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Effects of portal versus systemic venous drainage in kidney-pancreas recipients

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Abstract A randomized study of combined kidney-pancreas transplantation was performed on 30 insulin-dependent diabetic patients with end-stage renal disease to compare the consequences of pancreas transplantation with portal venous (PV) and systemic venous (SV) drainage. Fourteen patients (SV group) received systemically drained and sixteen (PV group) portally drained pancreas allografts. Enteric drainage was performed in both groups. The routine follow-up included documentation of the clinical course and detailed endocrine studies. At 1 year after transplantation, the patient survival rate was 92% for the SV group and 96% for the PV group; the graft survival rate was 78% and 82%, respectively. Endocrine studies indicated no difference in fasting and stimulated glucose or in glycosylated hemoglobin between the two groups. In addition, no hyperinsulinemia and lipidic abnormalities were evidenced in either group Long-term studies are required to conclude whether PV and SV drainage in pancreas transplantation are equivalent in terms of patient and graft survival as well as metabolic consequences.

Key words Kidney-pancreas transplantation · Systemic drainage · Portal drainage

Introduction

The most common surgical approach to pancreatic transplantation employs the drainage of exocrine secretions into the bladder and the diversion of venous outflow into the systemic circulation [13]. Despite its widespread acceptance, this procedure has shown potential surgical and metabolic complications such as chemical cystitis, infection, recurrent hematuria, repeated episodes of pancreatitis, and metabolic acidosis [16, 17]. To avoid these complications, enteric drainage has been performed by several groups [17, 18]. In addition, it has also been reported that the majority of transplant patients have systemic hyperinsulinemia since the secreted insulin does not pass through the liver before reaching the muscle and the adipose tissue; therefore, a portal hypoinsulinemia with lipid abnormalities has been described [3, 5, 14]. Consequently, portal-enteric drainage of the pancreas allograft has been proposed due to the theoretical advantages associated with the maintenance of physiological drainage of endocrine and exocrine pancreas secretion. Even though recent emphasis [2, 4, 9, 10, 15] has been given to the beneficial metabolic consequences of this technique, it is difficult to draw uniform conclusions from the current studies because they are contradictory and often compromised by small numbers of patients and/or a lack of appropriate control subjects [3, 9, 10, 15]; moreover, these investigations compare the systemic-bladder drainage with the portal-enteric drainage.

In the present study, we performed combined kidney-pancreas transplantation to compare the consequences of pancreas transplantation with portal venous (PV) diversion vs systemic venous (SV) diversion during the 1st year after transplantation. The site of venous drainage of the pancreas was the only difference since enteric drainage was employed in both procedures.

Materials and methods

This study included 30 patients with type I diabetes mellitus and end-stage renal disease who underwent simultaneous pancreas-kidney transplantation. Informed consent was obtained from all patients. They were randomly assigned to two groups: the first group consisted of 14 patients who received the pancreas allograft with SV drainage of the organ the second group comprised 16 patients who received the pancreas allograft with PV drainage (Table 1). The patient characteristics of the SV and PV groups were similar with respect to age, sex distribution, duration of diabetes, preoperative dialysis, and human leukocytes antigen matching.

Organ procurement and allograft preparation techniques were the same for both groups. Standard procurement procedures were employed with in situ cold-flush preservation using University of Wisconsin solution. The pancreas and kidney were removed from multiorgan cadaveric donors, so the common hepatic artery and celiac axis were kept with the liver. The whole pancreas was always removed with the duodenal segment and the spleen. The duodenum was closed on both ends by means of a double-row automatic stapler.

On the back table, the portal vein was extended by the donor external iliac vein, and the donor's arterial iliac bifurcation was used to connect the graft's superior mesenteric artery and splenic artery to provide a single well-sized arterial vessel for anastomosis.

