Transplant Int (1992) 5: 19–22

TRANSPLANT
International

Pancreatic flush injury in combined pancreas-liver recovery

D. D. Nghiem[1] and E. M. Cottington[2]

[1] Transplantation Services, Department of Surgery, Allegheny General Hospital, 320 East North Avenue, and
[2] Allegheny-Singer Research Institute, Pittsburgh, PA 15212, USA

Received March 19, 1991/Received after revision July 9, 1991/Accepted August 28, 1991

Abstract. The function of pancreatic grafts harvested from six pancreas-liver (PL) donors was compared to that of nine pancreas-alone (PA) donors. All donors had comparable physiological parameters. Pancreas and liver were flushed in situ with 4C Collins solution and the portal vein was vented immediately. The pancreaticoduodenal grafts were reflushed and stored in Collins solution (three PA and two PL), silica gel-filtered plasma (six PA and two PL), or University of Wisconsin solution (two PL). Later they were revascularized by the iliac vessels and drained into the bladder. All pancreas recipients were insulin-dependent. Serum glucose, amylase, lipase, blood urea nitrogen (BUN), creatinine, protein, albumin, and urine amylase, bicarbonate and pH were monitored for 12 days. Data were analyzed using the Mann-Whitney U-test and Fischer's exact test. The PL grafts received a significantly higher aortic flush volume (5983 cc vs 1622 cc, $P = 0.001$) than those in the other group. Recipients of PL grafts had higher serum amylase (335 vs 250 IU/l) and lipase (1048 vs 424 IU/l), significantly lower levels of urine bicarbonate (11.2 vs 27.1 mEq/l, $P = 0.01$), pH (6.8 vs 7.3, $P = 0.04$), and amylase (9202 vs 19 981 IU/l, $P = 0.05$) than those in the PA group. Moreover, they required longer periods of gastric suction (4.8 ± 1.7 vs 2.7 ± 3.1 days, $P = 0.04$), and despite central venous nutrition (4/6 vs 1/9 patients, $P = 0.02$) had significantly lower serum protein (6.0 ± 0.7 vs 5.2 ± 0.4 g/dl, $P = 0.02$) and albumin (2.7 ± 0.3 vs 3.3 ± 0.4 g/dl, $P = 0.01$) when compared to the other group and to the pre-transplant values ($P = 0.03$). These data suggest that high volume aortic flush induces pancreatic graft injury. Suggestions for improvement are discussed.

Key words: Pancreas transplantation, preservation – Preservation, pancreas, clinical – Perfusion injury, pancreas preservation

In situ visceral cold perfusion is an accepted method to abolish warm ischemia during organ procurement. Hart et al. [8] initiated aortic perfusion of livers and kidneys and obtained good primary function of all organs. In 1975, Garcia-Rinaldi et al. [6] reported on 18 cadaver kidneys cooled in situ by aortic perfusion with sodium bicarbonate-enriched lactated Ringer's solution that functioned immediately without acute tubular necrosis. According to Rolles et al. [17], when Ross and Marshall solutions were used, 38% of the recipients of kidneys removed from liver donors required post-transplant hemodialysis.

As the success of transplantation and the number of extrarenal transplants rapidly increased, organ procurement also progressed to such an extent that all organs could be removed safely and more frequently. Shaw et al. described the combination donor hepatectomy and nephrectomy with a 15% rate of dysfunction of transplanted organs [20]. They subsequently reported on simultaneous donor cardiectomy and nephrectomy with a 12% acute tubular necrosis rate [21]. Nghiem et al. were able to remove heart, pancreas, and kidneys from the same donor with an overall 96.6% primary function rate of 75 organs harvested from 25 donors [15]. More recently, other techniques have described the procurement of liver and pancreas from the same donor [4, 12, 22, 25]. All have reported satisfactory graft function but none have given any account of the detrimental effects that have resulted from the procedures. This paper describes graft pancreatitis caused by excessive in situ flushing of the donor pancreas during simultaneous removal of both organs and offers different approaches to avoid this complication.

Materials and methods

Fifteen multiple organ (liver, pancreas, kidney, heart, heart-lung) cadaver donors were divided into two groups – pancreas-liver (PL) and pancreas-alone (PA) donors – depending on whether or not the pancreas was removed concomitantly with the liver.

