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First clinical realization of continuous monitoring of liver microcirculation after transplantation by thermodiffusion

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Abstract To date, no method is available for the continuous long-term monitoring of liver microcirculation in patients. Experimentally, thermodiffusion has been validated in the quantification of hepatic perfusion. In an attempt to investigate the practicability of thermodiffusion technology in patients after liver transplantation thermodiffusion probes were inserted into the graft in seven patients during liver transplantation. Continous monitoring started intraoperatively and was performed until day 7, when the probes were extracted transcutaneously. No probe-related complications (i.e., hemorrhage, infection) were observed. In four patients with normal graft function, liver perfusion recovered within 12 h from the intraoperative reduction to a range between 85 and 93 ml/100 g per min. In contrast, primary graft failure ($n = 1$) was characterized by a constant decrease of hepatic perfusion (< 50 ml/100 g per min). In prolonged reperfusion injury ($n = 1$), a second peak of transaminases was paralled by an impairment of liver microcirculation. In one patient, R2 rejection on day 7 was preceded by a drop in hepatic perfusion 48 h earlier. Thus, thermodiffusion is a safe and reliable method for the continuous quantification of liver microcirculation after transplantation in patients. Measurements are reproducible for at least 7 days. Changes in hepatic perfusion during postoperative complications can be detected. The characteristics of microcirculatory disorders will have to be defined in a larger number of patients.

Key words Liver transplantation · Liver microcirculation · Thermodiffusion · Clinical monitoring · Liver graft function

Introduction

Hepatic microcirculation plays a pathophysiological key role during the early postoperative phase after liver transplantation [1]. The methods currently available for the assessment of liver perfusion preclude clinical application after abdominal closure. We have recently validated a newly developed thermodiffusion probe allowing for continuous monitoring of the hepatic microcirculation for at least 1 week postoperatively [2]. In the present study we tested the clinical practicability of the thermodiffusion method with regard to the assessment of liver perfusion after transplantation.

Patients and methods

The study was approved by the Ethics Committee of the Medical Faculty of Heidelberg and complied with the Declaration of Helsinki. Before surgery a written consent to implant the probes was obtained from each patient. One thermodiffusion probe was inserted into liver segment IV B of seven patients and exited transcutaneously during liver transplantation 60 min after arterial reperfusion. The mean age of the patients was 40 years ranging, from

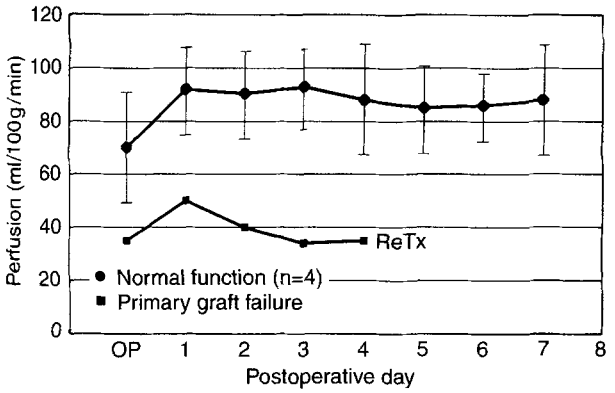

Fig. 1 Hepatic perfusion after liver transplantation. The upper curve represents four patients with normal graft function ($n = 4$). After an intraoperative reduction, liver perfusion increased within 12 h to a near-normal level, which was maintained during 7 days postoperatively. In contrast, primary graft failure was characterized by a primary reduction in liver perfusion without tendency to recover. (*Re Tx* Retransplantation)

