Transpl Int (1996) 9 [Suppl 1]: S 100–S 104

M. Oishi
N. Tanaka
K. Orita

Beneficial effects of prostaglandin E_1 on hemodynamic changes during liver transplantation in pigs

M. Oishi (✉) · N. Tanaka · K. Orita
First department of surgery, Okayama University Medical School,
2-5-1 Shikata-cho, Okayama 700, Japan

Abstract The vasodilative action of prostaglandin E_1 (PGE_1) on the systemic and pulmonary circulation was investigated in swine models of orthotopic liver transplantation. In the PGE_1-treated group ($n = 8$), PGE_1 (0.05 μg/kg per minute) was intravenously infused from the onset of the anhepatic stage to 30 min after revascularization. During the anhepatic stage, PGE_1 decreased systemic vascular resistance without a corresponding hypotension, so cardiac output was maintained at a higher level. In the control group ($n = 8$), pulmonary vascular resistance increased to 3 times the anhepatic value during reperfusion, accompanied by a decline in cardiac output with a 28 % decrease in blood pressure. In the PGE_1-treated group, on the other hand, pulmonary vascular resistance was maintained within the normal range without any associated decrease in cardiac output. The blood pressure decreased slightly by 12 %. In conclusion, in this model, PGE_1 increased cardiac output without hypotension during the anhepatic stage and also prevented postreperfusion pulmonary hypertension and the subsequent systemic hypotension.

Key words Liver transplantation · Pulmonary hypertension · Postreperfusion syndrome

Introduction

Prostaglandin E_1 (PGE_1) has been widely used in clinical liver transplantation because of its cytoprotective effect [1]. Recently, PGE_1 has been shown to protect the liver graft from antibody-mediated rejection [2]. On the other hand, PGE_1 has several actions on the circulatory system, including a direct vasodilator action on the peripheral vascular bed, a reflex increase in cardiac output due to the decrease in peripheral vascular resistance, and a direct positive inotropic action on the myocardium [3]. However, there have been only a limited number of studies of the effects of PGE_1 on vascular dynamics in liver transplantation [4]. Therefore, it would be interesting to examine how PGE_1 as a vasodilator affects the markedly changing and complicated hemodynamics in liver transplantation.

During the anhepatic stage of the operation, decreased venous return leads to a compensatory elevation in systemic vascular resistance in spite of the use of the venovenous bypass [5, 6]. In addition, the venovenous bypass itself causes an increase in systemic vascular resistance due to a non-physiological venous return. PGE_1 may suppress systemic vasoconstriction and maintain stable systemic hemodynamics.

In liver transplantation in pigs, marked pulmonary hypertension appears immediately after graft reperfusion [7, 8], with impaired hemodynamics after reperfusion. When PGE_1 is administered intravenously, it is almost completely metabolized in the lung during the first pass [9], exerting a vasodilative action predominantly on the pulmonary blood vessels and decreasing right ventricular afterload. Therefore, PGE_1 may suppress pulmonary hypertension in pigs undergoing liver transplantation. The species is generally recognized to be suscep-

tible to pulmonary hypertension and lung edema. The pig accordingly appears to be a suitable animal for the study of pulmonary vasomotion [10]. The purpose of this study was to investigate the vasodilative action of PGE_1 during liver transplantation, particularly its effects on the hemodynamics during the anhepatic stage and on postreperfusion pulmonary hypertension.

Materials and methods

Animals

Thirty-two large white pigs weighing 20–25 kg were used to perform 16 orthotopic liver transplantations.

Anesthesia

Following premedication with 300 mg ketamine and 250 mg thiopental, each pig was orally intubated and ventilated to maintain the arterial Pco_2 at 30–40 mm Hg. Anesthesia was maintained with a mixture of nitrous oxide-oxygen (1:1) and halothane (0.5 %). Ringer's solution was infused intravenously through the right jugular vein at 20–25 ml/kg per hour and 400–800 ml whole blood was given to the recipient, depending on the amount of blood loss.

