ORIGINAL ARTICLE

A 9-Year Experience With 126 Pancreas Transplants With Portal Enteric Drainage

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Hypothesis: A novel technique of pancreas transplantation (PTX) with portal venous delivery of insulin and enteric exocrine drainage (portal enteric) was developed at our center to improve the PTX procedure.

Design: Case series.

Setting: Single-center experience at a university hospital.

Patients and Intervention: From October 1990 through December 1999, we performed 126 PTXs with portal enteric drainage, including 90 simultaneous kidney PTXs (SKPT) and 36 solitary PTXs (18 sequential PTXs after kidney transplantation and 18 PTXs alone).

Main Outcome Measures: Patient and graft survival rates; medical and surgical morbidity. Three groups, representing 3 eras of immunosuppression, were compared. Thirty patients underwent SKPT with muromonab-CD3 induction and cyclosporine-based therapy in era 1 (October 1990 through June 1995); 42 SKPTs received tacrolimus and mycophenolate mofetil-based immunosuppression without antibody induction in era 2 (July 1995 through May 1998); and 18 SKPTs were performed in era 3 (June 1998 through December 1999) with either basiliximab or daclizumab induction.

Results: One-year patient survival rates after SKPT were 77% in era 1, 93% in era 2, and 100% in era 3 ($P=.03$). The 1-year kidney graft survival rates were 77% in era 1, 93% in era 2, and 94% in era 3 ($P=.08$). The 1-year pancreas graft survival rates after SKPT were 60% in era 1, 83% in era 2, and 83% in era 3 ($P=.06$). The incidences of rejection (63% vs 33% vs 39%; $P<.001$) and thrombosis (20% vs 7% vs 6%; $P<.001$) were decreased in eras 2 and 3.

Conclusion: Simultaneous kidney PTXs with portal enteric drainage can be performed with improved outcomes.

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THE OUTCOMES of vascularized pancreas transplantation (PTX) continue to improve as a result of refinements in surgical techniques and advances in immunosuppression. As of August 2000, nearly 14 000 pancreas transplants were reported to the International Pancreas Transplant Registry.[1] In the United States, more than 1200 PTXs are performed annually, with 83% being simultaneous kidney and PTXs (SKPTs). The current 1-year actuarial patient, kidney, and pancreas (with complete insulin independence) graft survival rates after SKPT are 95%, 92%, and 84%, respectively.[1] Solitary PTXs comprise the remaining 17% of PTXs performed annually, including either sequential pancreas after kidney transplantations (PAKTs) (12%) or PTXs alone (5%). The current 1-year actuarial pancreas graft survival rates are 73% for PAKT and 70% for PTX alone.[1]

According to International Pancreas Transplant Registry data, most PTXs are performed with systemic venous delivery of insulin and either bladder (systemic bladder [SB]) or enteric (systemic enteric [SE]) drainage of the exocrine secretions.[1,2] From 1988 through 1995, more than 90% of PTXs were performed by the standard technique of SB drainage.[2] However, in the last few years, the number of PTX procedures performed using primary enteric drainage has steadily increased, accounting for 60% of cases in 1999.[1]

Despite an evolution in surgical techniques, most PTXs with enteric drainage are performed with systemic venous delivery of insulin.[1,2] To improve the physiology of PTX and to avoid the potential complications of systemic hyperinsu-

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METHODS

The PTX program at the University of Tennessee (Memphis) was started in 1989 (**Figure 1**). The first SKPT with PE drainage was performed in October 1990, and this patient continues to demonstrate excellent dual allograft function more than 10 years later. During the 9 years that followed, we performed 126 PTXs with PE drainage (**Figure 2**), including 90 SKPTs and 36 solitary PTXs (18 PAKT, 18 PTXs alone). This study represents a case series and our collective experience with the PE technique.[10]

ORGAN PROCUREMENT, PRESERVATION, AND PREPARATION

The pancreas and/or kidneys were procured from heart-beating cadaveric donors in conjunction with multiple organ retrieval using standardized techniques.[11] UW solution (Viaspan; Dupont Pharmaceuticals, Atlanta, Ga) was used for both in situ flush and storage of all organs under cold storage conditions. Whole-organ pancreaticoduodenosplenectomy was performed by an en bloc technique.[11] Cold ischemia was kept to a minimum and pancreas preservation times were less than 24 hours in all cases and less than 12 hours in about one third of cases.[12] Prior to transplantation, the pancreas was reconstructed with a donor iliac artery bifurcation Y-graft to the splenic and superior mesenteric arteries.[10,13] The PE procedure requires that the arterial bifurcation graft be constructed with enough length for subsequent arterialization. The donor portal vein was mobilized and dissected back to the splenic and superior mesenteric venous confluence without the need for a venous extension graft. The proximal duodenal staple line (just distal to the pylorus) was inverted with sutures, and the distal duodenal closure incorporated the third and a variable length of the fourth portion of the duodenum, as previously described.[3,4] The closure of the mesenteric root was reinforced with a running suture. The spleen was attached on the left to the tail of the pancreas to be used as a handle, but in some cases the splenic hilar structures were ligated in continuity before revascularization. The kidney was prepared using standard techniques. The pancreaticoduodenal graft was repackaged separately and in a sterile fashion in cold UW solution prior to implantation.