Two different procedures were used for the simultaneous pancreas-kidney transplantations. In the SV group, the right iliac fossa was prepared for the pancreatic graft. The pancreatic arterial supply was reconstructed using the Y-graft of the donor iliac artery anastomosed to the superior mesenteric and splenic arteries of the graft. An end-to-side anastomosis between the common iliac arteries of the donor and recipient was performed. The donor portal vein was anastomosed to the recipient external iliac vein. In the PV group, the donor pancreas was placed parallel to the aorta. Arterial revascularization was performed as described above. The donor portal vein was anastomosed in an end-to-side fashion to the superior mesenteric vein of the recipient. In both groups, a two-layered end-to-end duodenojejunal anastomosis between the donor duodenum and the defunctionalized limb of the Roux-en-Y of the recipient was performed after reperfusion.

In all patients, and after transplanting the pancreas, the kidney was placed intraperitoneally in the left iliac fossa with vascular anastomoses to the external iliac vessels.

After surgery, immunosuppression was achieved for all patients by means of quadruple immunosuppression therapy including induction with ATG (antihuman thymocyte globulin, 25 mg/20 kg per day) for the first 10 postoperative days, steroids (1 mg/kg per day, decreasing by 5 mg every 3 days down to 10 mg/day by 3 months), azathioprine (2 mg/kg per day; dose adjustments were made upon peripheral white cell count), and cyclosporine (2 mg/kg per day starting on the 1st postoperative day, then 6 mg/kg per day p.o. during the maintenance period, whereupon the dose depended on renal function and cyclosporine serum levels). The diagnosis of rejection was established by monitoring the serum creatinine level and subsequent renal biopsy, if indicated.

Table 1 Characteristics of patients undergoing simultaneous pancreas-kidney transplantation with systemic venous (*SV*) or portal venous (*PV*) drainage

Characteristic	SV ($n = 14$)	PV ($n = 16$)
Mean age (range)	43 (29–54) years	39 (29–56) years
Mean duration of diabetes (range)	30 (19–40) years	26 (14–40) years
Sex		
Male	9	9
Female	5	7
Dialysis	85.7%	62.5%

The patient follow-up included the clinical course and routine metabolic studies, e.g., such concerning glycemia, creatinine, HbA_{1c}, fasting insulin and C peptide, and cholesterol and triglycerides.

In addition, oral glucose tolerance tests (OGTTs) were undertaken 3, 6, and 12 months after transplantation, and then at annual intervals, for all functioning pancreatic grafts. After overnight fasting, OGTTs were performed following ingestion of 1 g/kg body weight of sugar in 300 ml of water with a maximum dose of 100 g. Blood samples were collected at 30-min intervals for 3 h. Insulin and C peptide levels were measured by radioimmunoassay.

There are results presented as mean ± standard error of the mean; the median number was also calculated. Because of the small amount of patients and large patient-to-patient variability, glucose tolerance values were analyzed at each time point and compared with those of normal subjects. Between-group differences were determined with repeated measures of analysis of variance. If a significant difference was documented (p value < 0.05), a Duncan test (between groups) and a t-test (for each time point) were performed.

Results

At 1 year after transplantation (Tx), the patient survival rate was 92% for the SV group and 96% for the PV group. In the SV group, one patient died of septic complications 30 days after transplantation; in the PV group, one patient died of bleeding 1 day after transplantation.

Pancreas graft survival, defined as freedom from exogenous insulin, was 78% for the SV group and 82% for the PV group at 1 year.

Early loss of pancreatic graft due to venous thrombosis occurred in one patient of each group. In addition, one pancreas was lost to irreversible rejection (5 months after Tx) and one to iliac artery thrombosis (3 months after-Tx) in the SV group. No kidney loss occurred in the SV group. In the PV group, one pancreas and one kidney allograft were lost to rejection (10 months after Tx), and one pancreas was lost due to unknown cause (12 months after Tx).