Donor and recipient operation

Liver transplantation was performed orthotopically as described previously [11]. The donor liver was perfused with 1500 ml of UW solution at 4 °C and also preserved with 500 ml of UW solution at 4 °C for 2 h. In the recipient, following laparotomy using a midline incision, the left iliac vein, portal vein, and left external jugular vein were prepared for placement of the venovenous bypass. During the anhepatic stage, the venovenous bypass was used at flow rates ranging from 600 to 1200 ml/min to prevent congestion in the gut and lower extremities. Before placement of the venous bypass, the pig received a bolus injection of 2000 IU heparin. The order of anastomoses was as follows: suprahepatic vena cava (4-0 polypropylene suture); portal vein using the growth factor procedure (6-0 polypropylene suture); aortic conduit after reperfusion of the liver (end-to-side with 6-0 polypropylene suture); infrahepatic vena cava (4-0 polypropylene suture). The liver was flushed with 300 ml of cold Ringer's solution prior to the portal vein anastomosis. The portal vein was anatomosed without removing the portal cannula for the venous bypass until the suturing of the last two or three stitches to keep the portal occlusion time as brief as possible (maximal period of portal occlusion, 1 min). All recipient operations were performed without technical problems, and the recipient pigs recovered uneventfully from the surgical procedure.

Experimental design

The recipients were divided into group A ($n = 8$), which received no further treatment, and group B ($n = 8$), which received PGE_1 (0.05 μg/kg per minute; Ono Pharmaceutical Ltd) intravenously from the onset of the anhepatic phase to 30 min after revascularization.

Monitoring

Electrocardiography was used to monitor heart rate (HR) and to detect arrhythmia. Mean arterial pressure (MAP) was measured using a catheter placed in the right external carotid artery. A 5-Fr Swan-Ganz catheter was inserted via the right external jugular vein to monitor mean pulmonary artery pressure (MPAP), central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), cardiac output (CO), systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR). CO was measured by the thermodilution technique. As described in a previous report [5], the above hemodynamic profiles were measured at the following six sequential time points during surgery: 5 min before the onset of the anhepatic stage (II-5), 5 min after the onset of the anhepatic stage (II + 5); 5 min before the start of reperfusion (III – 5); 3, 30, and 60 min after the start of reperfusion (III + 3, III + 30, III + 60). Before and after reperfusion, blood samples were obtained via the arterial line for analysis of blood gases and also for measurement of serum electrolytes.

Statistical analysis

Values are expressed as the mean value or mean ± standard deviation (SD). The significance of differences between mean values were determined using Student's unpaired t-test. A P value of less than 0.05 was considered significant.

Results

Systemic and pulmonary hemodynamic variables and other factors affecting the hemodynamics are presented in Figs. 1–3 and Table 1. At the start of the venovenous bypass (II + 5) in group A, the reduced venous return caused an immediate decrease in CVP (34 %) and CO (27 %) and a compensatory increase in SVR (32 %) and PVR (35 %). Because of these compensatory responses, the MAP and MPAP were well maintained. The flow rate in the venovenous bypass was sufficient to maintain venous return (Table 1). At the end of the bypass (III – 5), the CVP was returned to almost its preanhepatic value with the infusion of fluid and blood, but adequate CO was not maintained despite the adequate preload. SVR and PVR showed a tendency to increase. Reperfusion of the liver graft in the control group caused a slight increase in CVP (5 %) and a marked increase in PVR (threefold) and MPAP (54 %). As a result of the increase in right ventricular afterload, the CO and MAP decreased by 30 % and 27.9 %, respectively (CO from 1.52 ± 0.28 to 1.07 ± 0.45 l/min, MAP from 101.4 ± 13.6 to 73.2 ± 19.4 mm Hg). During the anhepatic and reperfusion stage, the PCWP showed changes similar to those of the CVP (data not shown). No changes were observed in HR and cardiac rhythm.

In the PGE_1-treated pigs, hemodynamic changes similar to those in the control pigs were seen for the first 5 min of the anhepatic stage (II + 5). However, at the end of this stage (III – 5), the increases in SVR and PVR were suppressed and the CO was maintained at a