RECIPIENT SELECTION AND OPERATIVE PROCEDURE

Patients were selected for transplantation based on ABO blood type compatibility, period of time on the waiting list, and a negative T-lymphocytotoxic cross-match, in accordance with United Network for Organ Sharing guidelines. After preparation of the organ(s), the recipient operation was performed through a midline intraperitoneal approach. Portal enteric drainage has been previously described in detail by our group (**Figure 3**).[4,10] The portal vein of the pancreas graft is anastomosed end-to-side to a major tributary of the superior mesenteric vein. The donor iliac artery bifurcation graft is brought through a window made in the distal ileal mesentery and anastomosed end-to-side to the right common iliac artery. The transplanted duodenum is anastomosed to a diverting Roux-en Y limb of the recipient jejunum. Splenectomy is performed after revascularization, and an attempt is made to anchor the tail of the pancreas to the anterior abdominal wall with interrupted sutures. These anchoring sutures permit subsequent percutaneous, ultrasound-guided pancreas allograft biopsies to be performed as needed.[14]

IMMUNOSUPPRESSIVE ERAS

Figure 4 summarizes the immunosuppressive therapy performed in each era. From October 1990 through June 1995 (era 1), 30 SKPTs with PE drainage were performed at our center with quadruple therapy consisting of muromonab-CD3 induction in combination with cyclosporine (Sandimmune; Sandoz Pharmaceuticals Corp, Hanover, NJ), prednisone, and azathioprine sodium.[6] The cyclosporine dose was titrated to achieve a target 12-hour trough level of greater than 300 ng/mL for the first 3 months after transplantation and greater than 200 ng/mL thereafter. The azathioprine dosage was 1 to 2 mg/kg per day. The prednisone dose was tapered to achieve a dose of 10 mg/d by 1 year and 5 mg/d by 2 years after transplantation.

From July 1995 through May 1998 (era 2), 42 SKPTs and 23 solitary PTXs (11 PAKTs, 12 PTXs alone) received tacrolimus (TAC), prednisone, and mycophenolate mofetil (MMF) triple therapy without antibody induction.[15,16] The tacrolimus dose was titrated to a 12-hour trough level of 15 to 25 ng/mL for the first 3 months after transplantation. After 3 months, TAC blood levels were maintained at 10 to 15 ng/mL. Oral MMF therapy was started immediately after transplantation at 2 to 3 g/d in 2 to 4 divided doses. The MMF dose was reduced in patients with gastrointestinal intolerance (nausea, vomiting, diarrhea) or when the complete white blood cell count was less than 3.0×10^9. Mycophenolate mofetil therapy was discontinued temporarily in patients with active cytomegalovirus infection or septicemia, or when the complete white blood cell count was less than 2.0×10^9; it was restarted later at a reduced dose. The prednisone dose was gradually tapered to achieve a dose of 5 mg/d at 1 year.

From June 1998 through December 1999 (era 3), 18 SKPTs and 13 solitary PTXs (7 PAKT, 6 PTXs alone) received TAC, MMF, and prednisone immunosuppression

linemia such as dyslipidemia, accelerated atherosclerosis, and insulin resistance, a new surgical technique was developed at our center using portal venous delivery of insulin and enteric drainage of the exocrine secretions (portal enteric [PE] drainage).[3,4] We have previously reported our initial experience with PE drainage, including both retrospective and prospective comparisons with control groups of patients who underwent SKPT with either SB or SE drainage.[5-10] We report the chronology of our 9-year single-center experience with 126 PTXs with PE drainage spanning different immunosuppressive eras.

RESULTS

The PE group included 69 men and 57 women with a mean age of 39 years (**Table 1**). The mean duration of pretransplant diabetes was 24 years (range, 8-50 years). Most recipients were white, although 15 recipients (12%) were African American. A total of 13 patients (10%) un-

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with or without either basiliximab or daclizumab antibody induction (**Figure 5**). Half of the SKPT and all of the solitary PTX recipients received either basiliximab (20 mg intravenously on days 0 and 4) or daclizumab (1 mg/kg on day 0 and then at 2-week intervals for a total of 5 doses) as induction therapy.[17]

The diagnosis of rejection was based on clinical criteria,[18] renal allograft dysfunction, serum amylase, lipase,[19] and glucose levels, a change in the slope of glucose disappearance,[20] and renal or pancreas allograft histopathology.[14] Renal allograft rejection was suggested by an unexplained rise in serum creatinine of 0.3 mg/dL (26.52 µmol/L) or greater and confirmed by ultrasound-guided percutaneous biopsy. Pancreas allograft rejection was suggested by an unexplained elevation in serum amylase, lipase, or glucose, and confirmed by ultrasound-guided percutaneous biopsy.[14,18-20] The severity of rejection was defined according to the Banff criteria for kidney biopsies[21] and by a modification of the Maryland classification of allograft rejection for pancreas biopsies.[22] Mild renal allograft rejection was treated with intravenous methylprednisolone, 500 to 1000 mg/d, for 3 days. Antilymphocyte therapy with muromonab-CD3, antithymocyte gamma globulin (Upjohn Laboratories, Kalamazoo, Mich), or thymoglobulin for 5 to 10 days was used as the initial treatment for moderate or severe renal allograft rejection or for any pancreas allograft rejection. Steroid-resistant mild renal allograft rejection was also treated with antilymphocyte therapy.