Table 2 Metabolic characteristics of pancreas allograft patients with systemic venous (*SV*) and portal venous (*PV*) drainage. Differences between the transplant recipients of the SV and PV groups were not statistically significant at 3, 6, and 12 months after transplantation. Values are mean ± SEM

	SV group			PV group		
	3 months	6 months	12 months	3 months	6 months	12 months
Creatinine (μmol/l)	132 ± 33	123 ± 21	119 ± 21	118 ± 30	139 ± 37	117 ± 16
Glucose (mmol/l)	4.6 ± 0.5	4.3 ± 0.4	4.3 ± 0.1	4.6 ± 0.4	4.5 ± 0.4	4.6 ± 0.4
HbA_{1c} (%)	5.1 ± 0.2	5.4 ± 0.3	5.3 ± 0.3	5.0 ± 0.4	5.5 ± 0.8	5.6 ± 0.2
Fasting insulin (mU/l)	12.6 ± 5.0	9.7 ± 2.2	9.1 ± 5.2	9.4 ± 1.7	7.5 ± 2.2	7.5 ± 1.5
Fasting C peptide (μg/l)	2.9 ± 1.1	2.3 ± 0.7	1.5 ± 0.8	2.2 ± 0.6	2.7 ± 0.6	2.3 ± 0.4
Cholesterol (mmol/l)	4.3 ± 0.8	4.1 ± 0.9	4.4 ± 0.7	4.9 ± 0.9	5.3 ± 0.5	5.2 ± 0.7
Triglycerides (mmol/l)	1.4 ± 0.5	1.0 ± 0.2	1.1 ± 0.4	1.6 ± 0.4	1.5 ± 0.4	1.3 ± 0.3

During the follow-up period, one patient of the SV group presented bowel leakage, and three patients of the same group presented bowel occlusion. All the complications called for additional surgical procedures. In the PV group, there were no instances of bowel leakage or occlusion; a thrombosis of a minor pancreatic vein occurred in one patient, who was successfully treated with heparin.

Five patients of both groups presented one or more rejection episodes; within the PV and SV groups it was more common to have kidney rejection episodes than pancreas rejection episodes. All rejection episodes were initially treated with steroids, and one episode not responding to steroids, with OKT3.

Excluding graft losses as described above, there was no difference in allograft function between the two groups at 1 year as well as at each time point (Table 2), as reflected by mean serum creatinine (119.37 ± 21.62 μmol/l in the SV group vs 117.16 ± 10.83 μmol/l in the PV group) or fasting blood glucose (4.34 ± 0.17 mmol/l in the SV group vs 4.68 ± 0.45 mmol/l in the PV group). No significant difference in HbA_{1c} levels was found between the two groups (5.37 ± 0.35 % in the SV group vs. 5.68 ± 0.25 % in the PV group). Fasting insulin and C peptide levels (Table 2) were not significantly different in both groups and were not higher when compared with normal subjects.

During OGTTs, glucose profiles were similar in both groups (Fig. 1); although marked variability was present in the levels of insulin and C peptide in both groups, differences between the two groups in plasma insulin curves as well as in C peptide curves did not reach significance as shown in Figs. 2 and 3.

The PV group as well as the SV group did not show any significant difference in cholesterol and triglyceride levels (5.26 ± 0.77 mmol/l in the PV group vs 4.48 ± 0.72 mmol/l in the SV group, and 1.30 ± 0.37 mmol/l in the PV group vs 1.12 ± 0.4 mmol/l in the SV group, respectively), and none of the results were higher when compared with those of normal subjects.