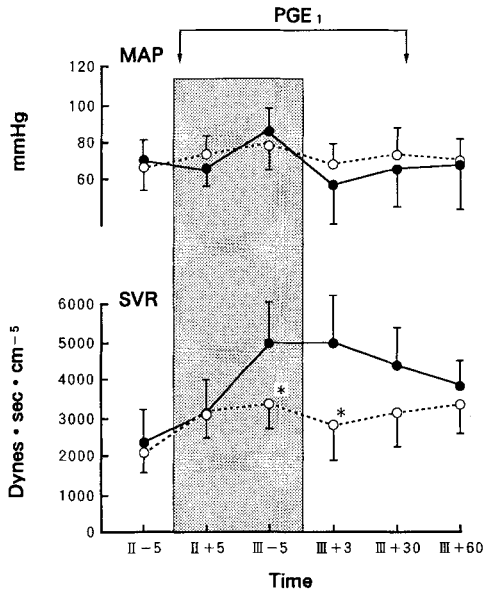

Fig. 1 Mean arterial pressure (MAP) and systemic vascular resistance (SVR) values (mean ± SD) measured in eight control (●) and eight PGE_1-treated pigs (○) at six sequential time points. The *shaded area* indicates the anhepatic period. * $P < 0.05$ compared with the control group

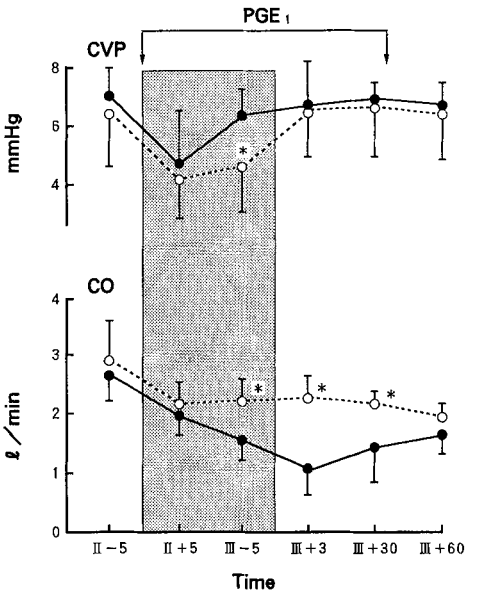

Fig. 3 Central venous pressure (CVP) and cardiac output (CO) values (mean ± SD) measured in eight control (●) and eight PGE_1-treated pigs (○) at six sequential time points. The *shaded area* indicates the anhepatic period. * $P < 0.05$ compared with the control group

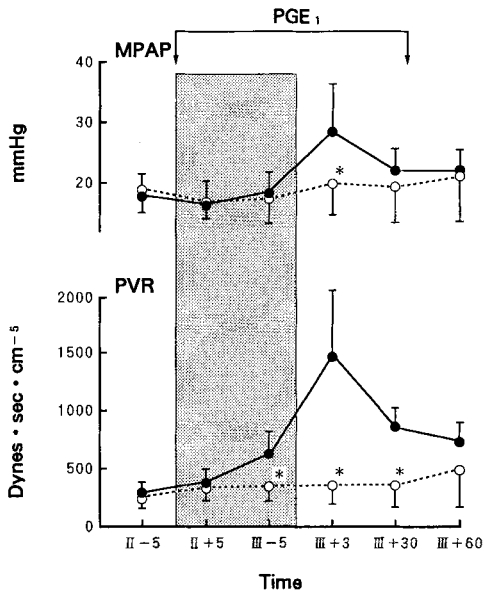

Fig. 2 Mean pulmonary arterial pressure (MPAP) and pulmonary vascular resistance (PVR) values (mean ± SD) measured in eight control (●) and eight PGE_1-treated pigs (○) at six sequential time points. The *shaded area* indicates the anhepatic period. * $P < 0.05$ compared with the control group

higher level than that in group A (1.52 ± 0.28 vs 2.17 ± 0.44 l/min, $P < 0.05$). As a result, hypotension did not occur in spite of the infusion of PGE_1. In addition, a high CO was obtained with a lower CVP compared with that in group A. There was no difference between the two groups in the extra volume administered during the anhepatic stage or in the flow rate of the venovenous bypass. At 3 min after the start of the reperfusion stage (III + 3), no changes in PVR or MPAP were observed, in contrast to group A. Consequently, CO was well maintained, showing a change from 2.17 ± 0.44 to 2.22 ± 0.52 l/min. Because PVR was low and consequently CO was high, the MAP showed only a slight change (from 95.3 ± 13.9 to 84.2 ± 13.1 mm Hg). A significant difference in the MAP between the two groups was not demonstrated at III + 3, but the percentage decrease in MAP, accompanied by revascularization, was significantly less in group B (12.0 ± 7.5 %, $P < 0.05$) compared with that in group A (27.9 ± 16.2 %). There was no difference between the groups in the degree of increase in blood potassium concentration, decrease in base excess, or drop in temperature. In the PGE_1-treated group, persistent wheezing or requirement for further blood transfusion was not observed.