PERIOPERATIVE MANAGEMENT

Perioperative antibiotic prophylaxis consisted of a preoperative, intraoperative, and 3 postoperative doses of cefazolin sodium (1 g intravenously). All patients received single-strength sulfamethoxazole/trimethoprim sulfate, 1 tablet per day, for 6 to 12 months as prophylaxis for *Pneumocystis* pneumonia. Patients who were allergic to sulfa medications received inhaled pentamidine therapy. Antifungal prophylaxis consisted of either oral nystatin (swish and swallow 5 mL, 4 times daily) or oral fluconazole, 200 mg/d, for 2 to 3 months.[23] Antiviral prophylaxis consisted of either oral acyclovir sodium for 3 months (era 1), intravenous ganciclovir sodium followed by oral acyclovir for 3 months (era 2),[24] or intravenous ganciclovir (2.5-5 mg/kg twice daily) during the initial hospitalization, followed by oral ganciclovir (1 g 3 times daily) for 3 months (era 3).[25]

Patients were monitored in the intensive care unit for 24 to 36 hours before being transferred to the transplant unit. Nasogastric tube decompression was maintained for 2 to 3 days, closed-suction drainage for 3 to 5 days, and urethral catheter drainage for 5 to 7 days. Antiplatelet therapy consisting of oral aspirin (81 mg/d) was administered to all patients. In addition, 2000 to 3000 U of intravenous heparin sodium was administered as a single dose during surgery before implantation of the pancreas. In most cases, heparin prophylaxis was continued after surgery (5000 U subcutaneously twice daily) for 3 to 5 days. Oral warfarin sodium in a single dose of 1 mg/d was administered to patients requiring prolonged vascular access or those with subsequent placement of a permanent central venous catheter. Several management protocols evolved over time, including (1) donor selection restricted to ideal situations, particularly in solitary PTX; (2) protective cytomegalovirus-matching (seronegative donor organs transplanted into a seronegative recipient)[25]; (3) minimizing cold ischemia, particularly for nonideal donors[12]; (4) routine anticoagulation and HLA matching, especially in retransplants and solitary PTXs; (5) routine ganciclovir and fluconazole prophylaxis[23]; and (6) surveillance pancreas biopsy monitoring (particularly for solitary PTX recipients).[26]

POSTOPERATIVE MONITORING

After transplantation, duplex ultrasonography of the pancreas and/or the kidney was performed on the first postoperative day and whenever clinically indicated. Recipients were serially monitored for daily fasting serum glucose, amylase, and lipase levels, renal profiles, cyclosporine or TAC levels, and complete blood cell counts. Metabolic control and hormonal profiles were assessed by intravenous glucose tolerance testing, fasting and stimulated C-peptide levels, lipid profiles, and glycosylated hemoglobin levels.[6,10,20,27]

Cytomegalovirus infection was defined as a positive blood culture, antigenemia, or an immunoglobulin M titer.[25] Invasive cytomegalovirus infection was defined as symptomatic cytomegalovirus infection or histologic evidence of tissue invasion. Treatment consisted of intravenous ganciclovir for 2 to 4 weeks and a reduction in immunosuppression. Oral acyclovir or ganciclovir was given for a variable period after treatment of a documented cytomegalovirus infection. Other infections were recorded, with major infection defined as the need for hospitalization for diagnosis or treatment.

STATISTICAL ANALYSIS

Minimum follow-up was 11 months (mean, 4-6 years). Renal allograft loss was defined as death with function, transplant nephrectomy, return to dialysis, or return to the pretransplant serum creatinine level. Pancreas graft loss was defined as death with function, transplant pancreatectomy, or the need for daily insulin therapy.

derwent pancreas retransplantation with the PE technique. Most patients had poor HLA matching (mean, 1.4; range, 0-5), and the mean pancreas cold ischemia was 13 hours (range, 6-23 hours).

Thirty patients underwent SKPT in era 1 and were compared with 42 SKPTs performed in era 2 and 18 in era 3. We also compared 23 solitary PTXs (11 PAKTs, 12 PTXs alone) performed in era 2 with 13 (7 PAKTs, 6 PTXs alone) performed in era 3 (Figure 2). One-year patient survival rates after SKPT were 77% in era 1, 93% in era 2, and 100% in era 3 ($P=.03$). The 1-year kidney graft survival rates were 77%, 93%, and 94%, respectively ($P=.08$). The 1-year pancreas graft survival rates after SKPT were 60%, 83%, and 83% ($P=.06$) (**Figure 6**). The most common causes of kidney graft loss were death with function and chronic rejection (**Table 2**). The overall incidence of kidney graft loss decreased from 56% in era 1 to 23% in era 2 to 11% in era 3 ($P<.001$). The most common causes of pancreas graft loss were thrombosis, death with function, chronic rejection, and infection

