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Impairment of pancreatic microcirculation in the early reperfusion period during simultaneous pancreas-kidney transplantation

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Abstract The most likely cause of graft pancreatitis is the ischemia/reperfusion injury which can be a major problem in simultaneous pancreas-kidney transplantation. Animal experiments suggest the important role in this process of an impaired microcirculation after reperfusion. We have investigated pancreatic microcirculation in the early reperfusion period during clinical pancreas-kidney transplantation. Tissue PO_2 (PO_2ti) was monitored by a PO_2-sensitive electrode. After reperfusion (a. r.) samples were taken from the venous effluent of the pancreas and simultaneously from the radial artery. After an initial peak a transient fall of PO_2 was found. Total blood flow and hemoglobin oxygen saturation ($sHbO_2$) in the venous effluent increased until 90 min a. r. (107 ml/min, 97.1 %) High venous $sHbO_2$ and high PO_2ti correlated with good graft outcome. These findings can be explained by an impairment of capillary perfusion (no reflow) and concomitant shunt perfusion. The data suggest the considerable relevance of pancreatic microcirculation in the early reperfusion period during clinical pancreas transplantation.

Key words Pancreas transplantation · Microcirculation · Graft pancreatitis · Oxymetry

Introduction

Graft pancreatitis can cause considerable morbidity and even graft loss after pancreas transplantation. The mild and moderate forms of graft pancreatitis which are equivalent to edematous pancreatitis do not require any intervention. However, severe graft pancreatitis which resembles acute necrotizing pancreatitis requires a complex management with relaparatomies and closed continuous peritoneal lavage in order to save the graft and the patient. The pathogenesis of postimplantation pancreatitis is still unclear. It is, however, accepted that the ischemia/reperfusion injury plays a key role. In various organs and models of ischemia/reperfusion [1], a postischemic impairment of capillary perfusion (no reflow phenomenon) has been described, which might lead to secondary ischemia and organ damage. Since the transition from acute edematous pancreatitis into acute necrotizing pancreatitis seems to be associated with a failure of capillary perfusion [2], it can be hypothesized that the postischemic impairment of capillary perfusion in pancreas grafts might be of major importance for the development of postimplantation pancreatitis. Therefore, we have investigated postischemic microcirculation in human pancreas grafts.

Patients and methods

Eleven patients undergoing simultaneous pancreas-kidney transplantation for diabetes type I and end-stage renal disease were included in the study. All organs were preserved in UW solution. In order to take blood samples from the venous effluent of the pancreas, a 16 CH catheter was inserted in the distal part of the splenic vein of the pancreas graft during back-table preparation. Tissue PO_2 (PO_2ti) was continuously measured by a PO_2-sensitive electrode (Licox; GMS, Germany) that was implanted into the pancre-

atic tail ($n = 6$). After reperfusion (a.r.) blood samples (0, 1, 2, 5, 10, 30, 90 min) were taken from the catheter in the splenic vein and simultaneously from the radial artery. Further control samples from the radial artery were taken 30 and 5 min before reperfusion. During the sampling from the catheter in the distal part of the splenic vein, the anastomosis of the portal vein was compressed in order to divert the whole venous effluent through the catheter. Thus total pancreatic blood flow could be determined by the venous outflow method. Furthermore, oxygen consumption could be calculated from blood-gas analyses from the venous effluent of the pancreas, the samples from the radial artery, and the pancreatic blood flow. As previously described, patients were grouped according to the degree of graft pancreatitis into mild (G0), moderate (GI), and severe (GII). Additionally, the peak C-reactive protein level (CRP) within the first 48 h after reperfusion was used for statistical correlation (Pearson's correlation). Means were compared using Student's t-test for paired samples.

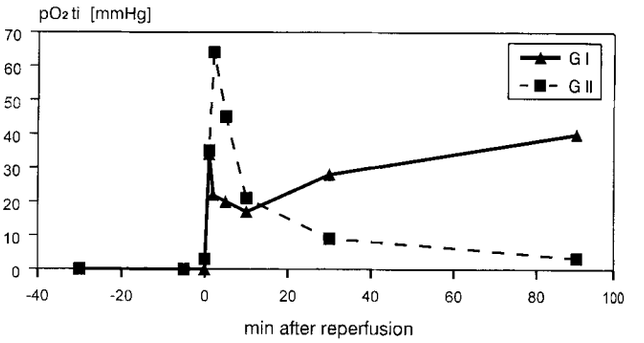

Fig. 1 Tissue PO_2 (PO_2ti) recording during reperfusion from a patient who developed mild *(GI)* and another patient who developed severe *(GII)* graft pancreatitis

