Changes of nitric oxide and endothelin, thromboxane A2 and prostaglandin in cirrhotic patients undergoing liver transplantation

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Supported by the National Natural Science Foundation of China, No. 30271254, and the Medical Development Foundation of Guangdong Province, No. 2004B3501005
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Received: 2006-02-16 Accepted: 2006-03-27

Abstract

AIM: To investigate the perioperative changes of nitric oxide (NO) and endothelin (ET), thromboxane A_2 (TXA_2) and prostaglandin (PGI_2) during liver transplantation in end-stage liver disease patients.

METHODS: Twenty-seven patients with end-stage cirrhosis undergoing liver transplantation were enrolled in this prospective study. Blood samples were obtained from superior vena at five different surgical stages. Plasma concentrations of nitrate and nitrite were determined to reflect plasma NO levels. Plasma levels of ET-1, 6-keto-PGF1 alpha and thromboxane B_2 (TXB_2), the latter two being stable metabolites of PGI_2 and TXA_2 respectively, were measured.

RESULTS: The NO level decreased significantly after vascular cross-clamping and increased significantly at 30 min after reperfusion. While the ET levels at 30 min after clamping and after reperfusion were significantly elevated. The ratio of NO/ET decreased significantly at 30 min after vascular cross-clamping and at the end of surgery. The PGI_2 level and the TXA_2 during liver transplantation were significantly higher than the baseline level, but the ratio of TXA_2/PGI_2 decreased significantly at 30 min after clamping.

CONCLUSION: NO/ET and TXA_2/PGI_2 change during liver transplantation. Although the precise mechanism remains unknown, they may play a role in the pathobiology of a variety of liver transplant-relevant processes.
Anesthesia was induced with midazolam (0.05-0.1 mg/kg), propofol (1-2 mg/kg) and fentanyl (5 μg/kg) intravenously (IV) and neuromuscular blockade was accomplished with succinurium (0.1 mg/kg). Mechanical ventilation was performed with O2, using a tidal volume necessary to maintain ETCO2 tension between 4-4.66 kPa (30-35 mmHg). Anesthesia was maintained with both isoflurane at a concentration of 1.0%-3.5% (inhalation) and intermittent fentanyl (50-100 μg, IV). After induction of anesthesia, a continuous dopamine infusion (2-6 μg/kg per min) was administered. Blood samples were obtained from the superior vena cava at five different surgical stages: induction of anesthesia (T1), 60 min after beginning of operation (T2), 30 min after vascular cross-clamping (T3), 30 min postreperfusion of new liver (T4) and at the end of surgery (T5). Plasma concentrations of nitrate and nitrite, two metabolites of NO, were determined to reflect plasma NO levels. Plasma ET-1 levels were measured by radioimmunoassay (RIA) and systemic 6-keto-PGF1α and TXB2, stable metabolites of PGI2 and TXA2 respectively, were measured by RIA also.

Detection of NO
Two milliliters of superior vena cava blood were collected and placed in ice-cooled propylene tubes. These samples were immediately centrifuged at 3000 r/min for 10 min and stored at -40°C for late assay. Test kits (Science and Technology Development Center of The General Hospital of PLA, Beijing, China) for NO analysis were used. The optical density value was read in a spectrophotometer set at 546 nm. The NO numeric value was calculated based on a standard and empty tube according to the equation. The calculated results were expressed as μmol/L.

Detection of ET
Two milliliters of superior vena cava blood were collected and placed in ice-cooled propylene tubes containing 40 μL aprotinin and 30 μL EDTA. These samples were immediately centrifuged at 3000 r/min for 10 min. Collected plasma was stored at -40°C until batched assays were performed. Plasma ET levels were evaluated with ET detection kit (Science and Technology Development Center of The General Hospital of PLA, Beijing, China) according to the manufacturer's instructions.

Detection of TXA2 and PGI2
Three milliliters of superior vena cava blood were collected with a five-milliliter syringe containing 200 μL EDTA 2Na, mixed fully and injected into a tube. These tubes were immediately centrifuged at 3500 r/min for 15 min. Collected plasma was stored at -40°C until use. Detection of the level of TXA2 and PGI2 was performed according to the manufacturer's instructions (Science and Technology Development Center of The General Hospital of PLA, Beijing, China).

Statistical analysis
Data are shown as mean ± SD. Data of the various time points were compared using ANOVA analysis (SPSS statistical package, version 11.0). Significant difference was accepted at P < 0.05.

| Table 1 | Changes of TXB2 and 6-keto-PGF1α levels in plasma during liver transplantation (mean ± SD, n = 27) |
| --- | --- | --- |
| TXB2 (ng/L) | 6-keto-PGF1α (ng/L) | TXB2/6-keto-PGF1α |
| T1 | 152.94 ± 68.67 | 118.27 ± 63.99 | 0.89 ± 0.37 |
| T2 | 932.71 ± 63.99 | 297.45 ± 127.13 | 0.47 ± 0.25 |
| T3 | 895.83 ± 300.71 | 265.15 ± 127.34 | 0.33 ± 0.14 |
| T4 | 620.94 ± 282.41 | 271.26 ± 140.48 | 0.49 ± 0.21 |
| T5 | 591.12 ± 336.57 | 208.32 ± 90.98 | 0.43 ± 0.20 |

RESULTS
A total of 27 patients (81% men, age 49 ± 11 year, BSA 1.72 ± 0.15) were enrolled in this study. Among these patients, 15 had hepatitis B virus associated cirrhosis, 12 had cirrhosis and liver cancer.