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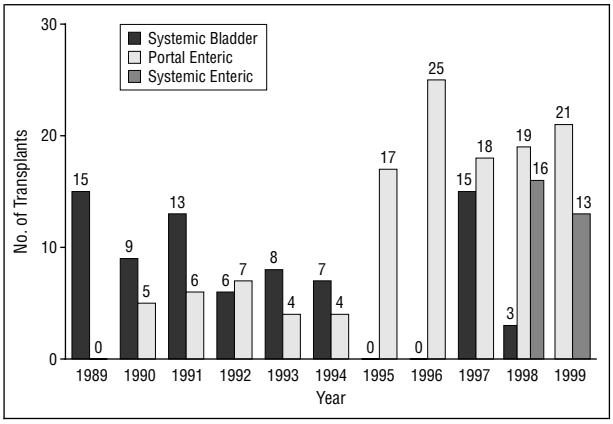

Figure 1. A decade of experience in pancreas transplantation at the University of Tennesee (Memphis) according to technique of transplantation.

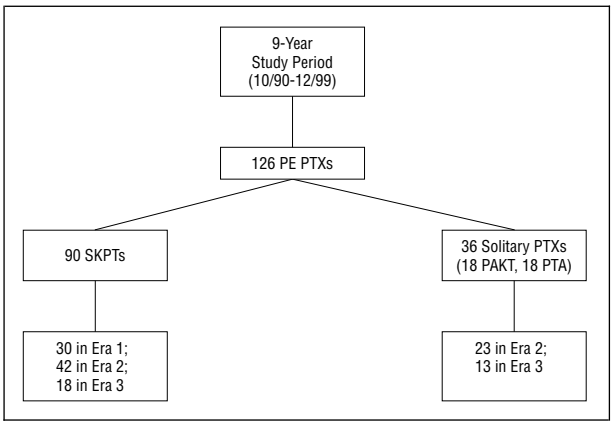

Figure 2. Overall experience in pancreas transplantation (PTX) with portal-enteric (PE) drainage spanning different immunosuppressive eras. SKPT indicates simultaneous kidney PTX; PAKT, sequential pancreas after kidney transplant; and PTA, pancreas transplant alone.

(Table 2). The overall incidence of pancreas graft loss decreased from 60% in era 1 to 31% in era 2 to 22% in era 3 ($P<.001$).

The incidences of rejection in eras 1, 2, and 3 (63% vs 33% vs 39%, respectively; $P<.001$) and major infection (60% vs 43% vs 44%; $P=.14$) after SKPT were decreased in consecutive eras (**Figure 7**). The rates of thrombosis (20% vs 7% vs 6%; $P<.001$) and early relaparotomy (47% vs 31% vs 33%; $P=.15$) after SKPT were also decreased in consecutive eras (**Figure 8**).

The 1-year patient survival rates after solitary PTX were 100% in eras 2 and 3, while the corresponding pancreas graft survival rates were 61% and 69%, respectively (**Table 3**). The most common causes of graft loss after solitary PTX were thrombosis and chronic rejection. The overall incidence of pancreas graft loss after solitary PTX decreased from 70% in era 2 to 31% in era 3 ($P=.02$). The rates of acute rejection (57% vs 38%), major infection (35% vs 31%), thrombosis (22% vs 15%), and relaparotomy (43% vs 38%) after solitary PTX were all slightly improved in era 3 compared with era 2 ($P=.36$).

COMMENT

The history of clinical PTX largely revolves around the development and application of various surgical techniques.[28] As surgical techniques evolve, an increasing number of PTXs are performed with enteric drainage (about 60% of cases in 1999).[1] However, the proportion of cases with enteric exocrine drainage coupled with portal venous delivery of insulin has remained low and represents only 15% to 20% of enteric-drained PTXs.[2] In a

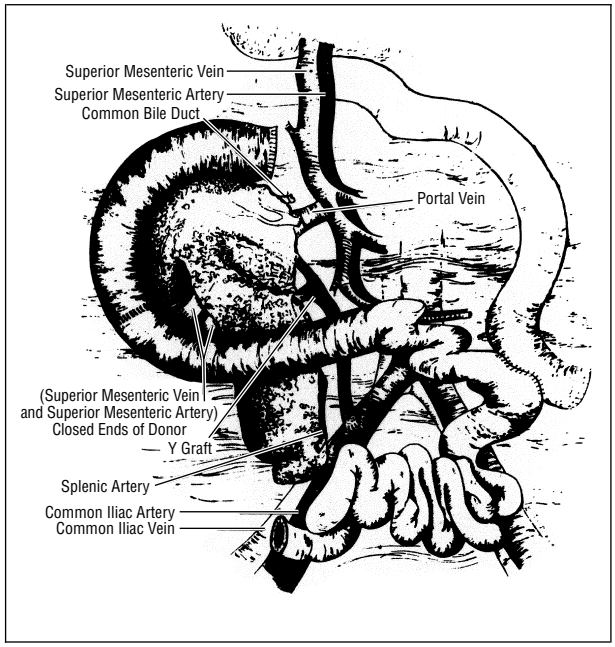

Figure 3. Technique of pancreas transplantation with portal enteric drainage.

