOVA and Scheffe's F analysis. A confidence level of 95% or higher was considered significant. All the calculations for the statistical analysis were performed using the Stat View computer software (Abacus Concepts, Berkeley, CA.).

RESULTS

Liver tissue blood flow during CPB

Changes in liver tissue blood flow (LBF) under the constant pump flow (at 90 ml/kg/min) are demonstrated in Fig.1. All results are presented as percent changes from the baseline value, because the flux signal does not provide absolute values of blood flow. LBF decreased gradually during the first 30 minutes (85.1 ± 4.4%; p=0.0581), and returned to baseline values (108.3 ± 16.9%; p=0.5214) in group I. In group II, LBF significantly decreased to 66.9% of the baseline values after CPB for 30 minutes (p=0.0055), and increased during the following rewarming phase, however, it did not return to the baseline level at the end of CPB (84.3 ± 3.3%; p=0.0070).

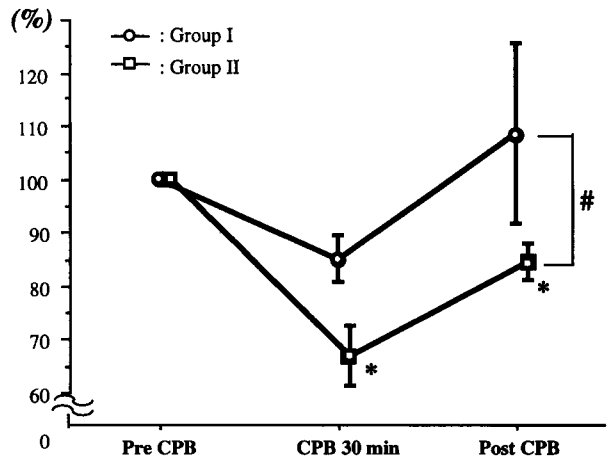


Fig. 1. Serial changes in liver tissue blood flow.

*p < 0.01 versus values at pre CPB
#p < 0.05 Group I values versus Group II values

Gut metabolic condition

In group I, ΔBE was similar to baseline values throughout CPB. While in group II, the value kept the baseline until 30 minutes but remarkably decreased at rewarming phase of CPB (Table I).

Table I. Gut metabolic condition (ΔBE = BE PV - BE RA).

Group	I	II	ANOVA (groups)	ANOVA (time points)
No.	6	6	p = 0.4595	p = 0.7315
Pre CPB	-1.28 ± 0.87	-2.03 ± 1.23		
CPB 30 min	-1.10 ± 1.04	-2.15 ± 2.35		
Post CPB	-1.75 ± 1.15	-4.45 ± 1.86		

Results are expressed as mean ± SEM.

Plasma ET-1 levels

In group I, the plasma level of ET-1 value was below 2.7 pg/ml before CPB and increased to 5.92 ± 0.56 pg/ml in mixed venous ($p < 0.05$) and 7.32 ± 0.50 in portal blood ($p < 0.01$) at the end of CPB. While in group II, the plasma level of ET-1 increased to 9.29 ± 0.61 pg/ml in portal blood and 8.20 ± 0.41 pg/ml in mixed venous blood ($p < 0.01$ vs baseline value). Portal ET-1 levels were significantly higher than in mixed venous blood in group II ($p < 0.01$) (Table II).

Liver enzymes levels and correlation with portal ET-1

At the end of CPB, the serum GPT levels were considerably increased in both groups and the levels were much higher in group II, although statistically not significant. Serum levels of GOT and

LDH also revealed the same tendency. The arterial levels of ammonia were significantly higher in group II than in group I at the end of CPB (Table III).

A significant positive correlation was found between portal ET-1 and serum GOT, GPT and LDH levels (r=0.784, 0.805 and 0.794, respectively) (Fig. 2).

Table II. Endothelin-1 concentrations.

Group	I (n = 6)		II (n = 6)	
Endothelin-1 (pg/ml)	Mixed venous	Portal vein	Mixed venous	Portal vein
Pre CPB	2.48 ± 0.24	2.37 ± 0.27	2.66 ± 0.35	2.66 ± 0.34
Post CPB	5.92 ± 0.56 [a]	7.32 ± 0.50 [a]	8.20 ± 0.41 [a,b]	9.29 ± 0.61 [a,b,c]

Results are expressed as mean ± SEM.
[a] Significant versus pre CPB.
[b] Significant versus group I.
[c] Significant versus mixed venous.

Table III. Liver enzyme and arterial ammonia levels.

Group	I	II
No.	6	5
GPT (IU/L)		
Pre CPB	25.86 ± 3.49	23.60 ± 1.70
Post CPB	39.61 ± 4.77 [a]	56.92 ± 14.73 [a]
GOT (IU/L)		
Pre CPB	25.80 ± 3.63	24.50 ± 2.97
Post CPB	42.82 ± 4.59 [a]	103.97 ± 27.92 [a]
LDH (IU/L)		
Pre CPB	221.83 ± 33.11	247.00 ± 41.43
Post CPB	438.45 ± 46.47 [a]	495.34 ± 76.92 [a]
A-ammonia (μg/dl)		
Pre CPB	47.73 ± 8.61	40.45 ± 9.49
Post CPB	73.05 ± 19.61	276.40 ± 123.72 [a]

Results are expressed as mean ± SEM.
[a] Significant versus pre CPB.