Contrary to most organ donors, who developed brain death from cerebrovascular accidents, pancreas donors were chosen from among young victims to avoid atherosclerosis of the splanchnic arteries. Two patients in each group had gunshot wounds to the head. One PL patient ruptured a berry aneurysm at the base of the brain.

Offprint requests to: D. D. Nghiem

Table 1. Donor demographic data. Values are expressed as mean ± SD

	PL group ($n = 6$)	PA group ($n = 9$)	P
Age (years)	21.4 ± 6.4	27.7 ± 7.4	0.16
Weight (kg)	58.9 ± 16.7	62.0 ± 16.9	0.72
T. Bil (mg/dl)	0.9 ± 0.7	0.6 ± 0.4	0.32
SGPT (IU/l)	47.0 ± 58.4	64.5 ± 45.1	0.08
Alk. phosphatase (IU/l)	52.0 ± 7.0	56.0 ± 32.0	0.69
Hematocrit (%)	35.3 ± 6.5	33.7 ± 5.3	0.60
Serum glucose (mg/dl)	223.1 ± 135.0	195.0 ± 62.0	0.69
Serum amylase (IU/l)	68.0 ± 44.0	151.0 ± 165.0	0.46
Serum lipase (IU/l)	27.5 ± 6.4	210.0[a]	0.22
Urine amylase (IU/l)	97.0 ± 107.0	40.0 ± 7.0	0.45
BUN (mg/dl)	13.3 ± 3.7	13.5 ± 4.5	0.95
Serum creatinine (mg/dl)	1.1 ± 0.2	1.0 ± 0.2	0.55
Dopamine (μg/h)	14.5 ± 1.0	10.7 ± 6.6	0.29
High systemic BP (mm Hg)	151.0 ± 13.0	143.0 ± 39.0	0.25
Low systemic BP (mm Hg)	103.0 ± 24.0	56.0 ± 22.0	0.004
Urine during recovery (ml)	225.0 ± 86.0	785.0 ± 682.0	0.08
Transfusion (units)	6.3 ± 3.2	2.0 ± 0.0	0.07
Aortic flush (ml)	5983 ± 1637	1622 ± 725	0.001
Kidneys procured	12	18	–
Hearts procured	5	5	–
Heart-lung	1	0	–

[a] One measurement

Table 2. Recipient demographic data. Values are expressed as mean ± SD

Pretransplant	PL group ($n = 6$)	PA group ($n = 9$)	P
Age (years)	33.5 ± 3.8	34.1 ± 7.7	0.95
Weight (kg)	70.0 ± 13	60.7 ± 15	0.31
Duration diabetes mellitus (years)	23.7 ± 6.5	23.9 ± 6.1	0.87
Serum glucose (mg/dl)	215 ± 115	317 ± 161	0.45
Serum protein (g/dl)	6.9 ± 1.7	6.8 ± 1.5	0.67
Serum albumin (g/dl)	3.4 ± 1.0	3.6 ± 0.5	0.52
Serum amylase (IU/l)	115 ± 40	131 ± 72	0.85
Serum lipase (IU/l)	247 ± 57	199 ± 61	0.73
HLA DR mismatch (antigen)	1.6 ± 0.5	1.4 ± 0.5	1.0
HLA AB mismatch (antigen)	1.7 ± 0.5	1.7 ± 0.5	1.0
Cold ischemia time (min)	337 ± 167	284 ± 92	0.76
Post-transplant			
Normal pancreas	2/6 (33%)	5/9 (55%)	0.38
Edematous pancreas	4/6 (66%)	4/9 (44%)	0.17
Blotchy pancreas	3/6 (50%)	2/9 (22%)	0.29
Serum amylase (IU/l)	335 ± 379	250 ± 128	0.63
Serum lipase (IU/l)	1048 ± 834	424 ± 252	0.15
Serum glucose (mg/dl)	131 ± 67	114 ± 21	0.28
Urine output (ml/24 h)	3632 ± 1072	3569 ± 786	0.90
BUN (mg/dl)	44 ± 17	41 ± 19	0.81
Serum creatinine (mg/dl)	2.4 ± 1.0	2.0 ± 0.7	0.47
Urine amylase (IU/l)	9202 ± 5435	19981 ± 9826	0.05
Urine bicarbonate (mEq/l)	11.2 ± 6.4	27.1 ± 8.0	0.01
Urine pH	6.8 ± 0.3	7.3 ± 0.2	0.04
Serum protein (g/l)	5.2 ± 2.4	6.0 ± 0.7	0.02
Serum albumin (g/l)	2.7 ± 0.3	3.3 ± 0.4	0.01
Gastric decompression (days)	4.8 ± 1.7	2.7 ± 3.1	0.04
Central venous nutrition	4/6 patients	1/9 patients	0.02