Era 1 (10/90-6/95):
- 30 SKPTs with PE drainage received muromonab-CD3 induction, Sandimmune cyclosporine, prednisone, and azathioprine

Era 2 (7/95-5/98):
- 42 SKPTs and 23 solitary PTXs (11 PAKT, 12 PTA) received TAC, prednisone, and MMF w/o antibody induction

Era 3 (6/98-12/99):
- 18 SKPTs and 13 solitary PTXs (7 PAKT, 6 PTA) received TAC, MMF, and prednisone ± either basiliximab or daclizumab induction

Figure 4. Chronology of experience in pancreas transplantation (PTX) with portal enteric (PE) drainage according to immunosuppressive era. SKPT indicates simultaneous kidney PTX; PAKT, sequential pancreas after kidney transplants; PTA, pancreas transplant alone; TAC, tacrolimus; and MMF, mycophenolate mofetil. Sandimmune is a product of Sandoz Pharmaceuticals Corp, Hanover, NJ.

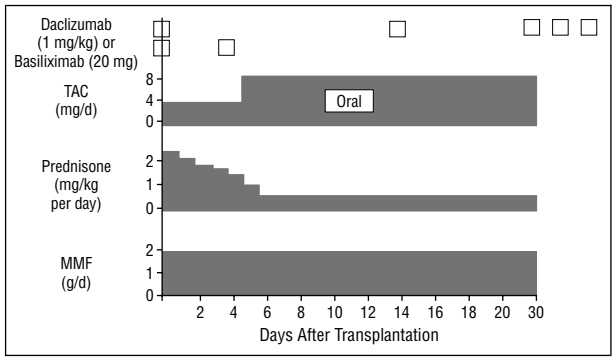

Figure 5. Regimen of immunosuppression in era 3 with selective use of monoclonal antibodies directed against the interleukin 2 receptor as induction therapy. Maintenance immunosuppression is triple therapy with tacrolimus (TAC), mycophenolate mofetil (MMF), and steroids.

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Table 1. Demographic and Transplant Characteristics*

Characteristic	N = 126
Age, y (range)	39 (19-56)
Sex	
Female	57 (45)
Male	69 (55)
Race	
White	111 (88)
African American	15 (12)
Years (range) of diabetes	24 (8-50)
Transplant type	
SKPT	90 (72)
PAKT	18 (14)
PA	18 (14)
Prior PTX	13 (10)
HLA match	1.4 (0-5)
Pancreas cold ischemia, h (range)	13 (6-23)

*Data are given as number (percentage) of patients unless otherwise indicated. SKPT indicates simultaneous kidney and pancreas transplantation; PAKT, sequential pancreas transplantation after kidney transplantation; PTA, pancreas transplantation alone; PTX, pancreas transplantation; and HLA, human leukocyte antigen.

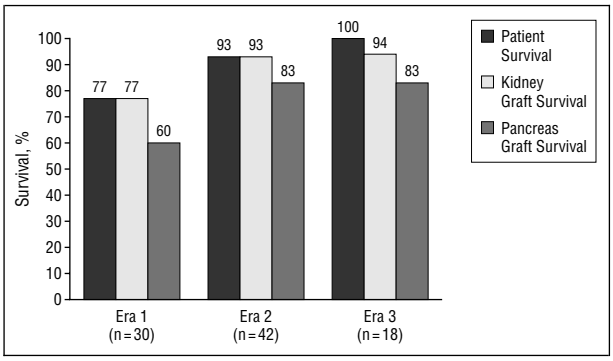

Figure 6. One-year patient and graft survival rates according to immunosuppressive era. Survival rates were similar in eras 2 and 3 and significantly improved compared with era 1; $P \leq .06$.

Table 2. Results of Simultaneous Kidney PTXs*

	era 1 (n = 30)	Era 2 (n = 42)	Era 3 (n = 18)	*P*
One-year survival				
Patient	23 (77)	39 (93)	18 (100)	.03
Kidney	23 (77)	39 (93)	17 (94)	.08
Pancreas	18 (60)	35 (83)	15 (83)	.06
Acute rejection	19 (63)	14 (33)	7 (39)	<.001
Major infection	18 (60)	18 (43)	8 (44)	NS
Thrombosis	6 (20)	3 (7)	1 (6)	<.001
Relaparotomy	14 (47)	13 (31)	6 (33)	NS
Overall graft loss				
Kidney	17 (56)	10 (23)	2 (11)	<.001
Pancreas	18 (60)	13 (31)	4 (22)	<.001
Causes of kidney graft loss				
DWFG	7 (23)	5 (12)	1 (5.5)	<.001
Chronic rejection	4 (13)	3 (7)	1 (5.5)	NS
Infection	2 (7)	1 (2)	0	NS
Acute rejection	1 (3)	0	0	NS
PTLD	2 (7)	1 (2)	0	NS
Thrombosis	1 (3)	0	0	NS
Causes of pancreas graft loss				
Thrombosis	6 (20)	3 (7)	1 (5.5)	<.001
DWFG	5 (17)	2 (5)	1 (5.5)	<.001
Chronic rejection	1 (3)	5 (12)	1 (5.5)	NS
Infection	3 (10)	1 (2)	1 (5.5)	NS
PTLD	2 (7)	1 (2)	0	NS
Acute rejection	1 (3)	1 (2)	0	NS

*Data are given as number (percentage) of patients unless otherwise indicated. PTX indicates pancreas transplantation; DWFG, death with functioning graft; PTLD, posttransplantation lymphoproliferative disease; and NS, not significant.