Discussion

It has been reported that PGE_1 is effective in the treatment of primary nonfunction [1], humoral rejection,

Table 1 Summary of systemic variables in the two groups. Date are presented as mean ± SD. Group A is the control group and group B, the PGE_1-treated group

	A	B
Anhepatic time (min)	57 ± 7.8	54 ± 10.8
Bypass flow rate (ml/min)	0.78 ± 0.20	0.78 ± 0.14
Blood transfusion (ml)	550 ± 193	480 ± 160
Fluid infusion during anhepatic stage (ml)	420 ± 122	440 ± 108
Changes after reperfusion in:		
Potassium (mEq/l)	0.23 ± 1.29	0.33 ± 0.37
Base excess (mmol/l)	− 1.80 ± 1.38	− 1.53 ± 1.07
Temperature (°C)	− 1.26 ± 0.51	− 0.92 ± 0.25

and nephrotoxicity of FK506 following liver transplantation [2]. PGE_1 also has adverse effects, such as an inhibitory effect on platelet aggregation, hypotension, and severe diarrhea. In particular, hypotension limits the use of PGE_1 [1, 2]. In our study, the administration of PGE_1 (0.05 μg/kg per minute) during liver transplantation in pigs resulted in no decrease in MAP and did not result in a hemorrhagic diathesis.

Some previous clinical assessments [5, 6] have suggested that venous return is decreased in the anhepatic stage in spite of use of the venovenous bypass, which can lead to a decrease in CO and cause a compensatory elevation in SVR. Venovenous bypass is not totally effective in maintaining venous return. Another reason for the elevation in SVR is that the venovenous bypass itself leads to an increase in SVR due to a nonphysiological venous return. In our control group, the CVP and MAP returned to the preanhepatic values at the end of bypass, but the SVR showed a tendency to increase. This pattern indicated that the main reason for the increased SVR at the end of bypass is the nonphysiological venous return rather than a decreased venous return. We had anticipated that the administration of PGE_1, under such conditions as increased SVR, would be result in cardiovascular instability. Contrary to this expectation, stable hemodynamics were maintained without a decrease in MAP after the administration of PGE_1. This stable state may be sustained by the increased CO as a consequence of the vasodilator action of PGE_1. In addition, PGE_1 may exert a direct positive inotropic action on the myocardium during the anhepatic stage. From these results, we suggest that PGE_1 may have a cardiovascular support action during the anhepatic stage under venovenous bypass.

In the present study, reperfusion in liver transplantation in pigs was found to be associated with the onset of marked pulmonary hypertension causing systemic hypotension [7, 8]. PVR increased to about triple the level before reperfusion in the control group, CO was decreased by this phenomenon, and blood pressure decreased by 28% compared to the level before reperfusion. None of these pigs, however, showed bradyarrhythmia or rapid decreases in SVR. These results suggested that an elevation in PVR during reperfusion is the primary cause of systemic hypotension during reperfusion.

Post et al. [12] have reported that prostaglandin I_2 (PGI_2), prostaglandin E_2 (PGE_2), and thromboxane A_2 (TXA_2) are released from the transplanted liver during reperfusion following cold storage. PGI_2 and PGE_2 have a vasodilative action, whereas TXA_2 has a vasoconstrictive action. Therefore, the predominant vasomotor action depends on the ratio between PGI_2 and TXA_2. On the other hand, macrophages in pulmonary capillaries have been shown to metabolize arachidonic acid [13]. These intravascular macrophages appear to regulate the pressure in the pulmonary microcirculation by adjustment of the ratio between PGI_2 and TXA_2. There are interspecies differences in the size and number of the macrophages, which are larger in pigs than in other species [14, 15]. Since the sensitivity to TXA_2 is believed to be higher in the lungs of pigs than in humans, the postreperfusion pulmonary hypertension in pigs is thought to be caused by TXA_2 released from the transplanted liver during reperfusion.