Those who had closed or open head injuries deteriorated rapidly within a few hours, whereas those who had intra-abdominal injuries arrived at organ procurement within 10–12 h of admission. This allowed plenty of time for resuscitation and prerecovery tissue typing. All donors were ventilated and all maintained stable hemodynamic parameters using blood and/or blood components, electrolyte-balanced solutions, or inotropic support. All had urine outputs exceeding 100 ml/h during the hours preceding organ removal. There was one cardiac arrest in the PA group and three transient post-traumatic hypotensive episodes in both groups. In the majority of cases, parameters were similar in both groups (Table 1). During the multi-organ harvest procedure, patients were fluid-loaded and received large doses of mannitol and loop diuretics. The technique of pancreatectomy and hepatectomy described in detail elsewhere [14, 15, 20] consisted of isolation of both pancreas and liver with their blood supplies. Whereas pancreatectomy had always been carried out by a single senior surgeon in this series within 2 h of operating time, later, when the liver was offered for transplantation and removed by different outside teams, the operating time needed for the removal of both organs was lengthened considerably and blood transfusion requirements consequently tripled. Despite these adverse conditions, the donors remained stable (Table 1). Once both organs were connected to the donors only by their blood supplies, perfusion was started via an aortic cannula, after clamping the aorta above the celiac axis. The portal vein was perfused by a cannula inserted through either mesenteric vein and vented immediately by venotomy to avoid venous congestion and edema of the pancreas. Primary cooling was initiated with 4C Collins solution, followed on the back table by reflushing of the pancreaticoduodenal grafts with 300 ml of Collins solution (three PA and two PL), silica gel-filtered plasma (six PA and two PL), or University of Wisconsin (UW) solution (two PL).

The pancreata were transplanted with vascularization via the external iliac vessels and bladder drainage of the pancreatic secretions [14]. The vascularization of the pancreatic graft varied depending on whether it was harvested from a PL or from a PA donor. In the former, the blood supply consisted of an aortic patch bearing the splenic artery, the common hepatic artery minus the hepatic propria artery, and the superior mesenteric artery. In the latter, the pancreas received an additional blood supply from the preserved gastroduodenal artery. Vascular reconstruction of the pancreas was not necessary in the PL group and did not cause any harmful effects, such as ischemia of the pancreas and/or duodenum, as assessed by intraoperative Doppler (Bach Simpson, London, Ontario, Canada) after revascularization. After transplantation the macroscopic aspect of the pancreas was graded as normal, edematous, or blotchy. Recipients' demographic data are given in Table 2. Post-transplant fasting serum glucose, amylase, lipase, blood urea nitrogen (BUN), creatinine, protein, albumin, and fasting random urine amylase, bicarbonate, and pH were monitored thrice daily for 12 days and their values averaged [16]. Postoperative gastric decompression and central venous nutrition (CVN) were indicated by the degree and severity of abdominal distension and gastrointestinal dysfunction. Immunosuppression consisted of triple drug therapy, i.e., 2 mg/kg cyclosporin given intravenously twice daily, the dosage regulated to maintain a whole blood HPLC level of 250 ng/ml; 2 mg/kg azathioprine daily; and 2 mg/kg methylprednisolone, decreasing by 5-mg increments daily to a dose of 0.5 mg/kg. Pancreas rejection was diagnosed on the basis of decreasing urine amylase, pH, bicarbonate and, in eight instances, by the presence of lymphocytic infiltrates seen on duodenal mucosa biopsies [10]. Rejection episodes were treated with 5 mg/kg methylprednisolone for 3 days and the monoclonal antibody OKT3 (5 mg/day; Orthoclone, Ortho, N. J., USA) for 10–14 days.

Data from the first 12 days post-transplantation were analyzed using the Mann-Whitney U-test and Fischer's exact test.