Water content of liver tissue

tWC was 68.21 ± 0.28 % before CPB. It increased to 70.72 ± 0.19 % in group I and 72.09 ± 0.29 % in group II at the end of CPB. tWC in group II was significantly higher than in group I ($p < 0.01$) (Fig. 3).

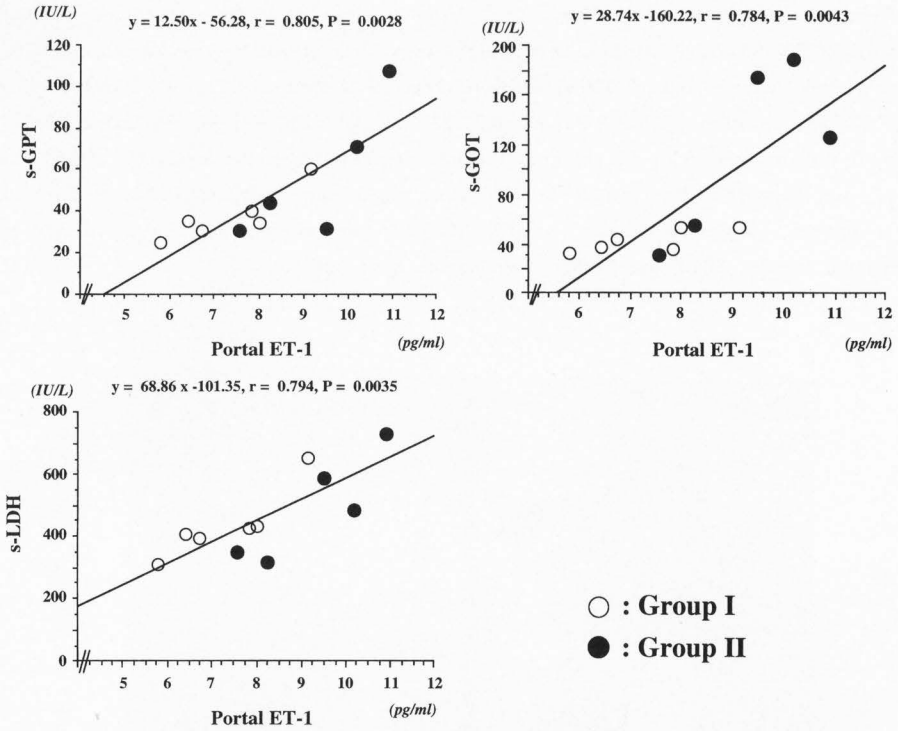


Fig. 2. Relationships between liver enzymes and portal ET-1 levels.

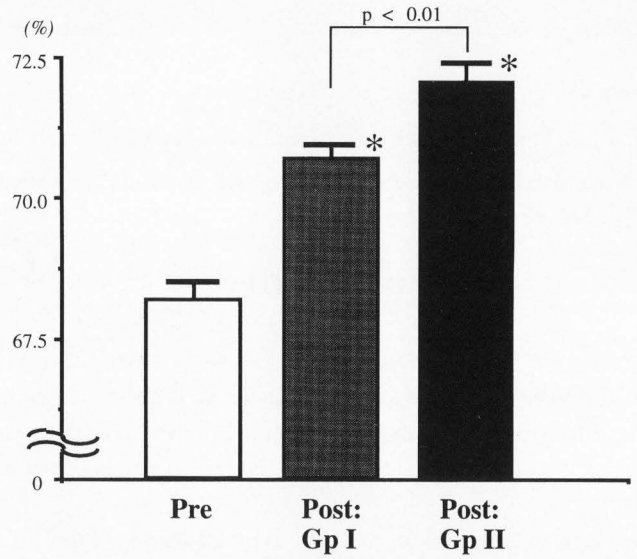
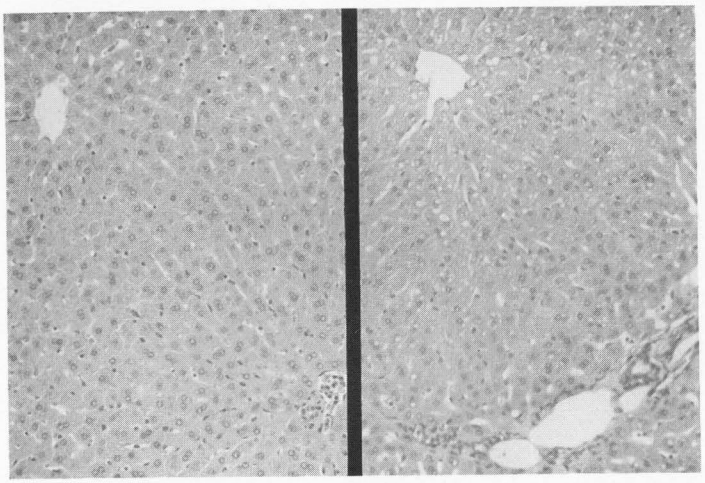