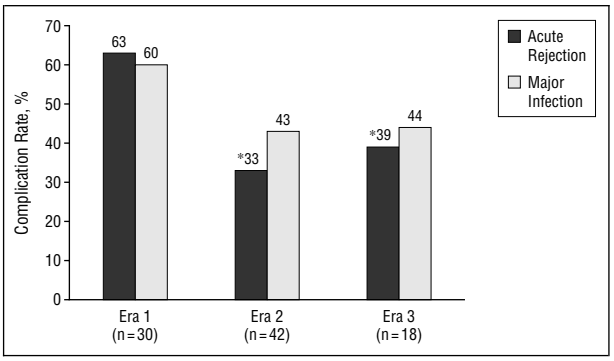

Figure 7. The incidence of acute rejection was similar in eras 2 and 3 and significantly decreased compared with era 1. Asterisks indicate $P<.05$.

recent survey of surgical techniques among PTX centers, 7 reported experience with the PE technique, of which 5 used a diverting Roux limb.[29] The International Pancreas Transplant Registry analysis of PTXs performed between 1996 and 1999 reported that the 1-year pancreas graft survival rates were similar for PE and SE drainage (83% and 84%, respectively).[1,2] We have previously reported our initial experience with PE drainage, including both retrospective and prospective comparisons with control groups of patients who underwent SKPT with either SB or SE drainage.[5-10]

Experience with PTX using portal venous delivery of insulin dates back to the mid 1980s. Initial attempts employed segmental PTX with either gastric,[30] pyelic,[31] or jejunal[32,33] drainage. Whole-organ PTX using the PE technique was first described clinically by our group in 1992[3] and was based on experimental work by Shokouh-Amiri et al[34-36] in a porcine model. This new technique employed a tributary of the superior mesenteric vein to reestablish portal venous drainage and differed substantially from other initial reports of whole-organ PTX with portal venous drainage. In 1990, Muhlbacher et al[37] described a technique involving an end-to-side anastomosis between the distal splenic vein of the donor and the recipient's portal vein in combination with bladder drainage. In 1992, Rosenlof et al[38] applied Calne's[30] original technique to whole organ PTX using an end-to-side anastomosis between the donor portal vein and recipient splenic vein coupled with enteric drainage. In each of these other series, however, the procedure was not widely applied because of technical problems associated with the vascular reconstruction.[39]

In 1993, our group reported that PTX with PE drainage with Roux limb diversion not only achieved acceptable metabolic control and eliminated hyperinsulinemia but was also associated with reduced postoperative complications.[5] In 1995, we compared 19 patients un-

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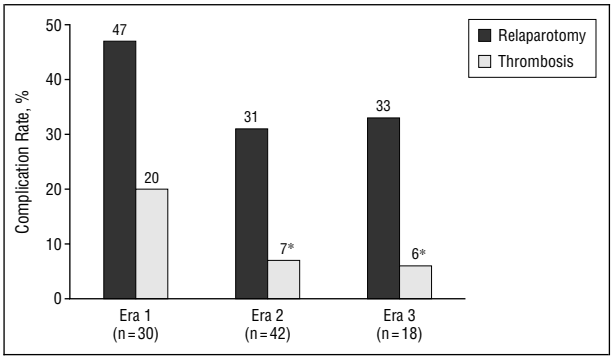

Figure 8. The incidence of pancreas allograft thrombosis was similar in eras 2 and 3 and significantly decreased compared with era 1. Asterisks indicate $P<.05$.

Table 3. Results of Solitary PTX*

	No. (%) of Patients	
	Era 2 (n = 23)	Era 3 (n = 13)
PAKT	11 (48)	7 (54)
PA	12 (52)	6 (46)
One-year survival		
Patient	23 (100)	13 (100)
Pancreas	14 (61)	9 (69)
Acute rejection	13 (57)	5 (38)
Major infection	8 (35)	4 (31)
Thrombosis	5 (22)	2 (15)
Relaparotomy	10 (43)	5 (38)
Overall pancreas graft loss	16 (70)	4 (31)
Causes of graft loss		
Thrombosis	5 (22)	2 (15)
Chronic rejection	4 (17)	2 (15)
Infection/PTLD	3 (13)	0
Acute rejection	2 (9)	0
Primary nonfunction	1 (4)	0
DWFG	1 (4)	0

*PTX indicates pancreas transplantation; PAKT, sequential PTX after kidney transplantation; PA, PTX alone; DWFG, death with functioning graft; and PTLD, posttransplant lymphoproliferative disease.
†P=.02; all other P values were nonsignificant.

dergoing SKPT with PE drainage with a retrospective control group of 28 patients receiving SKPT with the conventional SB technique.[6] Actuarial patient and graft survival rates at 1 and 3 years were no different between the 2 groups. Metabolic and urologic complications and urinary tract infections were more common in the SB group. Metabolic control was comparable between groups, and peripheral hyperinsulinemia did not occur in patients with PE drainage.