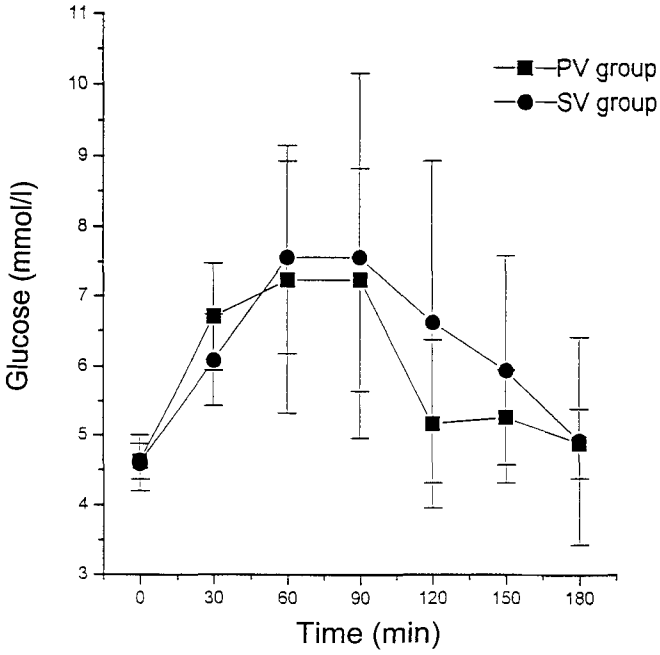

Fig. 1 Serum glucose levels in response to oral glucose tolerance tests in 12 recipients of pancreas allografts with portal venous (*PV*) drainage (■) compared with 9 recipients of pancreas allografts with systemic venous (*SV*) drainage (●)

Discussion

The limited number of patients and the short period of follow-up did not allow us to evidence any significant difference in patient and graft survival between the PV and SV groups, although there was a trend toward improved graft survival as well as a decreased incidence of complications and reoperations in the PV group. There was no difference in the incidence of venous thrombosis between the SV and PV groups.

The data in this report did not address any difference in rejection episodes between the two groups, although Gaber et al. reported a decreased incidence of rejection episodes and graft loss [11]. In the PV group as well as in

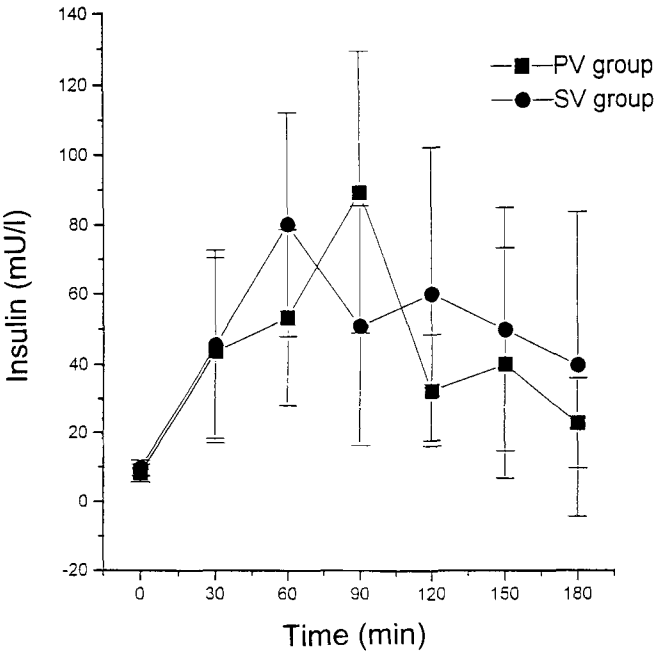

Fig. 2 Serum insulin levels in response to oral glucose tolerance tests in 12 recipients of pancreas allografts with portal venous (*PV*) drainage (■) and 9 recipients of pancreas allografts with systemic venous (*SV*) drainage (●).