Pettiet et al. [7] have reported that administration of a cyclooxygenase inhibitor, indomethacin, inhibits the synthesis of TXA_2 in the reperfused liver and suppresses pulmonary hypertension, as well as the postreperfusion syndrome. PGE_1 prevented pulmonary hypertension in this experiment, probably because PGE_1 efficiently antagonized the vasoconstrictive action of TXA_2. As a result, PGE_1 alleviated right ventricular afterload and subsequently prevented the decrease in CO in the postreperfusion stage. Although Blankensteijn [4] has reported deleterious effects of PGE_1 on the hemodynamics during liver transplantation, their experiment differed from ours in that the doses used in their experiment were smaller and the administration of PGE_1 was discontinued immediately before reperfusion.

Postreperfusion pulmonary hypertension is specific to pigs and is not found in humans. However, a similar phenomenon has caused trouble in some clinical settings. Pulmonary hypertension is not uncommon in end-stage liver disease [16]. In these patients, sudden occurrence of pulmonary hypertension during the operation is fatal [17]. In order to avoid mortality in these patients, administration of PGE_1 must be considered.

In summary, in this study in pigs a continuous infusion of PGE_1 increased CO without any adverse effect on the hemodynamics during the anhepatic stage and it also prevented pulmonary hypertension during reperfusion. Hence, we suggest that the administration of PGE_1 should be considered in clinical liver transplantation.

References

1. Greig PD, Woolf GM, Sinclair SB, et al (1989) Treatment of primary liver graft non-function with prostaglandin E_1. Transplantation 48: 453
2. Takaya S, Iwaki Y, Starzl TE (1992) Liver transplantation in positive cytotoxic crossmatch cases using FK506, high dose steroids, and prostaglandins E_1. Transplantation 54: 927
3. Nakao J, McCurdy IR (1967) Cardiovascular effects of prostaglandin E_1. J Pharmacol Exp Ther 156: 538
4. Blankensteijn JD, Schlejen PM, Groenland THN, Terpstra OT (1992) The effects of long-term graft preservation and prostaglandin E_1 on intraoperative hemodynamic changes in liver transplantation. Transplantation 54: 423
5. Rettke S, Janossy TA, Chantigian RC, et al (1989) Hemodynamic and metabolic changes in hepatic transplantation. Mayo Clin Proc 64: 232
6. Shaw BW, Martin DJ, Marquez JM, et al (1984) Venous bypass in clinical liver transplantation. Ann Surg 200: 524
7. Pittet J-F, Morel DR, Mentha G, Le Coultre C, Suter PM, Rohner A (1991) Protective effect of indomethacin in the development of the postreperfusion syndrome during liver transplantation. Transplant Proc 23: 2290
8. Miichi N (1989) Hemodynamic effects of anesthetic agents and bypass flow during orthotopic liver transplantation (in Japanese). Nippon Geka Gakkai Zasshi 90: 1907
9. Ferreira SH, Vane JR (1967) Prostaglandins, their disappearance from and release into the circulation. Nature 216: 868
10. Attinger EO, Cahill JM (1960) Cardiopulmonary mechanics in anesthetized pigs and dogs. Am J Physiol 198: 346
11. Sakagami K, Toda K, Nakai H, et al (1987) Improved techniques for orthotopic liver transplantation: a preliminary study. Hiroshima J Med Sci 36: 211
12. Post S, Goerig M, Otto G, et al (1990) Prostanoid release in experimental liver transplantation. Transplantation 49: 490
13. Bertram TA, Overby LH, Danilowicz R, Eling TE, Brody AR (1988) Pulmonary intravascular macrophages metabolize arachidonic acid in vitro. Am Rev Respir Dis 138: 936
14. Winkler GC, Cheville NF (1985) Monocytic origin and postnatal mitosis of intravascular macrophages in the porcine lung. J Leukocyte Biol 38: 471
15. Crocker SH, Lowery BD, Eddy DO, Wismar BL, Buesching WJ, Obenauf RN (1981) Pulmonary clearance of blood-borne bacteria. Surg Gynecol Obstet 153: 845
16. McDonnell PJ, Toye PA, Hutchins GM (1983) Primary pulmonary hypertension and cirrhosis: are they related? Am Rev Respir Dis 127: 437
17. De Wolfe AM, Scott VL, Gasior T, Kang Y (1993) Pulmonary hypertension and liver transplantation. Anesthesiology 78: 213