In 1995, Newell et al[40] reported their initial experience with a similar PE technique in 12 SKPT recipients compared with a retrospective matched control group of 12 SKPT patients with SB drainage. Six-month patient and graft survival rates were comparable, and the PE group had less acidosis, dehydration, hematuria, rejection, and need for enteric conversion. There were no differences in technical complications, and renal and pancreas allograft functions were similar. In 1996, Newell et al[41] presented a 12-month follow-up on the same 2 groups with similar findings. In addition, the initial length of stay and total in patient days in the first year after transplantation were slightly lower in the PE group. There were no significant differences in costs, no delay in the diagnosis of rejection, and the authors concluded that their results confirmed the safety and efficacy of this new technique.

In 1997, Nymann et al,[42] from our group, reported improving outcomes with increased experience with the PE technique. Two groups were compared: 23 SKPTs with PE drainage performed between 1991 and 1994 vs 23 PTXs with PE drainage (17 SKPTs, 3 PAKTs, 3 PTXs alone) performed between 1995 and 1996. The latter group received TAC-based immunosuppression, while the former group was managed with cyclosporine. Cold ischemia time and perioperative blood transfusions were significantly lower in the latter group. In addition, the incidence of technical graft loss was reduced from 26% to 9%. Consequently, 1-year patient and pancreas graft survival rates were improved in the latter era. In 1998, Nymann et al[18] analyzed 47 SKPTs with graft function at 1 month, including 30 with SB and 17 with PE drainage. All patients had received cyclosporine-based therapy. Although the authors noted comparable patient and graft survival and surgical complication rates, the incidences of rejection, graft loss owing to rejection, and the density of rejection, were all lower in patients with PE drainage. In 1998, Eubanks et al,[8] also from our group, compared 12 solitary PTXs with SB drainage performed between 1991 and 1995 with 16 solitary PTXs with PE drainage performed between July 1995 and March 1997. The former group was managed with cyclosporine and the latter with TAC-based immunosuppression. One patient in each group experienced graft loss as a result of thrombosis. In the remaining patients, the incidence and density of rejection was lower in the more recent era, leading to an improvement in the 1-year pancreas graft survival rate to 80%. In each of these studies, the authors concluded that the results of PTX using the PE technique are comparable with the other reported techniques.

In 1998, Bruce et al[43] reported their experience with 70 consecutive SKPTs with PE drainage performed between January 1992 and August 1997. They compared this group with a "historical" control group of 70 SKPTs with SB drainage performed between January 1987 and December 1994. One-year patient, kidney, and pancreas graft survival rates were comparable between groups. There were no significant differences in technical or immunologic graft failure rates since no enteric or anastomotic leaks were reported in this series. Renal and pancreas allograft functions at 1 year were similar. However, the total number of hospital days and operative complications in the first year were significantly higher in the SB group, with the difference in these results almost entirely accounted for by a 21% rate of enteric conversion in patients with SB drainage. In addition, the authors noted a possible learning curve effect, with improved results in the latter 35 vs the former 35 SKPTs with PE drainage. In 1998, Busing et al[44] reported on 70 consecutive SKPTs without anastomotic complications, including 2 with PE drainage. Busing et al[45] later updated the previous experience to 10 SKPTs with PE drainage, without

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using a Roux limb. Kidney and pancreas graft survival rates were both 90%, with 1 graft loss caused by thrombosis. Buell et al[46] also updated the Busing et al[44] experience, including 16 SKPTs with PE drainage without a Roux limb. This group also reported good initial results with the PE technique in the absence of a diverting Roux limb.

In 1999, Reddy et al[47] reported a reduction in the surgical complication rate after PTX with PE drainage that was attributed to increased experience with the technique. Also in 1999, Stratta et al[48] reported that the incidence of allograft pancreatectomy was not influenced by the surgical technique of implantation.

In 1999, Philosophe et al[49] reported their initial experience with 66 PTXs using PE drainage compared with 183 PTXs using SE drainage. Graft survival rates of recipients of SKPTs, PAKTs, and PTXs alone were similar. However, when stratified for HLA matching, the incidence of rejection was lower in patients with PE drainage. In a follow-up report in 2000, Philosophe et al[50] compared 117 solitary PTXs using PE drainage with 70 using SE drainage. The authors noted not only an improvement in the pancreas graft survival rate, but also a decrease in the incidence and severity of rejection in patients with PE drainage. The authors concluded that PE drainage may be associated with an immunologic advantage.