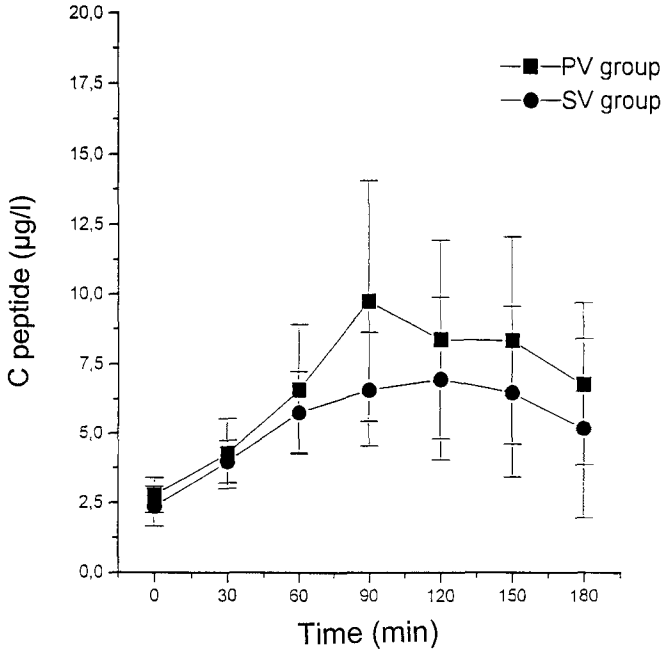

Fig. 3 Serum C-peptide levels in response to oral glucose tolerance tests in 12 recipients of pancreas allografts with portal venous (*PV*) drainage (■) compared with 9 recipients of pancreas allografts with systemic venous (*SV*) drainage (●)

the SV group, the diagnosis of acute pancreas rejection remains a problem due to the lack of a sensitive and reliable marker such as the decrease in urine-amylase concentration, which was the clinical indicator of rejection when bladder drainage was performed.

Although pancreas transplantation achieves normoglycemia and insulin independence in most recipients, the differences in control of glucose homeostasis from the native pancreas include a denervated organ, heterotopic location, and an increased peripheral insulin resistance related to immunosuppressive therapy. As generally performed, the venous effluent of the pancreas allograft is drained into the inferior cava vein; thereby, first-pass hepatic insulin is bypassed, and the normal portal-peripheral insulin gradient is abolished. Consequently, in pancreas-kidney transplantation with SV outflow and bladder drainage, several authors reported hyperinsulinemia, insulin resistance, and resistance to the action of insulin on lipid metabolism that might be caused at least in part by insulin receptor down-regulation [2–4, 6, 14, 15].

In this study, and excluding graft loss, fasting glucose levels were normal throughout the follow-up period accompanied by fasting normoinsulinemia in the PV group as well as in the SV group. Therefore, pancreatic transplant endocrine function assessed by OGTTs showed an excellent glucose homeostasis for up to 3 months after transplantation in both groups. In addition, no significant differences were evidenced in stimulated insulin levels between the PV and SV groups. Interestingly, basal insulin as well as insulin levels in response to OGTTs were not higher in either group than the values of normal subjects. Despite the majority of investigators [2–5, 9, 14, 15] having demonstrated normal carbohydrate metabolism with increased peripheral insulin concentrations and different degrees of insulin resistance in SV drainage pancreas allografts, it was impossible to find any differences in insulin secretion between the SV and PV groups in the present study. Mild basal hyperinsulinemia even less pronounced after OGTTs has been reported by other authors such as Pfeffer [12], who showed almost identical insulin levels in pancreas-kidney transplantation with SV drainage and in kidney transplant patients. The predominant reason for mild hyperinsulinemia after transplantation might be the immunosuppressive therapy with steroids. Basal and stimulated C peptide was investigated in the patients of both groups since it is not degraded by the liver and its concentration in the systemic circulation should be independent of the type of pancreatic venous drainage. No significant difference in basal and stimulated C peptide levels between the pancreas recipients of both groups was evidenced.

Subtle modifications in lipid metabolism between PV and SV patients have been reported by several authors [1, 6, 7, 8]. In this study, however, the type of pancreatic

venous drainage did not have any impact on cholesterol and triglyceride levels, and substantial lipid abnormalities were not observed between the recipients of either groups and normal subjects.

Long-term studies are required to conclude whether PV and SV drainage in pancreas transplantation are equivalent in terms of patient and graft survival as well as metabolic consequences.

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