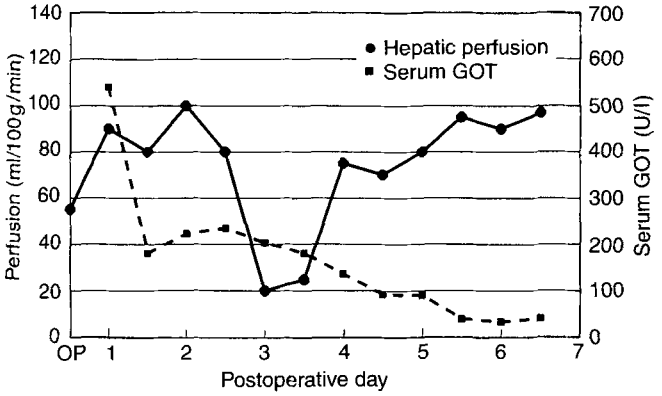

Fig. 2 Hepatic perfusion and serum GOT in a patient developing a second peak of serum transaminases after reperfusion. The increase of GOT is paralleled by a reduction in liver perfusion. Simultaneous normalization of both parameters following day 4 continued with an uneventful course thereafter

14 to 60 years. The underlying liver disease for transplantation was alcoholic cirrhosis ($n = 3$), cirrhosis due to autoimmune hepatitis ($n = 1$), acute liver failure of unknown etiology ($n = 1$), fulminant hepatitis B ($n = 1$), and fibrolamellar carcinoma ($n = 1$). Four patients had an uneventful postoperative course. In one patient, primary graft failure occurred, necessitating retransplantation on postoperative day 5. One patient developed early rejection on day 7, proven by biopsy. In one patient, a prolonged reperfusion injury was documented by a second peak of transaminases on day 2. The probe was extracted on postoperative day 7; a swab was taken for bacteriology.

The mechanism of thermodiffusion technology (Thermal Technologies, Cambridge, Mass.) as used in this study is the quantification of heating power required to maintain a temperature increment of 2 °C above the surrounding tissue. Thermal conductivity by local perfusion can be calculated from the difference of the effective thermal conductivity minus the intrinsic conductivity. The probe (diameter 0.9 mm) has a self-heated thermal transducer at the tip as well as a thermistor, 7 mm proximal. The intraparenchymal radius of measurement is dependent on the quality of perfusion: 2.7 mm at fast capillary flow, 4.5 mm under low flow conditions. Continuous monitoring of perfusion is based on one measurements. Perfusion data are displayed as mean values of 20-min sampling periods.

Results

Normal function ($n = 4$)

There was an increase in hepatic perfusion from 70 ± 20 ml/100 g per min to 92 ± 17 ml/100 g per min during a 12-h period after reperfusion. Liver perfusion was recorded within a stable range between 85 ± 17 ml/100 g per min and 93 ± 16 ml/100 g per min until the end of the observation period (Fig. 1).

Primary graft failure ($n = 1$)

Hepatic perfusion was primarily reduced without tendency to recover until retransplantation (34–50 ml/100 g per min (Fig. 1).

Prolonged reperfusion injury ($n = 1$)

After initial recovery of liver perfusion to 90 ml/100 g per min, a secondary reduction to 21 ml/100 g per min was recorded on day 3, in parallel with a second peak of transaminases. After normalization of transaminases and liver perfusion, the postoperative course was uneventful (Fig. 2).

Rejection ($n = 1$)

Intraoperatively, as well as during postoperative days 1–4, liver perfusion was comparable to the patient group with normal graft function. On day 5, a considerable reduction in perfusion from 80 to 35 ml/100 g per min was recorded. Due to a rise in transaminases on day 7, a liver biopsy was performed revealing R2 rejection (Fig. 3).

All patients

On day 7, extraction of the probe was performed without complications. Bacterial contamination of the probe could be excluded in all patients.

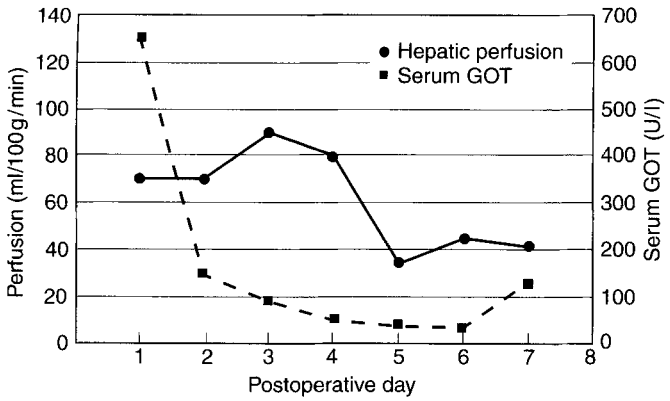

Fig. 3 Drastic reduction of liver perfusion on day 5 after transplantation. Increase of serum GOT on day 7. Liver biopsy revealed R2 rejection

Discussion

Thermodiffusion has been previously validated in pigs as a reliable method for the continuous monitoring of hepatic microcirculation following liver transplantation [2]. The measurements at baseline conditions as well as during intermittent occlusion of hepatic artery and/or portal vein were reproducible during the observation period of 7 days.