In 2000, Petruzzo et al[51] reported a prospective study of 34 SKPT recipients randomized to either receive SE or PE drainage with a Roux limb. Patient and graft survival rates and morbidity were similar between groups. In 2001, Stratta et al[9] prospectively compared 44 consecutive SKPTs performed with either SE (n=22) or PE (n=22) drainage. Again, patient and graft survival rates as well as medical and surgical morbidity were comparable between groups. Both of these studies concluded that whole organ PTX with a standardized technique of PE drainage can be performed with short-term results comparable to the conventional technique of SE drainage.

In 2000, Stratta et al[7] prospectively alternated 32 consecutive PTXs to either SB (n=16) or PE (n=16) drainage with standardized immunosuppression. Patient and graft survival rates and operative complications were comparable between groups after either SKPT or solitary PTX. There were no graft losses either to immunologic or infectious complications in either group, but the incidence of acute rejection was slightly higher in the SB group (SB, 44% vs PE, 31%; $P=.24$). Moreover, the SB group was characterized by a slight increase in the number of readmissions, urinary tract infections, urologic complications, metabolic acidosis, and dehydration. Also in 2000, Cattral et al[52] prospectively studied 20 SKPTs with SB drainage followed by a sequential cohort of 20 consecutive SKPTs with PE drainage. One-year patient and graft survival rates were similar between groups. However, medical morbidity, cytomegalovirus infections, and acute rejection were more common in the SB group. Zibari et al[53] reported their initial experience with 17 SKPTs with PE drainage and a Roux-en-Y venting jejunostomy to monitor for rejection and prevent anastomotic leak. Patient, kidney, and pancreas graft survival rates were 100%, 100%, and 94%, respectively, after a mean follow-up of 16 months. In each of these studies, the authors concluded that SKPT with PE drainage can be performed with excellent short-term outcomes and minimal morbidity.

Our study reports the chronology of our experience with PE drainage spanning different immunosuppressive eras. The major findings were that (1) inferior outcomes occurred after SKPT in era 1; (2) the results of SKPT in eras 2 and 3 were remarkably similar; and (3) the results of solitary PTX were slightly improved in era 3 compared with era 2. With regard to SKPT, patient and kidney graft survival rates were nearly identical in each era, reflecting the fact that death with function was the most common cause of kidney graft loss. In the first year after SKPT, kidney graft loss owing to either immunologic or technical complications was uncommon. When censoring for death with function, the differences in kidney graft survival rates between the eras were eliminated. In contrast, censoring for death with a functioning graft did not eliminate the differences in pancreas graft survival rates between the eras. In the first year after SKPT, pancreas graft loss was usually caused by either thrombosis or infection. Pancreas graft loss caused by rejection was uncommon. However, in patients with functioning grafts, the incidences of either acute rejection or thrombosis were significantly lower in eras 2 and 3 compared with era 1. Although era 1 may represent a "learning curve" effect, there is no question that the switch from cyclosporine (era 1) to TAC-based immunosuppression (eras 2 and 3) had a dramatic effect on outcomes.[10,15,16] Surprisingly, the addition of either basiliximab or daclizumab to TAC/MMF therapy (era 3) did not have any discernible effect on outcomes after SKPT.[17] The potent immunosuppressive state achieved with the combination of TAC, MMF, and steroids may have overshadowed any potential benefits of monoclonal antibodies directed at the interleukin-2 receptor.[17] Coincident with a decrease in the incidence of acute rejection achieved with TAC/MMF therapy, we also noted a reduction in the risk of thrombosis after SKPT with PE drainage. It has been suggested that many cases of pancreas allograft thrombosis are caused by immunologic rather than technical factors.[54] Other changes that occurred over time and possibly influenced the risk of thrombosis included restricted donor selection, protective cytomegalovirus matching,[25] minimizing cold ischemia,[12,42] and routine perioperative anticoagulation.[54]

With regard to solitary PTX, modest improvements were noted in all outcome parameters measured in era 3 compared with era 2. However, none of these differences were statistically significant because of small numbers. In contrast to SKPT, death with a functioning graft was not an early consideration, since the 1-year patient survival rates were 100% in both eras. The decrease in the rates of acute rejection and thrombosis occurring in era 3 are clinically significant, and might reach statistical significance with larger numbers. Further changes that occurred in management protocols that might have contributed to improved outcomes after solitary PTX in era 3 included routine anticoagula-

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tion, HLA matching, and surveillance pancreas biopsy monitoring.[26]

In summary, this overall experience demonstrates that SKPT and solitary PTX with PE drainage can be performed with improved outcomes. Increasing experience with the PE technique coupled with advances in immunosuppression are associated with (1) increasing patient, kidney, and pancreas graft survival rates; (2) less medical morbidity with a decreasing incidence of acute rejection and major infections; and (3) reduced surgical complications including decreasing rates of thrombosis and relaparotomy. The PE technique does not seem to incur any additional or unique risks and can be performed yielding results comparable with the other standard techniques of PTX. We believe that this technique should be included in the repertoire of PTX, because it offers potential physiologic,[5,36] metabolic,[6,27] and immunologic[18,50] advantages compared with the other techniques currently available.

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