The changes of nitrate, nitrite and ET levels in plasma during liver transplantation are shown in Table 1. The mean baseline value of NO (reflected by nitrate and nitrite) was 27.45 ± 5.70 μmol/L. The NO level decreased significantly after vascular cross-clamping, from 27.45 ± 5.70 μmol/L to 25.64 ± 5.64 μmol/L (P < 0.05). At 30 min after reperfusion, a significant elevation of NO was found, from 25.64 ± 5.64 μmol/L to 35.30 ± 11.23 μmol/L (P < 0.05).

The baseline ET concentration was 61.21 ± 25.38 ng/L. Compared with the baseline level, the ET levels at 30 min after clamping and after reperfusion were significantly elevated (110.61 ± 24.65 ng/L, 114.00 ± 26.73 ng/L respectively).

The changes of TXB2 and 6-keto-PGF1α levels in plasma during liver transplantation are shown in Table 2. The prostaglandin level and the TXA2 level presented the same changes. The concentrations at every time point were significantly higher than the baseline level. Peak levels of prostaglandin were 932.71 ± 25.66 ng/L and 895.83 ± 300.71 ng/L, detected at 60 min after operation and 30 min after vascular cross-clamping respectively. The mean baseline value of NO/ET was 0.54 ± 0.25. The ratio decreased significantly at 30 min after vascular cross-clamping and at the end of surgery. The mean
baseline value of TXA2/PGI2 was 0.89 ± 0.37, the ratio decreased significantly at 30 min after clamping. Compared with the value at 30 min after clamping, the ratio increased significantly at 30 min after reperfusion, from 0.33 ± 0.14 to 0.49 ± 0.21.

**DISCUSSION**

In this study we measured systemic NO and ET, TXA2 and PGI2 at five different surgical stages: basal, heptectomy, anhepatic, 30 min after graft reperfusion and the end of surgery. Overall results showed that the levels of these two groups of vasoactive substances changed at each stage during liver transplantation. Previous studies have demonstrated that NO and ET, TXA2 and PGI2 play an important role in the pathobiology of ischemia-reperfusion injury and postreperfusion syndrome[3,4]. It suggests that disturbed balance between these vasodilators and vasoconstrictors may contribute to some liver transplantation-relevant syndromes.

NO and ET are the most important local vasodilator and vasoconstrictor respectively. They seem to play a role in almost every organ and tissue. However, there is considerable confusion in understanding their roles. Some researches suggest that the important factors in determining the beneficial versus harmful effects of NO are the amount, duration, and site of NO production[3]. Ovadia et al demonstrated that the fetal pulmonary vasoconstriction after acute constriction of the ductus arteriosus is mediated by NO/ET-1 interactions[8]. Shirakami et al reported that the plasma ET level was increased before transplantation compared with that of healthy children, but decreased during the anhepatic phase[9]. It increased again after reperfusion and remained at high level in the early postoperative period. These suggest that ET production in the cirrhotic liver is augmented and ET plays some role in circulatory regulation during the perioperative period of pediatric liver transplantation. In the present study, although both NO and ET increased after graft reperfusion, the ratio of them was decreased. It suggested that the imbalance of NO and ET level may participate in the pathophysiology of systemic and local circulation disorders.

Many data about the relationship between another group of vasoactive substances, PGI2/TXA2 and hemodynamics have been reported[8,9]. TXA2 is both a vasoconstrictor and a potent stimulus for platelet aggregation. Its effect is antagonized by prostacyclin, which is released by vascular endothelial cells. Prostacyclin exerts a variety of effects on the cardiovascular system, including a decrease in blood pressure associated with a decrease in systemic vascular resistance. In clinical liver transplantation, Khoury et al[8] demonstrated 60% of patients undergoing orthotopic liver transplantation accumulated prostacyclin in the portal vein, which could be one of the causes of hypotension seen at reperfusion of the donor liver. As previously demonstrated, we found that the baseline levels of PGI2 and TXA2 in our patients were higher than normal values. It was most likely due to the decreased metabolism of them in patients with end-stage liver disease. In addition, we found PGI2 and TXA2 had the same changes during liver transplantation. The levels of PGI2 and TXA2 after reperfusion were elevated compared with the baseline level. However, the ratio of TXA2 and PGI2 was significantly lower than that of pre-reperfusion. This indicated that the disorder of TXA2 and PGI2 might also be involved in the circulation disorders during orthotopic liver transplantation.

In summary, two groups of endogenous vasoactive substance, NO/ET and TXA2/PGI2, are changed during liver transplantation. Although the precise mechanism remains unknown, they may play a role in the pathobiology of a variety of liver transplant-relevant processes.

**ACKNOWLEDGMENTS**

We thank Professor Bing-Xue Chen for his good advice and Xiu-Qin Liu for his assistance with the study.

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S-Editor Wang J  L-Editor Zhu LH  E-Editor Liu Y

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