The main finding of the current study is that the clinical application of thermodiffusion is reliable and safe. No complications (e.g., hemorrhage) were observed during insertion or extraction of the probes. The measurements in the group of patients with normal graft function followed the characteristic pattern observed from experimental studies in pigs [2, 3]. Hepatic perfusion recovered from an initial reduction to stable values between 85 and 93 ml/100 g per min over subsequent days. Total liver blood flow in man, as measured by portal venous and hepatic arterial flow, has been reported to be 120 ml/100 g per min [4]. The difference in liver perfusion recorded here could well be explained by an increase of shunt perfusion via arterioportal-venous anastomoses visualized in the rat by scanning electron microscopy [5] and documented functionally in man [6]. By means of H2-clearance, shunt perfusion has been shown to increase to 38 % of total liver blood flow early after reperfusion in pigs [7].

A constant reduction of liver perfusion was recorded in primary graft failure from the first measurement intraoperatively until retransplantation on day 5. This finding is consistent with the angiographic picture encountered in primary graft failure, the "leafless-tree" phenomenon, i.e., failure to visualize peripheral arterial branches in the liver parenchyma as a result of an increase in intracapsular pressure with subsequent parenchymal necrosis [8]. One patient in our study developed a second peak of transaminases after an initial continuous decrease, which was ascribed to prolonged preservation injury. In parallel, a decrease in hepatic perfusion was recorded by thermodiffusion for 2 days, followed by normalization of both parameters. One patient developed early acute rejection, which was suspected by a rise in transaminases on postoperative day 7 and confirmed (R2) by biopsy. In fact, on day 5, a decrease of hepatic perfusion was noted.

Injury of hepatic sinusoidal endothelium is the primary effect of ischemia-reperfusion injury and has been documented by conventional and scanning electron microscopy [9–12]. So far, functional assessment of hepatic microcirculation has been performed mainly experimentally by means of intravital microscopy [13, 14], laser doppler flowmetry [15], and gas clearance techniques using ^{85}Kr [4, 16] or hydrogen [3]. Intravital microscopy is not applicable clinically; laser doppler flowmetry, ^{85}Kr, and hydrogen clearance can only be used intraoperatively. Other clearance techniques, such as the use of indocyanine green [4, 17], represent indirect methods measuring total liver blood flow but not perfusion and are restricted to single measurements. Intraparenchymal laser doppler flowmetry has the drawback of covering only a small surface range of the liver tissue (1–2 mm^3), which may not be representative in the presence of redistribution phenomena, as documented after reperfusion [18]. In contrast, a larger tissue volume is integrated by thermodiffusion measurements ranging between 82 and 381 mm^3 in a flow-dependent fashion. Recently, an extractable autofocus doppler flow probe has been described allowing continuous blood flow measurement of hepatic artery and portal vein after liver transplantation in man [19]. Possible risks of the method originate from the mechanical irritation of the blood vessels: induction of vasospasm or kinking, with subsequent thrombosis.

In summary, it could be demonstrated that thermodiffusion is clinically applicable to the continuous monitoring of liver perfusion after transplantation. In accordance with the experimental validation of the method, measurements are reproducible for at least 1 week postoperatively. Hemorrhage upon extraction or contamination of the probe has not been encountered so far. Changes of liver perfusion in connection with reperfusion injury, primary graft failure, or rejection can be detected. Characteristic patterns of capillary flow impairment have to be evaluated in a larger series of patients with complicated postoperative course. Thermodiffusion is a promising method to further define the pathophysiological role of hepatic microcirculation after liver transplantation in man.

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