Results

The two groups of liver and non-liver pancreatic donors were similar with regard to age, weight, and biochemical data (Table 1). Although the PA group experienced significantly more hypotension (56 ± 22 mm Hg vs 103 ± 26 mm Hg, $P = 0.004$) than the PL group, the func-

tion of kidneys and pancreata at the time of organ procurement expressed by urine output, BUN, serum creatinine, amylase, and lipase was not affected. For reasons mentioned previously, the extensive dissection of both organs in the PL group required more blood transfusions (6.3 ± 3.2 units vs 2.0 ± 0.0 units, $P = 0.07$) than in the other. Also of significance was the large volume of aortic perfusion in the liver donor at the time of organ recovery (5983 ± 1637 vs 1622 ± 725 ml, $P = 0.001$), which reflected markedly on subsequent function of pancreatic allografts. Both groups of diabetic recipients were comparable in age, weight, duration of diabetes mellitus, metabolic data (serum glucose, protein, and albumin), allograft histocompatibility mismatching, and cold ischemia times (Table 2). After revascularization, fewer normal pancreata and more edematous and blotchy grafts were seen in the PL group.

While all grafts showed euglycemia, pancreatitis did occur in both groups with higher biochemical changes and clinically more severe symptoms in the recipients of PL grafts. These patients developed more abdominal distension, pain, and gastrointestinal paresis and required significantly longer periods of nasogastric decompression (4.8 ± 1.7 vs 2.7 ± 3.1 days, $P = 0.04$) and frequent intravenous hyperalimentation (4/6 patients vs 1/9, $P = 0.02$). Secondary to pancreatitis, the PL grafts produced significantly lower urine pancreatic exocrine secretions than those in the PA group with regard to bicarbonate ($P = 0.01$), pH ($P = 0.04$), and amylase ($P = 0.05$). Even with additional nutrition, the averaged levels of serum protein and albumin in the two groups dropped significantly during the post-transplant period, with P values of 0.02 and 0.01 respectively, and in the PL group between pre- and post-transplant values ($P = 0.03$).

Discussion

Maintenance of donors prior to and during the harvesting of organs is essential for obtaining good organs for transplantation, provided the latter had good primary function. Although both groups in this series were small and statistical analysis was not possible, the presence of cardiac arrest and hypotensive episodes was not detrimental to any organ. The fact that 66.6% of the hearts were able to be removed and transplanted attests to the intensity and the success of the resuscitative measures taken.

Postoperative elevated serum amylase values were observed whether the pancreas exocrine secretions drained via a cutaneous duodenostomy or jejunostomy catheter [7, 26] or to the bladder [14, 16]. Amylase levels usually peaked 24–48 h after transplantation and normalized by the 5th day. Post-transplant pancreatitis occurred in 3% [5] to 21% [7] of the grafts and its severity was related to the degree of ischemic injury to the graft [2, 11]. Thus, the longer the cold ischemia, the greater the rise in serum amylase. Since all organs in this series were transplanted within 9 h, it is unlikely that cold storage injury was instrumental in the development of pancreatitis in the PL group. This is in accordance with the findings of the International Pancreas Transplant Registry, which did not report any difference in graft survival between pancreata preserved for less than 6 h and those preserved for longer than 24 h [24]. In this regard, grading of the macroscopic aspect of the graft after transplantation could be subject to inaccuracies because of grade overlapping since a graft could be slightly edematous and still labeled as normal, whereas blotchy patches could coexist in both normal and edematous grafts. Moreover, these appellations did not reflect the degrees of post-transplant pancreatitis.

The fact that the role of preservation perfusates, e.g., Collins solution, silica gel-filtered plasma, and UW solution, used in this study could not be assessed is understandable due to the small number of cases involved and because of the current confusion in the pancreas transplantation literature as to what solution should be used and at what time. Experimentally, there was ample evidence that appropriate preservation could only be achieved by a fluid containing large molecular weight impermeants and high oncotic pressure and pH, e.g., University of Wisconsin solution [1, 27], and that it was best for organs to be perfused with and stored in the same solution [22]. In the clinical setting, however, most organs were still washed out and cooled with Collins solution but preserved in another fluid. Furthermore, small prospective series [27], as well as the report of the International Pancreas Transplant Registry [24], failed to show any significant superiority of one solution over another.