Fig. 3. Percentage of tissue water content of the liver.
*p < 0.01 versus values at pre CPB

Histopathological examinations

After CPB, microvesicular fatty change and hepatocellular edema of zone 3 associated with a remarkable decrease in sinusoidal diameter were observed in group II (Fig. 4). Those findings were not apparent in group I. Postbypass intestinal mucosal findings were also investigated. In group II, mucosal epithelium was almost normal and lymphangiectasia and angiectasia at the lamina propria and submucosal layer were observed, which might lead to edematous change of villi. In some sections, such microvascular damage advanced even into muscular layer followed by edematous changes. All of those findings were slighter in group I.



Group I **Group II**

Fig. 4. Photomicrographs of liver after CPB.

Microvesicular fatty infiltration and hepatocelluar edema of zone 3 were observed in group II. HE. x40.

DISCUSSION

The major findings of the present study are as follows: 1) portal ET-1 released from the splanchnic-hepato circulation significantly increased during CPB and overwhelmed the systemic levels. The high portal ET-1 levels had a significant positive correlation with postbypass hepatocellular damage. 2) The high portal ET-1 levels appeared to be related to steep rewarming of the body during CPB.

In this study, portal ET-1 levels significantly increased during CPB which overwhelmed systemic ET-1 levels. Previous studies have shown impaired gut mucosal perfusion in both

experimental and clinical CPB using laser Doppler flowmetry or tonometry.[10,19,22,23,28] Tao and associates[30] have also demonstrated significant gut mucosal ischemia during CPB despite normal indices of perfusion. Factors that contribute to mucosal ischemia include redistribution of blood, possibly because of regional vasoconstriction, and increased total gut metabolism.[30] Chou and associates[16] reported that microvascular blood flow was reduced in the gut during sepsis and was associated with enhanced ET-1 gene expression in rats. And Dikranian et al[9] have shown that hypoxia induces an increase of immunoreactivity to ET-1 in gut endothelium, especially epithelial cells in the colonic mucosa. These findings strongly implied that the increase of portal ET-1 levels associated with CPB would reflect the locally activated production and release of ET-1 from the visceral vascular bed.

ET-1 has been reported to play a central role in the regulation of regional blood flow, particularly during pathologic states.[34] Bauer et al[2] demonstrated that ET-1 works as an extremely potent constrictor in the liver microcirculation in vivo and acts at both extrasinusoidal and sinusoidal sites in rats. William et al[35] have reported a 20 % decrease in total hepatic blood flow in patients undergoing hypothermic, nonpulsatile CPB. On the contrary, Desai et al[7] found that regardless of the pump flow rate and type of perfusion, total liver blood flow was not reduced. Our results showed a 16 % decrease in rabbits undergoing hypothermic bypass even after the core temperature was fully rewarmed.

Endothelins have been shown to cause not only increase in the resistance of the portal circulation,[2,32] but also to influence several metabolic functions of the hepatocyte, such as glycogenolysis[34] and bile secretion, as well as metabolic functions of nonparenchymal cells,[3] such as eicosanoid release by Kuppfer cells.[12] Nakamura and associates[20] showed that the hepatic blood flow, bile flow, and survival rate were significantly improved in rats administered an anti ET-1 antibody after being subjected to warm hepatic ischemia. In our study, a positive linear correlation between portal ET-1 values and hepatic enzyme levels was recognized. Those data have suggested the strong relationship between the increased ET-1 levels and the liver damage.

The increased production of ET-1 was significantly greater in CPB under hypothermic (group II) compared to normothermic conditions (group I). The difference might depend on more severe endothelial damage involving mesenteric microcirculatory disturbances in group II, compatible with the histopathological findings of the intestinal mucosa. Gut mucosal hypoxia caused by shunting of blood toward the metabolically active mucosa occurs during CPB, particularly during the rewarming phase after hypothermic bypass.[22] This is probably because a disparity develops between mesenteric oxygen consumption and oxygen delivery with villus ischemia.[24] The acidosis detected in portal blood after CPB in group II might have reflected these conditions in the visceral tissues during the rewarming phase. Ammonia detoxification in liver mitochondria is known to consume considerable energy.[14,21] And the significantly higher ammonia level observed in group II at the end of CPB might be a result of a decreased hepatic energy level. Thus, steep rewarming after hypothermia might accelerate ET-1 expression in gut, resulted in both metabolic and structural deterioration of the liver. However, the mechanism of regulation of ET-1 synthesis and its

association with liver damage after changes of CPB temperature have not fully clarified in this study. Future studies are needed to elucidate the contribution of ET-1 to the progression of liver damage after hypothermic CPB with ET-1 receptor antagonist.[16)]

CONCLUSION

We confirmed that ET-1 production in the splanchnic-hepato circulation increased during cardiopulmonary bypass and high portal ET-1 levels might be responsible for the postbypass hepatocellular damage observed in rabbits. And these findings appeared to be related to steep changes of core temperature during CPB.

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