Results

Median ischemia time was 11.5 (7–15) h. Five patients developed mild (G0), 5 moderate (GI), and 1 severe (GII) graft pancreatitis. After reperfusion inpatients in the G0 and GI groups, the PO_2ti (Fig. 1) showed a steep increase up to 42.3 ± 12.4 mm Hg (2 min a.r.). This first peak, which was noted between 2 and 10 min a.r., was followed by a significant transient reduction of PO_2ti (Fig. 2) to 28.9 ± 10 mm Hg at 30 min a.r. ($P < 0.008$). Thereafter a slow recovery to 38.6 ± 6.8 mm Hg at 90 min a.r. occurred. In contrast, in the GII patient, PO_2ti did not recover after the initial maximum (65 mm Hg), but further decreased down to 3.3 mm Hg at 90 min a.r. The PO_2ti at 30 min a.r. correlated with the degree of graft pancreatitis ($r = -0.71$), however, this was not quite statistically significant ($P < 0.07$) in this small number of patients ($n = 6$). Total blood flow (G0, GI) increased continuously from 60 ± 33 ml/min immediately after reperfusion to 107.1 ± 50 ml/min at 90 min a.r. The lowest blood flow was observed in the GII patient (38 ml/min) at 90 min a.r. This correlation ($r = -0.51$, $P < 0.08$), however, was not statistically significant. Hemoglobin oxygen saturation ($sHbO_2$) in the venous effluent of the pancreas was somewhat variable in the first 2 min a.r., but showed a minimum at 5 min a.r. in all patients (83.4 ± 19%). It thereafter increased to 97.1 ± 1.3%. Immediately after reperfusion there was no correlation between the $sHbO_2$ and the peak CRP. However, toward the end of the observation period there was an increasing statistically significant correlation (Fig. 3) between these parameters ($r = -0.83$, $P < 0.005$ at 90 min a.r.), indicating a good prognosis for organs with a high $sHbO_2$ in the venous effluent. Oxygen consumption in the G0 and GI groups showed a maximum at 2 min a.r. (2.44 ± 4.5 mlO_2/min), but was fairly low afterward (0.35 ± 0.12 mlO_2/min). However, no correlation between oxygen consumption and the peak CRP was found.

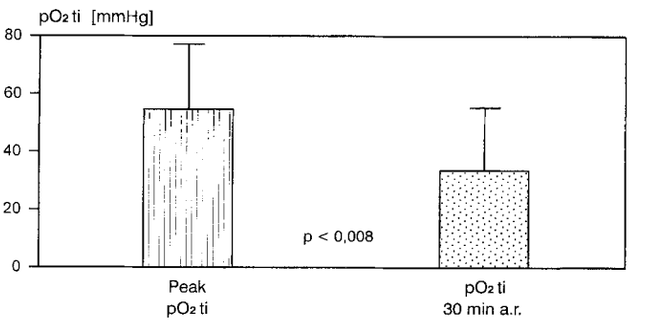

Fig. 2 Peak PO_2ti between 0 and 10 min after reperfusion *(a.r.)* and PO_2ti 30 min a.r.

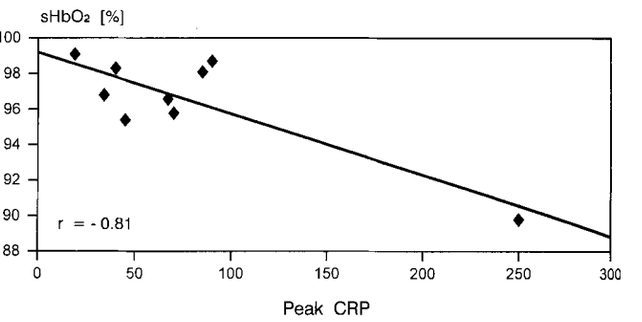

Fig. 3 Correlation between peak C-reactive protein levels *(CRP)* within 48 h of reperfusion and hemoglobin oxygen saturation *($sHbO_2$)* in the venous effluent of the pancreas graft 90 min a.r.

Discussion

Pancreatic microcirculation is believed to be of major importance in the development of acute necrotizing pancreatitis as well as in the pathogenesis of the ischemia/reperfusion injury and thus graft pancreatitis [1, 2]. However, the investigation of pancreatic microcirculation has always been confined to animal models.

In this study for the first time, parameters of human pancreatic microcirculation were determined. The anatomy of the pancreas graft makes it possible to temporarily divert the venous effluent of the pancreas through a catheter in the distal part of the splenic vein. Thus, a situation equivalent an isolated perfusion pancreas can be created in which the uptake and the release of a certain substance by the human pancreas can easily be measured [3]. In addition to the assessment of total pancreatic blood flow [4], oxygen consumption, and oxygen extraction, simultaneous information about the nutritive capillary perfusion was obtained by a continuous registration of the pancreatic PO_2ti. This method was used to investigate the initial events of the ischemia/reperfusion injury of the human pancreas during pancreas transplantation. The data show a profound alteration of pancreatic microcirculation after reperfusion of the graft. Despite a high blood flow and a hemoglobin oxygen saturation near 97% in the venous effluent of the pancreas graft, a decrease of tissue oxygenation in the early reperfusion period was noted. This can be explained by an impairment of capillary (nutritive) perfusion that leads to inadequate tissue oxygenation with a concomitant shunt perfusion [5]. As in the case of our patient who developed severe graft pancreatitis, it is a well-known clinical observation that pancreas grafts which have a patchy bluish appearance after reperfusion will very likely develop severe graft pancreatitis. It has always been hypothesized that this might be due to an impairment of capillary perfusion (no reflow) and thus reduction of nutritive perfusion. We were able to demonstrate for the first time a drastic persistent impairment of the microcirculation consistent with this lack of capillary reflow and shunt perfusion in such a pancreas graft. The observation of a transient high peak in PO_2ti with a following decrease favors a secondary rather than a primary capillary failure. This is in accordance with the concept of the 'reflow paradox' which leads to an impairment of capillary function after reperfusion [6, 7]. Similar to what has already been found in rat liver transplantation [8], we were also able to show that high $sHbO_2$ values in the venous effluent (indicating a high degree of shunt perfusion) were significantly associated with a good prognosis. This shows that although shunt perfusion may well be coexistent with an impaired microcirculation, it might not be a result of capillary failure, but rather an independent even beneficial mechanism in postischemic reperfusion. In conclusion, our data suggest that pancreatic microcirculation might play an important role in the development of graft pancreatitis after pancreas transplantation.

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