With regard to how much perfusate to use, all institutions have reported complications, i.e., thrombosis and edema, associated with a large volume of perfusate [27, 28] and have suggested restricting the flushing volume to 2000–3000 ml [12, 16, 22, 28]. Given the amount of flushing solution used in this series (close to 6000 ml), the occurrence of pancreatitis in the PL grafts was not unexpected.

The technique of combined pancreatectomy and hepatectomy is another controversial issue. Some authors prefer minimal dissection and en-bloc removal of both organs, which are later separated in vivo on the back table [22]. In contrast, we and others have advocated thorough mobilization of all organs with their vascular connections prior to their individual removal [5, 12, 13, 19, 22]. Although opposite in appearance, both techniques stress the importance of minimal manipulation of the pancreas in order to avoid edema and post-transplant pancreatitis. Thus, the additional removal, in this series, of other nonrenal organs, such as the heart and heart-lung, which was carried out at the outset of the intra-abdominal perfusion, was not in any way deleterious to long-term allograft function [13].

Many approaches could be taken to decrease post-transplant graft pancreatitis due to high-volume flush injury. Aortic perfusion at a lower volume and lower pressure could be used without any deleterious effects on the liver. The liver, in this instance, could be additionally core-cooled with portal infusion and surface-cooled with ice slush. Precooling for the liver described first in 1984 [23] should not be practiced in combined liver and pancreas procurement [22]. Indeed, there is ample evidence that flushing and preservation are best performed when using only one solution [22, 24]. Pharmacological manipulation

of the pancreas, which was advocated as early as 1983 [9] and which has culminated in the development of somatostatin analog SMS 201–995, could be used to reduce pancreatic secretion volume [18], amylase, and bicarbonate excretion [3], thus making it available for prophylaxis of pancreatitis. When the octreotide is administered, it is important that immunosuppressive drugs be given parenterally since the oral absorption of cyclosporin is impeded [18].

Lastly, a primordial aspect of multiple organ procurement should be addressed, namely, the cooperation between different surgical procurement teams. They should understand each other's goals and needs and should work together to procure anatomically and physiologically functional organs for transplantation.

References

1. Barr D, Munn SR, Perkins JD (1990) A prospective comparison of two preservation solutions in human pancreaticoduodenal transplantation. Transplant Proc 22: 529–531
2. Broe PJ, Zuidema GD, Cameron JL (1982) The role of ischemia in acute pancreatitis: studies with an isolated perfused canine pancreas. Surgery 91: 377–382
3. Daloze P, Beauregard H, St-Louis G, Corman J, Smeesters C, Aris-Jilwain N, Comtois R, Rusio C (1989) Clinical pancreas transplantation: a learning curve of its management. Transplant Proc 21: 2858
4. Delmonico FL, Jenkins RL, Auchincloss H Jr, Etienne TJ, Russell PS, Monaco AB, Cosimi AB (1989) Procurement of a whole pancreas and liver from the same cadaver donor. Surgery 105: 718–723
5. Dunn DL, Morel P, Schumpf R, Mayoral JL, Gillingham KJ, Moudry-Munns KC, Krom RA, Gruessner RWG, Payne WD, Sutherland DER, Najarian JC (1991) Evidence that combined procurement of pancreas and liver grafts does not affect transplant outcome. Transplantation 51: 150–157
6. Garcia-Rinaldi R, Lefrak EA, Defore WW, Feldman L, Noon GP, Jachimczyk JA, Debakey ME (1975) In situ preservation of cadaver kidneys for transplantation: laboratory observations and clinical application. Ann Surg 182: 576–582
7. Groth CG, Tyden G (1988) Segmental pancreatic transplantation with enteric exocrine drainage. In: Groth CG (ed) Pancreatic transplantation. Saunders, Philadelphia, pp 99–112
8. Hart AJL, Smellie WAB, Calne RY (1971) Fate of kidney allografts from cadaver donors whose livers were also transplanted. Lancet I: 103–104
9. Landgraf R, Abendroth D, Land W (1983) Mechanical and hormonal blockade of the pancreatic function in man. In: Land W, Landgraf R (eds) Segmental pancreatic transplantation international workshop, Munich-Spitzingee. Springer, Berlin
10. Lillehei RC, Simmons RL, Najarian JS, Weil R, Ucida H, Ruiz JO, Kjellstrand CM, Goetz FC (1970) Pancreaticoduodenal allotransplantation: experimental and clinical experience. Ann Surg 172: 405–410
11. Lundgren G, Wilczek H, Klintmalm G, Tyden G, Groth CG (1984) Procurement and preservation of human pancreatic grafts. Transplant Proc 16: 681–683
12. Marsh CL, Perkins JD, Hayes DH, Munn SR, Sterioff S (1989) Combined hepatic and pancreaticoduodenal procurement for transplantation. Diabetes 38 [Suppl 1]: 231
13. Nghiem DD (1990) Simultaneous recovery of whole pancreas without arterial reconstruction with multiple organ liver donor. Transplant Proc 22: 614–615
14. Nghiem DD, Corry RJ (1987) Technique of simultaneous pancreaticoduodenal transplantation with urinary drainage of pancreatic secretion. Am J Surg 153: 405
15. Nghiem DD, Corry RJ, Schulak JA, Beutel WD, Kisthard JA, Morrow R, Ganes E (1986) Function of organs obtained from pancreas donors. Transplant Proc 18: 538–539
16. Nghiem DD, Gonwa TA, Corry RJ (1987) Metabolic effects of urinary diversion of exocrine secretions in pancreas transplantation. Transplantation 43: 70–72
17. Rolles K, Calne RY, McMaster P (1979) Technique of organ removal and fate of kidney grafts from liver donors. Transplantation 28: 44–46
18. Rosenberg L, Dafoe DC, Schwartz R, Campbell DA Jr, Turcotte JG, Tsasi ST, Vinik A (1987) Administration of somatostatin analog (SMS 201–995) in the treatment of fistula occurring after pancreas transplantation. Interference with cyclosporine immunosuppression. Transplantation 43: 764
19. Sanseverino R, Martin X, Caldara R, Faure JL, Lefrancois N, Dubernard JM (1991) Technique of pancreas revascularization after combined liver and pancreas harvesting in the same cadaveric donor. Clin Transplant 5: 55–59
20. Shaw BW, Hakala T, Rosenthal JT, Broznik B, Starzl TE (1982) Combination donor hepatectomy and nephrectomy and early functional results of allografts. Surg Gynecol Obstet 155: 321–325
21. Shaw BW Jr, Rosenthal JT, Griffith BP, Hardesty RL, Broznik B, Hakala T, Bahnson HT (1983) Techniques for combined procurement of hearts and kidneys with satisfactory function of renal allografts. Surg Gynecol Obstet 157: 261–264
22. Sollinger HW, Vernon WB, D'Allessandro AM, Kalayoglu M, Stratta RJ, Belzer FO (1989) Combined liver and pancreas procurement with Belzer UW solution. Surgery 106: 685–691
23. Starzl TE, Hakala JH, Shaw BW Jr, Hardesty RL, Rosenthal TJ, Griffith BP, Iwatsuki S, Bahnson HT (1984) A flexible procedure for multiple cadaver organ procurement. Surg Gynecol Obstet 158: 223–228
24. Sutherland DER, Moudry-Munns K, Gillingham K (1989) Pancreas transplantation. Report from the International Registry and a preliminary analysis of United States results from the New United Network for Organ Sharing (UNOS) Registry. In: Terasaki PI (ed) Clinical transplantation. UCLA Tissue Typing Laboratory, Los Angeles, pp 19–43
25. Thistlewaite JR, Gaber AD, Stuart FP, Lloyd DW, Emond J, Rouch D, Broelsch CE (1988) Procurement of both liver and whole pancreas/duodenum allografts from a single donor without the use of interposition vascular grafts on transplantation. Transplant Proc 20: 833–834
26. Tyden G, Brattstrom C, Haggmark A, Groth CG (1987) Studies on the exocrine secretion of human segmental pancreatic grafts. Surg Gynecol Obstet 164: 404–407
27. Wahlberg JA, Love R, Landegaard L, Southard JH, Belzer FO (1987) 72-hour preservation of the canine pancreas. Transplantation 43: 5–8
28. Wright FH, Ames SA, Smith JL, Bowers VD, Corry RJ (1990) Pancreatic allograft thrombosis. Donor and retrieval factors and early post-perfusion graft rejection. Transplant Proc 22: 439–441